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| <p>Discussion draft dated 9/20/13</p> | <p>Page 16 of 19, line 8</p> | <p>Comment #5 from Elliot Kwok, Pharm.D., Abbott's Compounding Pharmacy, Inc. – #7</p> <p>Dr. Kwok indicated Abbott's Compounding Pharmacy's comment on "(5) Storage Limits: "24 hours at room temperature, 3 days at cold temperature and 45 days in solid frozen state." Dr. Kwok commented this is not practical in real life setting. According to the Handbook on Injectable Drugs, many sterile products are stable longer than your requirement. Dr. Kwok continued to state patients getting inhalation therapy or eye drops which are stable at cold temperature or room temperature, you cannot tell those patients to discard their expensive medication in a day to three days because there is not sterility testing done.</p> |
| <p>Future</p> | | <p>Comment #1 from Douglas Barcon, Pharm.D. – #14</p> <p>Dr. Barcon continued commenting by asking his comments to be considered and believes the board is moving in a positive direction that will improve patient safety throughout California.</p> |
| <p>General</p> | | <p>Comment #10 from Terry Lerma, Pharm.D., St. Joseph Hospital (Eureka, CA) - #3</p> <p>Dr. Lerma commented that noted in the attachment above that no harm to businesses within California in not anticipated by this proposed legislature. I would disagree. The capital cost alone will be an undue hardship to numerous facilities that are already struggling to keep doors open.</p> <p>Dr. Lerma supports the underpinnings of this legislature, to enhance the quality of sterile compounded pharmaceutical products prepared in California pharmacies. Many states attempted to achieve this goal with JCAHO in the early 2000's but the capital cost to rural facilities, CAH, and DSH prevented this paradigm shift from happening, which is why JCAHO modified the original patient safety goal.</p> <p>Dr. Lerma commented being relatively new to Eureka, CA. Dr. Lerma is now completing a gap analysis for three of our compounding pharmacies. With swift capital planning and a reasonable implementation timeframe I feel we can reach the "future state" detailed in the proposed legislature... I do not believe the deadline of July 1st 2014 is reasonable.</p> <p>Our Oncology program is in the process of integrating a local Oncology practice (physician operated) that will potentially increase triple chemo volume in the next 90 days. I am worried that the short timeframe of 6 months to achieve compliance with proposed legislature will hinder the provision of chemotherapy to our patients in Humboldt county.</p> <p>Additionally, I feel the legislature does not take into account the capital impact to organizations that are already struggling financially to keep their doors open, such as CAH and DSH hospitals. Additionally, vendor availability (construction, IV Hoods, etc..) is also something that may impact our ability to achieve the July 1st 2014 deadline.</p> <p>Because I am new to California State (Wa), I reached out to sister facilities located throughout California. Most of these facilities indicated that no action towards compliance with the proposed legislature had yet to be realized, as everyone was waiting for the legislature to become law. This again seems to reinforce my concerns regarding the timeframe and vendor availability. Prior to holding these conversations, I suspected that we were "behind" in terms of compliance.</p> |

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| | | Dr. Lerma commented and inquired if California State considered offering healthcare facilities (particularly DSH and CAH) tax deductions for assuming significant capital expenses related to this proposed legislature? |
| General | | <p>Comment #1 from Douglas Barcon, Pharm.D. – #1</p> <p>Dr. Barcon reviewed the draft compounding language and applicable sections of the United States Pharmacopeia, including General Chapters 797, 71, 1079, 1191, 85, 151, 1211, 1116, and 1208. Dr. Barcon stated he found several inconsistencies and areas that should be addressed in the draft regulations before they are finalized. Dr. Barcon noted that for all references to the United States Pharmacopeia his comments are referring to USP36-NF31 through the Second Supplement, which is official as of December 1, 2013 and supersedes earlier versions. Dr. Barcon suggests the Board members visit the Nevada Board of Pharmacy website and look at the sterile compounding regulations in that state. Dr. Barcon indicated Nevada codified USP 797 and other compounding standards into regulations that are more restrictive than California regulations.</p> |
| General | | <p>Comment #1 from Douglas Barcon, Pharm.D. – #13</p> <p>Dr. Barcon also commented as pointed out during the sterile compounding forum as CSHP Seminar 2013, problems also occur due to trainers who learned improper techniques and pass those bad skills on to others. Dr. Barcon stated training is an issue because some pharmacists and pharmacy technicians work at more than one pharmacy and have to remember the compounding procedures and processes used at each of those pharmacies while not confusing them with other pharmacies. Dr. Barcon suggested if more premixed products were available from FDA regulated manufacturers, much of these problems would go away. Dr. Barcon commented regardless, he believes the proposed sterile compounding regulations enacted for patient safety are needed.</p> |
| General | | <p>Comment #3 from Romic Eskandarian, Pharm.D., Glendale Adventist Medical Center, Adventist Health – #13</p> <p>Dr. Eskandarian commented on “Facility design and environmental controls.” Dr. Eskandarian indicated OSHPD requirements for renovations within the IV room in accordance to CA BOP and USP 797 requirements. The Board of Pharmacy should allow for approximately three months for submission of a document for strategic planning to meet the requirements for facility design and environmental controls. The Board of Pharmacy should allow for approximately six to twelve months to complete the required redesigning and renovations.</p> |
| General | | <p>Comment #4 from Dennis McAllister, R.Ph., D.Ph., FASHP, Express Scripts – #1</p> <p>Mr. McAllister commented that it is important to clearly define “product” which is manufactured and a “preparation” which is compounded. Mr. McAllister indicated these two definitions should be used correctly throughout the document and will align with other states and federal definitions.</p> |
| General | | <p>Comment #5 from Elliot Kwok, Pharm.D., Abbott’s Compounding Pharmacy, Inc. – #1</p> <p>Dr. Kwok commented Abbott’s Compounding Pharmacy agree with most of the changes to Title 16 because it is a real benefit to their patients, customers and the people of California. Dr.</p> |

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| | | Kwok also commented it levels the playing field for all compounding pharmacies within the State of California and out of state pharmacies. |
| General | | <p>Comment #7 from Doug O'Brien, Pharm.D., and Donald Kaplan, Pharm.D., Kaiser Permanente - #1</p> <p>Kaiser Permanente submits their comments on behalf of their 35 hospital pharmacies, eight licensed home infusion pharmacies, and 29 ambulatory oncology pharmacies that have board issued sterile compounding specialty licenses. Pharmacy managers and administrative pharmacy leaders reviewed the draft language.</p> <p>Although Title 24 language was not included in the draft regulations currently under review, Kaiser Permanente submitted comments for this as the board will pursue these changes at a later time.</p> |
| General | | <p>Comment #9 from Marie Cottman, Pharm.D., Owner/PIC Pacific Compounding Pharmacy and Consultations - #1</p> <p>The board's proposal removes "injectable" and replaces the word with "drug" when referring to sterile injectable compounding... SB 294 adds sterile compounding licensing requirements for sterile compounded drug products to include route of administration of injection as well as route of administration into the eye or inhalation.</p> <p>Recommendation #1 (Cottman): Removing the word "injectable" is prudent.</p> <p>Comment #1 (Cottman): Please note that the definition of "sterile compounded product (CSP)" by USP <797> is still more inclusive than injection, ophthalmic, or inhalation.</p> <p>Reference USP <797>: "For the purposes of this chapter, CSPs include any of the following: 1) Compounded biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals, including but not limited to the following dosage forms that must be sterile when they are administered to patients: aqueous bronchial and nasal inhalations, baths and soaks for live organs and tissues, injections (e.g., colloidal dispersions, emulsions, solutions, suspensions), irrigations for wounds and body cavities, ophthalmic drops and ointments, and tissue implants."</p> |
| General | | <p>Comment #9 from Marie Cottman, Pharm.D., Owner/PIC Pacific Compounding Pharmacy and Consultations - #13</p> <p>Comment #13 (Cottman): Not all sterile products need to be tested for pyrogens. For example, USP <797> specifically exempts ophthalmic drops and inhalations from testing for pyrogens.</p> |
| General | | <p>Comment #9 from Marie Cottman, Pharm.D., Owner/PIC Pacific Compounding Pharmacy and Consultations - #14</p> <p>Comment #14 (Cottman): A requirement to quarantine any product made as more than a single dose is too restrictive as some drug products are not chemically stable for 14 days (the time it takes to conduct a USP <71> sterility test). Additionally, since we compound sterile products on an as needed/ as prescribed basis, many patients are not able to wait 14 days for therapy.</p> |
| General | | Comment #9 from Marie Cottman, Pharm.D., Owner/PIC Pacific Compounding Pharmacy and |

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| | | <p>Consultations - #15</p> <p>Comment #15 (Cottman): The methodologies found in USP <71> are very difficult to attain. There are very few testing labs in the United States that is conducting true <71> testing for CSPs. It costs \$500-800 additional to perform this test. Additionally, the Board may want to consider allowing Rapid Scan RDI or other similar Sterility Tests that are not currently included in USP <71> but may be equivalent (but much faster) testing.</p> |
| General | | <p>Comment #9 from Marie Cottman, Pharm.D., Owner/PIC Pacific Compounding Pharmacy and Consultations - #17</p> <p>Dr. Cottman is a pharmacy owner and full-time compounding pharmacist. Involved in non-sterile compounding for 15 years and high-risk sterile compounding for two years. Taught Advanced Compounding Elective at University of Pacific for last 10 years and practicing pharmacists since 1997. Applauds board's efforts to keep compounding standards at their highest levels. Submitting comments to share practical experience to further the mutual goal of protecting patients while maintaining viable business practices.</p> |
| General | | <p>Comment #10 from Terry Lerma, Pharm.D., St. Joseph Hospital (Eureka, CA) - #1</p> <p>Dr. Lerma commented and inquired why California State Board of Pharmacy has proposed an implementation deadline of July 1st 2014 if the new legislature is not yet law until January 16th 2014? This seems to be an unusually aggressive timeframe given the extensive capital and construction ramifications required to transition to a compliant USP 797 solution.</p> |
| General | | <p>Comment #10 from Terry Lerma, Pharm.D., St. Joseph Hospital (Eureka, CA) - #2</p> <p>Dr. Lerma commented that one would anticipate a reasonable timeframe to organize construction and capital for such an endeavor. I would expect that a one year timeframe would be minimally granted to pharmacies to accommodate these changes. For some reason, 6-7 months seems a bit short. California is a very large state with a great number of hospital pharmacies that will be affected by this new legislature. I imagine that vendors will be overwhelmed within the next 12 months to accommodate requests for product and construction.</p> |
| General | | <p>Comment #14 from Hank Rahe, BSIM, MSE, Containment Technology Group, Inc. - #3</p> <p>Mr. Rahe commented the proposed changes do not include the low volume exemption of a nonnegative pressure room per USP 35 General Chapter 797. This should be added to the revisions. For consistency with USP 35 General Chapter 797 the following should be included in the revisions. "In facilities that prepare a low volume of hazardous drugs, use of two tier of containment (e.g., CSTD within a BSC or CACI that is located in a non-negative pressure room) is acceptable.</p> |
| General | | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children's Hospital Central California - #1</p> <p>The comments assembled were put together with input from multiple pharmacists from the San Joaquin Valley area. Dr. Sakai attended the regulation hearing on 1/16/14 to highlight those issues he considers will significantly adversely effect the organization and the care of the patients served.</p> |

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| General | | <p data-bbox="391 275 1523 306">Comment #16 from BJ Bartleson, RN, MS, NEA-BC, CA Hospital Association (CHA) - #1</p> <p data-bbox="391 344 1549 653">Ms. Bartleson commented CHA's commented on behalf of more than 400 member hospitals and health systems. CHA and its member hospitals agree that, in light of the recent national events with sterile compounding pharmacies, public protection along with efficient, effective delivery of pharmaceutical care is of utmost importance. We agree that updating the state compounding regulations to improve overall patient safety is paramount. With most hospitals following USP Chapter 797 guidelines, we urge the board to adopt and codify regulations that are fully aligned with USP Chapter 797 guidelines, including key provisions such as the immediate use provision and hazardous drug compounding which is not present in the draft regulations.</p> <p data-bbox="391 695 1549 968">CHA offers comments to the regulatory changes in support of these overarching principles while balancing protection of the public with efficient and effective interventions to enable all hospitals within the state, large and small, to collectively achieve them. Striving for a balance between public protection and appropriate regulatory changes so as to ensure continued hospital solvency is essential. California hospitals are under extreme financial constraints in a heavily regulated market. Unnecessary facility remodels and upgrades are in many cases cost prohibitive and ASHP reports the least expensive changes required by USP 797 tend to be the most effective in reducing compounding sterile pharmacy contamination and inaccuracy.</p> <p data-bbox="391 1010 1568 1283">Out-of-state compounding pharmacies play a vital role in providing California hospitals with necessary pharmaceuticals. Now, more than ever, they are providing solutions to the ongoing drug shortage dilemma. While recent national events revealed unsafe and hazardous national sterile compounding pharmacy examples, there are many high quality sterile compounding organizations that are fully compliant with USP 797 standards. To raise the bar above USP 797 standards with unique California requirements, may force some to no longer be interested in the California market. This could have unintended consequences for California hospitals who are unable to access critical medications essential for timely patient care.</p> <p data-bbox="391 1325 1568 1776">CHA applauds the board's urgency in putting forth this rulemaking through a six-month emergency formal regulation and rulemaking adoption process. We appreciate the opportunity to participate in regulatory reform that is fair, consistent and balanced with the hospitals' ability to understand the new requirements, perform their gap analysis and successfully be inspected for licensure. At the time of this writing, hospitals are aware they must submit their compounding pharmacy license application as soon as possible. We understand that while the timing of the adoption of the amendments to the articles may reflect new requirements a hospital will need for licensure, there has been no identified process established for hospitals to achieve recommended changes in a timely manner if modified regulatory language is not adopted in time for the July 1, 2014 date. Inability to meet regulatory requirements on yet unknown changes to obtain a sterile compounding license could result in hospital pharmacies being unable to provide essential patient care and risk unnecessary and harmful delays to patient care.</p> |
| General | | <p data-bbox="391 1818 971 1850">Comment #18 from Michael Moore, R.Ph. - #1</p> <p data-bbox="391 1892 1549 1986">Mr. Moore comments he is a pharmacist with nearly two decades of sterile intravenous compounding experience. Mr. Moore has worked directly in compounding these life-saving medications as well as supervising technicians and other pharmacists. Currently, a significant</p> |

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| | | <p>part of his business is focused on consulting other pharmacies in regulatory and safety compliance. Additionally, for five years he worked as a pharmacy manager for a national home infusion company that has been on the cutting edge of USP 797 compliance. This company currently, as far as he can determine, already employs ALL of the new, proposed regulatory requirements outlined in sections 1735 and 1751. Based on his background, he submits his comments to the board.</p> |
| General | | <p>Comment #18 from Michael Moore, R.Ph. - #8</p> <p>Mr. Moore comments generally that the dates and times for BUD seem to be fairly arbitrary – 24 hours, 7 days, 14 days, 45 days. He is curious what literature exists that supports these timeframes with hard data. Mr. Moore is reminded of a recent education event he attended where the idea that antibiotics are all prescribed for 7 to 10 days; not 4 or 13 days. As human beings we often desire to have things packaged in ways that make sense to us. Seven days seems normal because we are used to a 7 day week. But that alone should not dictate BUDs. Mr. Moore urges the board to require and publish rationale for the proposed BUDs in order for all clinicians and administrators to understand the reasons for the respective BUD dating. Mr. Moore further comments that the literature related to this topic explains that personnel technique is the source for most contamination risks. Those with good technique and a conscientious manner will be far less likely to jeopardize patient care than a careless individual that follows a seemingly arbitrary BUD timeline.</p> |
| General | | <p>Comment #19 from Arthur C. Whitney, R.Ph., Advantage Pharmaceuticals - #1</p> <p>Mr. Whitney comments he commend the California State Board of Pharmacy for strengthening the sterile compounding regulations in light of the NECC tragedy, but would like clarification on several amendments as well as changes in other amendments.</p> |
| General | | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #1</p> <p>CSHP commented on behalf of our nearly 5,000 pharmacy professional members practicing in a variety of clinical settings across the state. In accordance with our mission to “promote wellness, patient safety and optimal use of medications,” CSHP has long supported the Board’s efforts to ensure the integrity of compounding pharmacy. CSHP supported the Board’s 2012 sterile compounding legislation, Senate Bill 294 (Emmerson) as a sensible approach to improving patient safety without becoming onerous to the point where it could inhibit the ability of hospitals to provide care services to patients.</p> <p>It is with this spirit – ensuring the integrity of compounding pharmacy while also ensuring hospitals can continue to serve their critical public health role -- that we approach the proposed compounding regulatory rulemaking package. CSHP supports the work of the California Hospital Association, Kaiser Permanente, Dignity Health, Cedars Sinai, Providence Health and other institutions which have worked hard to craft meaningful recommendations.</p> |
| General | | <p>Comment #21 from Brian Warren, California Pharmacist Association (CPhA) - #14</p> <p>The California Pharmacists Association (CPhA) supports standards to ensure the safety of compounded drug products. As we all learned from the tragedy with the New England</p> |

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| | | <p>Compounding Center and other out-of-state facilities, sterile compounding requires specific safety regulations above and beyond what is required of non-sterile compounding. These standards should apply to all sterile compounders, including those located within California as well as compounding facilities that ship into California.</p> <p>CPhA submitted comments consistent with the intent of the proposed regulations released by the Board. CPhA shares the goal of providing the safest possible products to our patients. Overall, CPhA thanks the Board for the progress made towards greater consistency with Chapter 797 of the United States Pharmacopeia. CPhA’s comments generally call for greater consistency with this national standard.</p> |
| General | | <p>Comment #23 from William Jones, R.Ph., Central Admixture Pharmacy Services, Inc. (CAPS) - #1</p> <p>CAPS has a long history of providing compounded sterile preparations within California with three registered sterile compounding pharmacies.</p> |
| General | | <p>Comment #24 from Candace Fong, Pharm.D., and Rachelle Reyes Wenger, Dignity Health - #1</p> <p>On behalf of Dignity Health and our 30 hospital-based and three infusion center-based pharmacies, we are grateful for the opportunity to offer the following comments. Dignity Health, one of the nation’s five largest healthcare systems, is a 21-state network of nearly 9,000 physicians, 55,000 employees, and more than 380 care centers, including hospitals, urgent and occupational care centers, imaging centers, home health and primary care clinics. Dignity Health is dedicated to providing compassionate, high-quality and affordable patient-centered care with special attention to the poor and underserved.</p> <p>Central to our healing mission, Dignity Health is committed to patient and employee safety and continuous improvement to quality of care. Since our beginning and as we usher this unprecedented time of health care reform, our values call us to place public protection along with efficient, effective delivery of pharmaceutical care of primary importance. In light of the recent national events with sterile compounding pharmacies, Dignity Health stands with the California Board of Pharmacy and the entire hospital community to further reflect upon the existing Pharmacy Law, including the recently passed Senate Bill 294 (Emerson), and what opportunities we can create to advance meaningful change. We wholeheartedly agree that updating California’s compounding regulations to improve overall patient safety is paramount.</p> <p>As our hospitals have relied on and have been operating under the United States Pharmacopeia (USP) Chapter 797 Guidelines, "Pharmaceutical Compounding – Sterile Preparations" in the National Formulary, Dignity Health urges the California Board of Pharmacy to adopt and codify regulations that are fully aligned with the Guidelines, including key provisions such as the immediate use provision and the hazardous drug compounding that are not present in the proposed regulations</p> <p>During this time of transformation for California and the nation, Dignity Health is invested in successfully implementing the Affordable Care Act (ACA) and advancing the triple aim of 1) improving quality of care; 2) improving population health; 3) bending the healthcare cost curve. 2014 marks the year when core provisions of the ACA are being implemented and hospitals are adjusting to tremendous changes. Stewardship of resources is critical as hospitals are still in the early stages of fully realizing the fiscal and operational impacts of ACA and</p> |

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| | | <p>other state reform initiatives. While we welcome changes that support hospitals' ability deliver on our promise of high quality care to the communities we serve, Dignity Health believes that it is essential that final regulations strike the optimal balance between public protection and appropriate regulatory changes that protects access to care and continued hospital solvency. Dignity Health is encouraged by the Board's desire to ensure California compounding regulations that reflect at minimum the compounding standards used in the profession. Dignity Health urges the Board to finalize regulations that are aligned with USP 797 Guidelines. We have worked closely with the California Hospital Association (CHA) and other member hospitals to develop the hospital community's position on the Board's proposed regulations. We support the Board's principles and efforts to provide uniformity, eliminating redundancies and redefining particular definitions in alignment with national standards for pharmacies that carry out compounding in general, including sterile injectable.</p> |
| General | | <p>Oral Testimony #1 – Steven Gray, Pharm.D., JD; Doug O'Brien, Pharm.D.; and Donald Kaplan, Pharm.D., Kaiser Permanente (Kaiser) - #1</p> <p>Dr. Gray introduced himself on behalf of Kaiser as well as Dr. O'Brien who is the Northern California Regional Director for Inpatient Pharmacy Services and Dr. Kaplan who is the Southern California Inpatient Pharmacy Practice Coordinator.</p> <p>Dr. Gray provided additional written information dated January 15, 2014, on behalf of Kaiser in addition to a copy of the written comments previously submitted by Kaiser. Dr. Gray indicated his intent was to review the cover letter and emphasize briefly other items mentioned in the document.</p> <p>Dr. Gray provided for the record that Kaiser serves over 6 million California Members in more than 30 hospitals, hundreds of medical office facilities and over 300 pharmacies in California. The impact of the proposed regulations is big for Kaiser. Medication compounding by and under the supervision of pharmacists pursuant to orders and prescriptions occurs in all of those hospitals and most of the other facilities on a daily basis.</p> |
| General | | <p>Oral Testimony #1 – Steven Gray, Pharm.D., JD; Doug O'Brien, Pharm.D.; and Donald Kaplan, Pharm.D., Kaiser Permanente (Kaiser) - Additional Written Comment Submitted 1/15/14 from Kaiser - A</p> <p>Kaiser serves over 6 million California Members in more than 30 hospitals, hundreds of medical office facilities and pharmacies in California. Medication compounding by and under the supervision of pharmacists pursuant to orders and prescriptions occurs in all of those hospitals and most of the other facilities on a daily basis.</p> |
| General | | <p>Oral Testimony #2 – Dan Wills, Representing Self - #1</p> <p>Mr. Dan Wills commented he was there to represent feelings of things balancing in past and things being lost. His understanding is the board is tasked with protecting public. There is a fine balance between safety and access. If people don't have access people may die. Some regulations may limit access so much that in the interest of safety may be doing harm. Mr. Wills understands you don't want to look at cost factors as being things you want to make decisions but even the FDA has said cost is an issue.</p> |

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| General | | <p>Oral Testimony #2 – Dan Wills, Representing Self - #11</p> <p>Mr. Wills urged to remember patient access as important as patient safety. Without balance people will be harmed. Mr. Wills is concerned people will be harmed. Mr. Wills stated he has no personal interest other than consumer wanting an eye drop.</p> |
| General | | <p>Oral Testimony #3 – Jerra Banworth, R.Ph., FIACP, Representing Self - #1</p> <p>Ms. Banworth commented she was on a task force with CPhA. Ms. Banworth stated she appreciated being able to share her concerns and listen to her colleagues.</p> <p>Ms. Banworth wanted to remind the board that they are a light for the other state boards and setting standards for sterile compounding. Ms. Banworth commented the board has done an amazing job to ensure public safety through process validation, personnel validation and end product testing can produce viable therapeutic outcome for our patients.</p> |
| General | | <p>Oral Testimony #4 – Michael Tou, Providence Health & Services Southern California (Providence) - #</p> <p>Mr. Tou commented on behalf of Providence Health & Services Southern California. Providence operates six pharmacies in Southern California including one at the Disney Family Cancer Center. Providence supports the board’s efforts to increase compounding standards and more closely align those standards with USP 797.</p> |
| General | | <p>Oral Testimony #4 – Michael Tou, Providence Health & Services Southern California (Providence) - Additional Written Comment Submitted 1/16/14 from Providence - A</p> <p>Providence operates six pharmacies in Southern California including one at the Disney Family Cancer Center. Providence supports the board’s efforts to increase compounding standards and more closely align those standards with USP 797.</p> |
| General | | <p>Oral Testimony #4 – Michael Tou, Providence Health & Services Southern California (Providence) - Additional Written Comment Submitted 1/16/14 from Providence - B</p> <p>Providence supports the need for new compounding standard and strongly urges the board to adopt their recommendations. Providence offers overall recommendations to highlight changes needed to ensure Providence pharmacies and others in the state can continue to safely compound drugs and provide lifesaving therapy to our patients.</p> |
| General | | <p>Oral Testimony #4 – Michael Tou, Providence Health & Services Southern California (Providence) - Additional Written Comment Submitted 1/16/14 from Providence – G</p> <p>Without needed rule amendments to permit sterile compounding in environments other than cleanrooms, a hospital or facility without a cleanroom will not be able to prepare any sterile compounded medications for patients. If the board adopts the proposed regulations, Providence hospitals would not have enough time to come into compliance by July 1, 2014, and would be unable to provide intravenous therapy risking harm to their patients.</p> <p>Providence pharmacies have proven history of excellence in patient care and safety under existing national guidelines. Providence urges the board’s adoption of the outlined Providence recommendations.</p> |

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| General | | <p>Oral Testimony #6 – Gary Cacciatore and Richard Green, R.Ph., BCNP, Cardinal Health, Inc. - #1</p> <p>Mr. Gary Caccitore introduced himself as the Vice President of Regulatory Affairs for Cardinal Health as well as Richard Green with Cardinal Health’s Nuclear Pharmacy Services. Mr. Caccitore thanked the board for the opportunity to address the board. Mr. Caccitore stated Cardinal Health wanted to bring up unique issues for nuclear pharmacy. Mr. Green stated Cardinal Health has 11 nuclear pharmacies in the state with 65% of the market share.</p> |
| General | | <p>Oral Testimony #8 – Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California (CHCC) - #1</p> <p>Dr. Sakai commented on behalf of CHCC which is the 2nd largest pediatric hospital in California and home care for pediatrics. CHCC performs 26,000 surgeries and procedures a year with 250 patients a day. In order for pharmacists to work at bedside, use high degree of technology. CHCC dispenses 1.3 million doses of which 300,000 are injectable. CHCC uses patient specific and exact dosing.</p> |
| General | | <p>Oral Testimony #9 – Jeffrey Nehira, Pharm.D., Dignity Health – Mercy General Hospital - #1</p> <p>Dr. Nehira thanked the board for their work on compounding. Dr. Nehira stated the intent of 294 was to ensure that what happened in NECC wouldn’t happen in California. However, they were compounded outpatient batches. For acute care setting, these are very difficult especially when not for profit.</p> |
| General | Address two settings outpatient and acute hospitals | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #2</p> <p>CSHP strongly urges the board to separate the regulatory provisions into two domains – outpatient and acute hospitals. This can be accomplished by either having separately numbered subsections or by placing language in key regulations that explicitly applies to acute hospitals. CSHP believes this is critical for the following reasons:</p> <ol style="list-style-type: none"> 1. The treatment of patients in acute care hospitals with compounded sterile products is substantially different from treatment of patients in outpatient (non-acute hospital settings). Patients are usually more acutely ill and less stable. This increases the need for more timely therapy administration with more frequent changes. 2. Because the new regulations will cause many remodeling and structural changes for many hospitals that cannot be accomplished by the date regulations should be adopted. The time to implementation of such changes can be substantially slower for outpatient compounding pharmacies. Separation will allow different effective dates. |
| General | Allow hospitals to compound in a non- | <p>Comment #24 from Candace Fong, Pharm.D., and Rachelle Reyes Wenger, Dignity Health - #4</p> <p>Dignity Health recommends allowing hospital pharmacies to compound hazardous drugs in non-negative pressure room, such as a closed system vial transfer device within an ISO Class 5 biological safety cabinet or containment isolator.</p> |

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| | negative pressure room | Our hospitals have successfully compounded cytotoxic or other hazardous agents in non-negative pressure rooms with closed system vial transfer devices. According to USP 797 Guidelines, hazardous drug compounding can occur in a non-negative pressure room if using a closed system vial transfer device within an ISO Class 5 biological safety cabinet or barrier isolator. The ability for hospitals to use this has provided essential patient care to more patients who may otherwise be unable to receive these lifesaving treatments from hospitals due to facility plant space restrictions. |
| General | Beyond Use Dating | Oral Testimony #2 – Dan Wills, Representing Self - #10 Mr. Wills comment on beyond use dating. Mr. Wills sees real problems this will be the beyond use date for different things. D is not needed – copy and paste. This doesn’t allow for any other beyond use dates. It doesn’t allow for “changes can be this.” May add for medical necessity; recall if issue but without passing sterility test which takes 14 days, they may be limited. Mr. Wills stated you can’t follow the two laws at both times. |
| General | Cleaning | Oral Testimony #12 – Lynn Paulsen, University of California (UC) - #3 Ms. Paulsen stated automation/robots the recommendation is to only clean every 30 days. Contamination source is the cleaning process for robots. Embrace technology and have input from manufactures what would be appropriate. Every 30 minutes is not a great idea. Some clarity would be appreciated. |
| General | Cleaning | Oral Testimony #12 – Lynn Paulsen, University of California (UC) - #8 Ms. Paulsen indicated cleaning IV hood takes about 1 hour. Ms. Paulsen thinks a wipedown is what is intended ever 30 minutes and clarification would be helpful. |
| General | Compounding Area | Oral Testimony #1 – Steven Gray, Pharm.D., JD; Doug O’Brien, Pharm.D.; and Donald Kaplan, Pharm.D., Kaiser Permanente (Kaiser) - #4 Dr. Gray also was concerned there was no definition of what areas and criteria are used to identify compounding areas. Dr. Gray queried if this would only apply if pharmacy personnel were involved in compounding. Dr. Gray stated if so, this may incent various organizations to not use those people in those environments as they may believe board wouldn’t apply the standards. Dr. Gray encouraged the board to review this process and allow for hospitals. Dr. Gray noted he is not arguing this is not needed; just more time is required. |
| General | Compounding aseptic isolators | Oral Testimony #12 – Lynn Paulsen, University of California (UC) - #2 Ms. Paulsen stated compounding aseptic isolators are considered a modular cleanroom and that is not well identified in the regulations. |
| General | Compounding in the Acute Care Environment | Comment #6 from Muno Bholat, Goorgen Boghossian, Tawny Bui, Theresa Lee-Yu, and Hiroyuki Nishi, Providence Health & Services Southern California - #2 Providence Southern California commented critical medications in hospitals are compounded for emergent situations and direct patient administration including code blue responses, heart attacks and strokes. Preparation inside an ISO 5 hood within an ISO 7 buffer zone with |

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| | | <p>cleansing and garbing would cause significant delays to patient therapy and risk patient harm. Providence Southern California continued to comment that during code blue responses, hospital pharmacists mix or “compound” sterile drug products at the patient bedside to provide life sustaining IV medication to patients requiring cardiopulmonary resuscitation.</p> <p>Providence Southern California commented with the following recommendations:</p> <ul style="list-style-type: none"> • Add the immediate-use provision with a one-hour beyond-use date, as set out in USP 797 to allow for preparation of sterile compounded products outside of an ISO Class 5 hood for emergency or immediate patient administration. • Allow use of an ISO Class 5 hood within a segregated compounding area with a 12-hour beyond-use date for any hospital or facility currently compounding drugs safely without a cleanroom (ante-area and buffer room). • Allow hospital pharmacies to compound hazardous drugs in non-negative pressure rooms, such as a closed-system vial transfer device within an ISO Class 5 biological safety cabinet or containment isolator. Hospital pharmacies have safely prepared chemotherapy for cancer patients within this environment, which is permitted under USP 797 guidelines. |
| General | Compounding in the Acute Care Environment | <p>Comment #6 from Munro Bholat, Goorgen Boghossian, Tawny Bui, Theresa Lee-Yu, and Hiroyuki Nishi, Providence Health & Services Southern California - #3</p> <p>Providence Southern California commented without needed rule amendments to permit sterile compounding in environments other than cleanrooms, a hospital or facility without a cleanroom will not be able to prepare any sterile compounded medications for patients. If adopted, the proposed regulations would not allow hospitals enough time to come into compliance and would be unable to provide timely intravenous therapy risking harm to patients.</p> <p>Providence Southern California commented adding that their least preferred option would be to extend the timeframe needed to allow facility changes and construction to be completed in compliance with state building regulations and hospital licensure requirements. Without this, patients will not receive life-saving therapy.</p> |
| General | Costs | <p>Oral Testimony #9 – Jeffrey Nehira, Pharm.D., Dignity Health – Mercy General Hospital - #3</p> <p>Dr. Nehira commented this will cost a lot of money. For his facility, it will cost about \$2 million for facility to upgrade cleanroom.</p> |
| General | Costs | <p>Comment #5 from Elliot Kwok, Pharm.D., Abbott’s Compounding Pharmacy, Inc. – #8</p> <p>Dr. Kwok indicated Abbott’s Compounding Pharmacy’s comment regarding cost impact on representative private person or business is that there would be a definite increase in cost to compounding pharmacies as more testing and separate compounding is required. Dr. Kwok indicated these costs would be passed onto patients/consumers.</p> |
| General | Costs | <p>Oral Testimony #1 – Steven Gray, Pharm.D., JD; Doug O’Brien, Pharm.D.; and Donald Kaplan, Pharm.D., Kaiser Permanente (Kaiser) - #4</p> <p>Dr. Kaplan highlighted a few issues most important to comments previously submitted by Kaiser. After USP 797 standards were published, Kaiser reassessed and embarked on capital improvement to remodel IV rooms. Kaiser is compliant with the 2004 USP version standards.</p> |

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| | | <p>In 2008 the standards were revised. Kaiser has to reassess building previously done and would have to spend an excess of \$25 million. Kaiser is assessing the same conflict with current proposed regulations.</p> |
| General | Definition of laminar air flow change to unidirectional flow | <p>Comment #14 from Hank Rahe, BSIM, MSE, Containment Technology Group, Inc. - #1</p> <p>Mr. Rahe commented in a number of places in the proposed changes the term “laminar air flow” is used. The more consistent term used by both USP 36 revision effective 8/1/13 of General Chapter 797 and the US Food and Drug Administration in their Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing – Good Manufacturing Practice, September 2004 is “unidirectional flow.” References to laminar airflow should be replaced with unidirectional airflow as laminar airflow has specific velocity requirements not consistent with the engineering controls used in pharmacy. The following definition should also be included:</p> <p>Unidirectional flow – An airflow moving in a single direction, in a robust and uniform manner, and at sufficient speed to reproducibly sweep particles away from the critical processing or testing area.</p> |
| General | Definitions | <p>Comment #16 from BJ Bartleson, RN, MS, NEA-BC, CA Hospital Association (CHA) - #4</p> <p>CHA commented most hospitals with sterile compounding pharmacies have been operating under USP 797 guidelines and while much of the regulatory language proposed by the board reflects USP 797, essential provisions are not reflected in the draft language. The proposed changes are lacking several key provisions of USP 797 that will assist hospitals in making affordable, safe patient care changes.</p> <p>Third, Include USP 797 definitions of “Batch,” “Beyond Use Date” and utilize USP 797 definitions within the code sections describing, “certificates of analysis,” “accuracy assessment,” “documentation requirements,” “disinfecting practices,” “sterility testing requirements,” “continuous temperature recording device” and “cytotoxic agents.”</p> <p>CHA recommends using USP 797 definitions where applicable and specific detailed recommendations are listed corresponding to each applicable section.</p> |
| General | Different Regulations for Hospitals | <p>Oral Testimony #1 – Steven Gray, Pharm.D., JD; Doug O’Brien, Pharm.D.; and Donald Kaplan, Pharm.D., Kaiser Permanente (Kaiser) - #2</p> <p>Dr. Gray noted additional concern to separate regulatory provision for those inside hospitals. Dr. Gray stated the reasons included a long history of compounding regulations with the board in trying to blend the two settings together as the two types of treatment environments are different. Acute level of care timing is different that long term/mid term care and compounding requirements. Dr. Gray indicated it would be much more complex to have one provision to apply to both environments. Dr. Gray also believes the main impetus the tragedies outside of California and could happen in California outside of hospitals is there was massive compounding being completed and outsourcing. Dr. Gray requested the board allow more time to adjust for hospital settings and possible varying implementation time periods available. There are different building codes for hospitals depending ownership. It is a very political and approval process for construction changes will make it difficult if not impossible to comply by projected dates. Dr. Gray stated he realized the board’s enforcement discretions but noted the</p> |

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| | | <p>changes are so big that political organizations will not move forward with the process based on board's enforcement discretion alone. Dr. Gray noted the main reasons for separation and believes it can be done in several ways. In one suggestion Dr. Gray offered different regulation numbers if applicable to hospital settings or in regulation call out the following date/provision is different for a hospital environment.</p> |
| General | Different Regulations for Hospitals | <p>Oral Testimony #1 – Steven Gray, Pharm.D., JD; Doug O'Brien, Pharm.D.; and Donald Kaplan, Pharm.D., Kaiser Permanente (Kaiser) - Additional Written Comment Submitted 1/15/14 from Kaiser - B</p> <p>Kaiser urges the board to separate the regulatory provisions for compounding in hospitals from the provisions for compounding in other environments by any means that will allow the Board to accomplish its need for expediency for certain non-hospital environments while allowing time and important medications to the provisions for hospitals to continue to provide care while adjustments are being made. This will allow the board to adopt more appropriate provisions for each environment and to adjust implementation date requirements in a more predictable and reasonable manner that balances the need for change with the realities of each environment. For example, hospitals require more time to become compliant with remodeling requirements.</p> <p>The vast majority of the impetus for change has clearly been recent events outside of hospital. Hospitals operate in a more structured, regulated and monitored environment than outpatient compounding pharmacies and medical offices. Hospitals affected are located in California while the non-hospital compounding organizations are not located in California. Hospitals that need more time to comply are larger hospitals within California and not-for-profit and government operated hospitals of all sizes. Without adjustments for implementation, there is concern about the ability of hospitals to continue to provide care to California residents during the adjustment of their operations and facilities. These changes are included in the proposed text for Title 16 and Title 24.</p> |
| General | Different Regulations for Hospitals | <p>Oral Testimony #6 – Steve Gray Pharm.D., JD; California Society of Health-Systems Pharmacists (CSHP) - #1</p> <p>Dr. Gray commented on behalf of CSHP. CSHP did submit written comments for consideration but also wanted to point out they were developed with other organizations such as California Hospital Associations and other organizations. CHSP urges the board to consider separation of regulations for hospitals. Dr. Gray reiterated there is a long history in compounding regulations that go back to Walnut Creek tragedy where the board did an amazing job in front by development of regulations, specialty license and inspections. Dr. Gray personally believes this is why there hasn't been other tragedies in California. Dr. Gray stated that process identified there were problems with regulations didn't separate for compounding in hospitals.</p> |
| General | Different Regulations for Hospitals | <p>Oral Testimony #8 – Richard Sakai, Pharm.D., FASHP, FCSHP, Children's Hospital Central California (CHCC) - #9</p> <p>Dr. Sakai stated he agreed with CHSP that there should be a separation of inpatient and outpatient regulations and possible exempt for inpatient.</p> |
| General | FDA | <p>Oral Testimony #1 – Steven Gray, Pharm.D., JD; Doug O'Brien, Pharm.D.; and Donald</p> |

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| | approved | <p>Kaplan, Pharm.D., Kaiser Permanente (Kaiser) - #10</p> <p>Dr. Gray added some organizations have suggested any component of the compounded product would have to be FDA registered or approved. Dr. Gray queried, if you were compounding syrup and needed to use sugar, are you to use sugar that was FDA approved? Dr. Gray doesn't believe it was the intent. He believes the intent was if you were using drug products they would be FDA approved. But some drug products that are bulk chemicals are available for manufacturing so there are some situations where even the drug product with the active ingredient will not be FDA approved as a finished product for general distribution. This section needs to be elaborated or teased out to ensure not shutting of the compounding because the definition does not fit every situation. By definition, compounding is usually done because of unavailability of a product that meets the patient's needs. Kaiser wants to maintain that ability for patient needs.</p> |
| General | Fingertip sampling | <p>Comment #26 from Dan Kardasinski, Pharm.D., Loma Linda University Medical Center - #1</p> <p>Loma Linda University Medical Center requested clarification on the fingertip sampling (page 18 of the draft*), does the set of follow up annual samplings need to be performed only once or three times, like the initial testing? Current USP <797> regulations call for the initial sampling to be performed three times, with the repeat sampling to be performed only once.</p> <p>(*Note: There is no reference to fingertip sampling on page 18 of the noticed proposed text.)</p> |
| General | Hazardous drug compounding | <p>Comment #16 from BJ Bartleson, RN, MS, NEA-BC, CA Hospital Association (CHA) - #3</p> <p>CHA commented most hospitals with sterile compounding pharmacies have been operating under USP 797 guidelines and while much of the regulatory language proposed by the board reflects USP 797, essential provisions are not reflected in the draft language. The proposed changes are lacking several key provisions of USP 797 that will assist hospitals in making affordable, safe patient care changes.</p> <p>Second, CHA hospitals have successfully compounded cytotoxic or other hazardous agents in non-negative pressure rooms with closed system vial transfer devices. According to USP 797 guidelines, hazardous drug compounding can occur in a non-negative pressure room if using a closed system vial-transfer device within an ISO Class 5 biological safety cabinet or barrier isolator. The ability for hospitals to use this has provided essential patient care to more patients who may otherwise be unable to receive these lifesaving treatments from hospitals due to facility plant space restrictions.</p> <p>CHA recommends allowing hospital pharmacies to compound hazardous drugs in non-negative pressure room, such as a closed system vial-transfer device within an ISO Class 5 biological safety cabinet or containment isolator. These recommendations are in full alignment with USP 797 guidelines.</p> |
| General | Hospital | <p>Oral Testimony #4 – Michael Tou, Providence Health & Services Southern California (Providence) - #5</p> |

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| | | <p>Mr. Tou highlighted a few of Providence’s suggestions.</p> <p>4. Allow hospital pharmacies to compound hazardous drugs in a non-negative pressure room such as a closed-system vial-transfer device within an ISO Class 5 biological safety cabinet or containment isolator. Providence hospital pharmacies safely prepared chemotherapy for cancer patients within this environment which is permitted under USP 797 guidelines.</p> |
| General | Hospital | <p>Oral Testimony #4 – Michael Tou, Providence Health & Services Southern California (Providence) - Additional Written Comment Submitted 1/16/14 from Providence – F</p> <p>4. Allow hospital pharmacies to compound hazardous drugs in a non-negative pressure room such as a closed-system vial-transfer device within an ISO Class 5 biological safety cabinet or containment isolator. Providence hospital pharmacies safely prepared chemotherapy for cancer patients within this environment which is permitted under USP 797 guidelines.</p> |
| General | Immediate Use Provision | <p>Oral Testimony #4 – Michael Tou, Providence Health & Services Southern California (Providence) - #3</p> <p>Mr. Tou highlighted a few of Providence’s suggestions.</p> <p>2. Add “immediate-use” provision with one hour beyond use date per USP 797 to allow preparation of sterile compounded products outside of an ISO Class 5 hood for emergency or immediate patient administration.</p> |
| General | Immediate Use Provision | <p>Oral Testimony #4 – Michael Tou, Providence Health & Services Southern California (Providence) - Additional Written Comment Submitted 1/16/14 from Providence – D</p> <p>2. Add “immediate-use” provision with one hour beyond use date per USP 797 to allow preparation of sterile compounded products outside of an ISO Class 5 hood for emergency or immediate patient administration.</p> |
| General | Immediate-use provision | <p>Comment #16 from BJ Bartleson, RN, MS, NEA-BC, CA Hospital Association (CHA) - #2</p> <p>CHA commented most hospitals with sterile compounding pharmacies have been operating under USP 797 guidelines and while much of the regulatory language proposed by the board reflects USP 797, essential provisions are not reflected in the draft language. The proposed changes are lacking several key provisions of USP 797 that will assist hospitals in making affordable, safe patient care changes.</p> <p>First, and most importantly, is the immediate-use provision that can eliminate unnecessary physical plant facility upgrade costs and prevent untimely patient care in fast-paced treatment areas where construction of a cleanroom (implied without the immediate-use provision) is not feasible, such as emergency departments, operating rooms, therapeutic radiology, cardiac catheterization, and respiratory therapy. Compounding in acute care hospitals requires speed and flexibility. Critical lifesaving medications in acute care hospitals are compounded in environments outside of pharmacies and cleanrooms; for instance, at the patient’s bedside.</p> <p>Without the immediate-use exemption provision, hospitals would be unable to provide IV therapy or life-sustaining medication during a code blue response or other essential patient care therapies requiring compounding within a one-hour or twelve-hour time period.</p> |

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| | | <p>CHA recommends adding the immediate-use provision with a one-hour beyond use date, as stated in USP 797 to allow preparation of sterile compounded products outside of an ISO Class 5 hood for emergency or immediate patient administration.</p> <p>CHA recommends use of an ISO Class 5 hood within a segregated compounding area with a 12-hour beyond-use date for any hospital or facility currently compounding drugs safely without a cleanroom (ante-area and buffer room).</p> |
| General | Independent pharmacy impact | <p>Comment #25 from Vivian Matsuo, Pharm.D., Silicon Valley Pharmacy - #1</p> <p>The impact on Silicon Valley Pharmacy, a small business, will be significant. In order to comply with the proposed amendments, we will have to undergo remodeling of our pharmacy at a significant expense. It is reasonable to extrapolate our concern with the independent pharmacies which compound the vast majority of drug products in the State of California, and most of which fall into the category of a small business.</p> <p>I request that the Board of Pharmacy conduct a survey of California independent compounding pharmacies for the purpose of collecting data in order to determine how these proposed amendments will affect their small businesses.</p> <p>I request that that survey collect data on how the cost to implement and practice pharmacy under these changes will impact the cost of care for the people of California who receive compounded drug products.</p> <p>I request that these proposals not be implemented until the survey can be conducted and the results evaluated.</p> <p>Also, I respectfully request an opinion from the Board of Pharmacy if a Standardized Regulatory Impact Assessment is required for this determination.</p> <p>If the Board of Pharmacy decides to implement the proposed amendments, I respectfully request that the Board of Pharmacy allow for a two year implementation period before enforcement begins.</p> |
| General | ISO Class 5 hood use for hospital or facility | <p>Comment #24 from Candace Fong, Pharm.D., and Rachelle Reyes Wenger, Dignity Health - #3</p> <p>Dignity Health recommends the use of an ISO Class 5 hood within a segregated compounding area with a 12-hour beyond use date for any hospital or facility currently compounding drugs safely without a cleanroom (ante-area and buffer room).</p> |
| General | Lack of consistency with USP 797 | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #3</p> <p>CSHP supports changes to compounding regulations. Most hospitals with CSP have been operating under USP guidelines and while most of the proposed language reflects USP 797, essential provisions are not reflected in the draft language that will assist hospitals in making affordable, safe, patient care changes.</p> |

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| | | <p>Most importantly is the “immediate-use provision” that can eliminate unnecessary physical plant facility update costs and prevent untimely patient care in fast-paced treatment areas where construction of a cleanroom (implied without the immediate-use provision) is not feasible, such as emergency departments, operating rooms, therapeutic radiology, cardiac catheterization, and respiratory therapy. Compounding in acute care hospitals requires speed and flexibility. Critical lifesaving medications in acute care hospitals are compounded in environments outside of pharmacies and cleanrooms; for instance, at the patient’s bedside.</p> <p>Without the immediate-use exemption provision, hospitals would be unable to provide IV therapy or life-sustaining medication during a code blue response or other essential patient care therapies requiring compounding within a one-hour or twelve-hour time period.</p> <p>CSHP recommends adding the immediate-use provision with a one-hour beyond use date, as stated in USP 797 to allow preparation of sterile compounded products outside of an ISO Class 5 hood and segregated compounding area for emergency or immediate patient administration.</p> <p>CSHP recommends use of only an ISO Class 5 hood within a specified, non-segregated compounding area with a 12-hour beyond-use date for any hospital or facility currently compounding drugs safely without a cleanroom, ante-area or buffer room.</p> |
| General | Lack of consistency with USP 797 | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #4</p> <p>CSHP supports changes to compounding regulations. Most hospitals with CSP have been operating under USP guidelines and while most of the proposed language reflects USP 797, essential provisions are not reflected in the draft language that will assist hospitals in making affordable, safe, patient care changes.</p> <p>California hospitals have successfully compounded cytotoxic or other hazardous agents in non-negative pressure rooms with closed system vial transfer devices. According to USP 797 guidelines, hazardous drug compounding can occur in a non-negative pressure room if using a closed system vial-transfer device within an ISO Class 5 biological safety cabinet or barrier isolator. The ability for hospitals to use this has provided essential patient care to more patients who may otherwise be unable to receive these lifesaving treatments from hospitals due to facility plant space restrictions.</p> <p>CSHP recommends allowing hospital pharmacies to compound hazardous drugs in non-negative pressure room, such as a closed system vial-transfer device within an ISO Class 5 biological safety cabinet or containment isolator. These recommendations are in full alignment with USP 797 guidelines.</p> |
| General | Lack of consistency with USP 797 | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #7</p> <p>CSHP supports changes to compounding regulations. Most hospitals with CSP have been operating under USP guidelines and while most of the proposed language reflects USP 797, essential provisions are not reflected in the draft language that will assist hospitals in making affordable, safe, patient care changes.</p> <p>Regarding definition within the code sections describing, “certificates of analysis,” “accuracy</p> |

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| | | assessment,” “documentation requirements,” “disinfecting practices,” “sterility testing requirements,” “continuous temperature recording device” and “cytotoxic agent,” CSHP recommends utilizing USP 797 definitions. |
| General | Licensing | <p>Comment #16 from BJ Bartleson, RN, MS, NEA-BC, CA Hospital Association (CHA) - #5</p> <p>CHA commented the sterile compounding pharmacy licensure process should be fair, consistent and achievable for hospitals while leveraging the need for public safety and quality patient care.</p> <p>CHA recommends a clear, detailed process on how the board will license and inspect hospitals to meet the July 1, 2014 deadline. Hospitals understand the need to apply for their compounding license but, absent the new regulatory amendments, they may be held to changes they cannot make in a timely manner. Guidance from the board will be necessary to assure there is no gap in delivery of care to patients receiving compounded medications across the state.</p> <p>CHA recommends that since a compounding self-assessment form must be completed prior to becoming licensed, it is essential that the self-assessment form reflect the approved regulatory amendments. If the projections for this are unlikely to be met, guidance and direction from the board on what self-assessment form to utilize is necessary.</p> |
| General | Licensing | <p>Oral Testimony #1 – Steven Gray, Pharm.D., JD; Doug O’Brien, Pharm.D.; and Donald Kaplan, Pharm.D., Kaiser Permanente (Kaiser) - #3</p> <p>Dr. Gray noted the second item of concern on the cover letter is that he has heard in recent board meeting that is not stated in the regulation but that the board will apply sterile licensing standard to different areas of the hospital not typically applied in the past including but not limited to satellites, nursing stations, ICUs, neonatal care, emergency room, etc. This is a concern. Dr. Gray noted board staff commented in the past the advantage of doing so is if an area of the hospital that was doing the sterile compounding had an issue, the whole hospital wouldn’t have to be shut down. Dr. Gray indicated the board should be able to do this through enforcement discretion rather than get a license for each area outside the traditional area.</p> |
| General | Licensing | <p>Oral Testimony #1 – Steven Gray, Pharm.D., JD; Doug O’Brien, Pharm.D.; and Donald Kaplan, Pharm.D., Kaiser Permanente (Kaiser) - Additional Written Comment Submitted 1/15/14 from Kaiser - C</p> <p>Kaiser is also concerned about the board’s intent to apply certain standards and separate licensing requirements throughout hospital areas that have not traditionally been considered part of the “hospital’s pharmacy.” Though advantages have been identified by board staff for hospitals to have such areas be separately pre-inspected, licensed and monitored as a part of separate regulatory compliance review, the proposed regulations are completely void of any specifics about the aspects of such compounding activity that would trigger such separate licensing requirements and standards compliance review. Would this apply to non-board licensed staff compound such as nurses, physicians and other whose scope of practice allow compounding for administration to patients in the licensed areas of the hospitals.</p> |
| General | Licensure | Comment #24 from Candace Fong, Pharm.D., and Rachelle Reyes Wenger, Dignity Health - #6 |

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| | | <p>Dignity Health seeks a CSP Licensure process that is fair, consistent, and achievable for hospitals while leveraging the need for public and worker safety and high quality patient care. We seek from the Board a detailed process on how the Board will license and inspect hospitals to meet SB 294’s July 1, 2014 deadline. Hospitals recognize the need to apply for licensure. However, absent final regulations, hospitals may not be able to make the changes required in a timely manner. Guidance from the Board is necessary to assure there is no gap in delivery of care to patients receiving medications across the state. Moreover, since compounding self-assessment form must be completed prior to becoming licensed, it is essential that the Board develop and implement a self-assessment form reflecting the approved regulatory amendments. If the projections for this are unlikely to be met, guidance and direction from the Board on what self-assessment form to utilize is necessary.</p> |
| General | Licensure Process | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #8</p> <p>The CSP Licensure process should be fair, consistent and achievable for hospitals while leveraging the need for public safety and quality patient care.</p> <p>CHSP recommends a clear, detailed process on how the board will license and inspect hospitals to meet the July 1, 2014, deadline. Hospitals understand they need to apply for their compounding license, but absent the new regulatory amendments, they may be held to changes they cannot make in a timely manner. Guidance from the board will be necessary to assure there is no gap in delivery of care to patients receiving compounded medications across the state.</p> <p>CSHP recommends that since a compounding self-assessment form must be completed prior to becoming licensed, it is essential that the self-assessment form reflect the approved regulatory amendments. If production of a compounded sterile products self-assessment form will not be ready by July 1, 2014, guidance and direction from the board on what self-assessment form to utilize is necessary.</p> |
| General | Nuclear Pharmacy | <p>Comment #22 from Michael Moné, R.Ph., J.D., FAPhA, Cardinal Health Nuclear Pharmacy Services - #1</p> <p>Cardinal Health Nuclear Pharmacy Services operates eleven nuclear pharmacies in California, dispensing approximately 85,000 patient doses of diagnostic and therapeutic radiopharmaceuticals every month. Cardinal Health Nuclear Pharmacy Services has 254 employees in California of which 39 are pharmacists, accounting for approximately \$16 million dollars in salary paid.</p> <p>Cardinal Health Nuclear Pharmacy Services believes that special consideration for nuclear pharmacy preparation of radiopharmaceuticals should be considered by the Board. At the outset of this discussion is a recognition that the preparation and the very nature of radiopharmaceuticals, among others: an extremely short half-life; the regulation of the preparation of radio pharmaceuticals by the California Board of Pharmacy, the California Radiologic Health Branch and the Nuclear Regulatory Commission; and the unique relationship between the prescribing practitioner and the nuclear pharmacist that prepares the prescription, are such that special consideration is warranted.</p> <p>As proposed the changes to amend sections of Articles 4.5 and 7 of Division 17 of Title 16 of</p> |

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| | | <p>the California Code of Regulations creates significant complications for the operation of nuclear pharmacies in California. Cardinal Health Nuclear Pharmacy Services proposes either:</p> <ol style="list-style-type: none"> 1. The adoption of the proposed changes in language contained in this response, or 2. The adoption of a statement by the Board of Pharmacy that these changes do not apply to nuclear pharmacy and the establishment of a Task Force to draft nuclear pharmacy specific regulations for the preparation of radiopharmaceuticals. Should the Board decide to establish such a Task Force, we would welcome that and offer our support and participation on that Task Force. |
| General | Outsourcing compounding pharmacies | <p>Oral Testimony #12 – Lynn Paulsen, University of California (UC) - #5</p> <p>Ms. Paulsen indicated UC had a question about what is the application of these regulations on the outsourcing compounding pharmacies. They will have to be licensed in CA with regulations and the FDA will have regulations. Where California regulations are more stringent, will these apply as well?</p> |
| General | Patient Safety | <p>Oral Testimony #4 – Michael Tou, Providence Health & Services Southern California (Providence) - #2</p> <p>Mr. Tou highlighted a few of Providence’s suggestions.</p> <ol style="list-style-type: none"> 1. The proposed regulations must improve overall patient safety consistent with USP 797. |
| General | Patient Safety | <p>Oral Testimony #4 – Michael Tou, Providence Health & Services Southern California (Providence) - Additional Written Comment Submitted 1/16/14 from Providence - C</p> <ol style="list-style-type: none"> 1. The proposed regulations must improve overall patient safety and consistently align with national guidelines for hospital-based pharmacies (USP 797). |
| General | Patient safety | <p>Oral Testimony #12 – Lynn Paulsen, University of California (UC) - #1</p> <p>Ms. Paulsen stated UC submitted their comments through CSHP. Ms. Paulsen stated everyone wants patients safe. Last spring UC had a concern with internal/external sources of compounding. UC engaged a risk management company evaluate. A few issues were found as listed below.</p> |
| General | Patients | <p>Oral Testimony #3 – Jerra Banworth, R.Ph., FIACP, Representing Self - #2</p> <p>Ms. Banworth commented she would like to bring to the board what does this mean for her patient. An eye drop may seem inconsequential. Ms. Banworth stated she’s received a telephone call from an ophthalmologist asking if she could get eye drops ready by 5 p.m. the same day. If the patient didn’t get the eye drops, the patient would have lost an eye due to an infection. Ms. Banworth stated she would want her family or herself to have access to the medication and confident that the facility is following the regulations and process validation to confidently use it.</p> |
| General | Patients | <p>Oral Testimony #3 – Jerra Banworth, R.Ph., FIACP, Representing Self - #3</p> <p>Ms. Banworth stated she has an autism patient we do B-12 for in a single use syringe. Ms. Banworth stated it is a vitamin and is a big different for the patient. It allows the patient to be more engaged with family. Without it, the patient is disassociated and combative. This applies</p> |

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| | | to all regulations will impact that one person to allow the child to relate to family and mother. Ms. Banworth stated it would be disheartening to tell the patient she could make it for the patient but the cost has gone up 400%. Ms. Banworth stated because it is a vitamin, insurance won't cover it for her patient. Ms. Banworth encouraged the board to look at the true cost to the patient versus cost to me. Ms. Banworth suggested the board reach out to different community members to sift through information today and through written comments and would be invaluable resource to you. |
| General | Risk definition | <p>Oral Testimony #12 – Lynn Paulsen, University of California (UC) - #6</p> <p>Ms. Paulsen commented on the definitions of high risk. It was the biggest finding of tours. If ever high risk product, considered high risk until used or discarded but that is not universally understood definition.</p> |
| General | Segregated compounding area | <p>Oral Testimony #4 – Michael Tou, Providence Health & Services Southern California (Providence) - #4</p> <p>Mr. Tou highlighted a few of Providence's suggestions.</p> <p>3. Allow use of ISO Class 5 hood in a segregated compounding area with a 12-hour beyond-use date for any hospital or facility currently compounding drugs safely without a cleanroom.</p> |
| General | Segregated compounding area | <p>Oral Testimony #4 – Michael Tou, Providence Health & Services Southern California (Providence) - Additional Written Comment Submitted 1/16/14 from Providence – E</p> <p>3. Allow use of ISO Class 5 hood in a segregated compounding area with a 12-hour beyond-use date for any hospital or facility currently compounding drugs safely without a cleanroom.</p> |
| General | Sterility and bacterial endotoxin testing | <p>Comment #26 from Dan Kardasinski, Pharm.D., Loma Linda University Medical Center - #2</p> <p>Loma Linda University Medical Center requested clarification regarding the new sterile compounding regulations. The new regulations state "For sterile batch compounding, written policies and procedures must be established for the use of master formulas and work sheets, and for appropriate documentation, and for sterility and bacterial endotoxin testing." The question that my colleagues and I have is that USP 797 requires bacterial endotoxin testing only for high risk non-sterile to sterile compounding. Thus, we are inquiring to verify if sterile to sterile compounding will also require endotoxin testing. Our main concern with this is that if endotoxin testing is required for all sterile to sterile batching with the standard specified beyond use dating of 30 hours @ RT, 7 days @ cold temp, and 45 days @ freezing, then compounded products at room temperature and refrigeration will spend a larger portion, if not all, of their usage time in being sequestered until the endotoxin results are final. This would be especially true if the samples need to be sent out for testing, resulting in increased wasted product.</p> |
| General | Support with changes | <p>Comment #6 from Muno Bholat, Goorgen Boghossian, Tawny Bui, Theresa Lee-Yu, and Hiroyuki Nishi, Providence Health & Services Southern California - #1</p> <p>The proposed compounding regulations are important as Providence Southern California operates pharmacies at each of their five medical centers and another pharmacy at the Disney Family Cancer Center in Burbank.</p> |

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| | | <p>Providence Southern California supports the goal of updating state compounding regulations to improve overall patient safety and consistently align with USP Chapter 797 guidelines. Comments and recommendations are offered to ensure collective achievement of this goal while maintaining our ability to safely compound treatment facilities for patients in all care settings. This is especially important when our pharmacies are responding to immediate needs and working with cytotoxic agents.</p> <p>Providence Southern California strongly urges the board to adopt regulations that reflect the best quality outcomes, and to codify the measures implement by hospital pharmacies, as documented, that already are protecting patient safety and are aligned with USP Chapter 797 guidelines.</p> |
| General | Temperatures | <p>Oral Testimony #11 – Elliot Kwok, Pharm.D., Abbotts Compounding Pharmacy – #5</p> <p>Dr. Kwok commented on section temperature indicated storing in pharmacy or expiration date for the patient and indicated this isn’t clear. Dr. Kwok recommended considering beyond use date.</p> |
| General | Testing | <p>Oral Testimony #9 – Jeffrey Nehira, Pharm.D., Dignity Health – Mercy General Hospital - #2</p> <p>Dr. Nehira stated most patients stay 3 days but to grow fungal bacteria it takes about 7-14 days and most batches are used within 24 hours.</p> |
| General | USP 797 | <p>Oral Testimony #12 – Lynn Paulsen, University of California (UC) - #7</p> <p>Ms. Paulsen stated UC understands USP 797 isn’t written as regulation it is what is used for hospitals for the last 10 years. Could there be an option to have full USP 797 compliance?</p> |
| Multiple sections | | <p>Comment #6 from Muno Bholat, Goorgen Boghossian, Tawny Bui, Theresa Lee-Yu, and Hiroyuki Nishi, Providence Health & Services Southern California - #5</p> <p>Providence Southern California commented and recommended striking the words “written” and “in writing” from all sections listed below in order to allow for pharmacies to maintain electronic policy and procedure manuals: 1735.2 (d), 1735.5 (a), 1751.3 (a), 1751.3 (b), 1751.3 (c), 1751.3 (d), 1751.3 (d)(3)(I), 1751.6 (e)(1), 1751.6 (e)(2), 1751.7 (a), and 1751.7 (a)(3).</p> |
| Nuclear | | <p>Oral Testimony #6 – Gary Cacciatore and Richard Green, R.Ph., BCNP, Cardinal Health, Inc. - #6</p> <p>Mr. Green stated there are currently no separate regulations for nuclear pharmacy. Options to have a call out in regulations or at a high level say these regulations do not apply to nuclear and have a committee to work on specific regulations. If uniqueness not taken into account, nuclear pharmacy will be shut down and will have an adverse impact on patients.</p> |
| 1735 | (a) | <p>Comment #6 from Muno Bholat, Goorgen Boghossian, Tawny Bui, Theresa Lee-Yu, and Hiroyuki Nishi, Providence Health & Services Southern California - #6</p> <p>Providence Southern California commented and requested “by or under the supervision of a licensed pharmacist,” be struck from section 1735 (a). Providence Southern California requests the removal of the reference to activity performed by a pharmacist to clarify that the regulations</p> |

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| | | do not apply outside of the licensed pharmacy. This will allow pharmacists to continue to prepare emergency sterile compounded drugs at the bedside during a code blue, and conform to the immediate use provision under USP Chapter 797. |
| 1735 | (a) | <p>Comment #16 from BJ Bartleson, RN, MS, NEA-BC, CA Hospital Association (CHA) - #7</p> <p>CHA comment – Remove “by or under the supervision of a licensed pharmacist” to imply that regulations do not apply outside of the licensed pharmacy. This section needs to be amended to allow preparation of emergency sterile compounding drugs outside of the pharmacy itself. This is fully permissible under USP 797 immediate use provision.</p> <p>CHA requests that 1735(a) be reworded to remove the reference to activity “by or under the supervision of a licensed pharmacist” to be defined as compounding. Stating that compounding includes activity not only occurring within a pharmacy but also performed by a licensed pharmacist would then apply these compounding regulations from 1735 and 1751 to any such activity outside of the pharmacy if done by a pharmacist. Section 1751(a) requires that any pharmacy engaging in sterile compounding also conform to 1735 et seq. Therefore mixing of IV drips at the patient bedside by a licensed pharmacist during a code blue resuscitation would count as sterile compounding and fall under all requirements from 1735 et seq. and 1751 et seq. USP Chapter 797 allows for this emergency preparation of sterile compounded drugs under their provision for Immediate-Use. Preparation under stricter conditions (such as within an ISO Class5 hood within a cleanroom) would subject patients to the risk of harm due to delays in therapy. Simple transfer of sterile products is allowed for immediate use in environments worse than Class 5 provided the drug product is administered immediately to a patient, not to begin more than 1 hour following the start of preparation. Emergency drug preparations meet these USP 797 Immediate-Use criteria.</p> |
| 1735 | (a) | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #10</p> <p>CSHP commented on the definition of “compounding” and recommended to remove “by or under the supervision of a licensed pharmacist” as the regulations should not apply outside of the licensed pharmacy. This section needs to be amended to allow preparation of emergency sterile compounding drugs outside of the pharmacy itself. This is fully permissible under USP 797 immediate use provision.</p> |
| 1735 | (b) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #1</p> <p>Dr. Blair commented recommending modifying the language to read: (b) “Compounding” does not include reconstitution of a drug pursuant to a manufacturer’s direction(s) for oral, rectal, topical, or injectable administration, nor does it include tablet splitting or the addition of flavoring agent(s) to enhance palatability.</p> |
| 1735 | (b) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #2</p> <p>Dr. Sakai commented there is a missing comma between the words rectal and topical. The impact of this is a minor edit.</p> |

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| 1735 | (b) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #3</p> <p>Dr. Sakai commented on the portion of this subsection that states “...nor does it include tablet splitting or the addition of flavoring agent(s) to enhance palatability.”</p> <p>Dr. Sakai commented in order to in order to administer medications to pediatric patients, tablets are crushed and/or capsules opened and placed in vehicles such as cherry syrup or pudding as appropriate.</p> <p>Dr. Sakai’s Recommendation is to add “tablet crushing” and “capsule opening”.</p> |
| 1735 | (c) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #4</p> <p>Dr. Sakai commented on the portion of this subsection that states “that is commercially available in the marketplace.”</p> <p>Dr. Sakai commented there may be organizations who elect to make an IV solution with an additive that is commercially available such as D5-NS with KCl 20mEq/L from a manufacturer, but elects to have staff make these products from a D5-NS IV bag and a vial of KCl, because the organization does not have a contract with that particular manufacturer. Infrequency of use, or even fiscally, it does not justify purchase of the commercially available product.</p> <p>Dr. Sakai’s Recommendation: It would be the professional judgment of the Pharmacist-in-Charge to make that determination.</p> |
| 1735.1 | | <p>Comment #5 from Elliot Kwok, Pharm.D., Abbott’s Compounding Pharmacy, Inc. – #2</p> <p>Dr. Kwok commented Abbott’s Compounding Pharmacy’s recommendation is to amend section 1735.1. Dr. Kwok indicated “batch” defines in Webster dictionary as a “group.” A “group” is three or more and not just more than one. It is impractical to either make two separate preparations of the same thing or have to test the “batch.” Dr. Kwok provided an example: A husband and wife with an eye infection want to have the same antibiotic eye medication compounded. It will take more time and cost more to prepare separate doses.</p> |
| 1735.1 | | <p>Oral Testimony #6 – Gary Cacciatore and Richard Green, R.Ph., BCNP, Cardinal Health, Inc. - #4</p> <p>Mr. Green stated the proposed regulations do not account for the uniqueness of nuclear pharmacy as carved out in USP 797 in the 2004 and 2008 revisions. Radio pharmaceuticals may prepare in ISO Class 7. Every syringe has to be enveloped and shielded in lead. USP 797 acknowledges uniqueness of nuclear pharmacy and allows ISO Class 8 where section 1735.1 requires ISO Class 7.</p> |
| 1735.1 | | <p>Oral Testimony #8 – Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California (CHCC) - #6</p> <p>Dr. Sakai commented on sections 1735.1, 1735.2 and 1735.3 that specific word to compound</p> |

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| | | product will create delays. Master formula for every change is impossible. Dr. Sakai suggested perhaps general format for class, 72 hours to develop. Requirement for development of master formula would delay. |
| 1735.1 | (a) | <p>Comment #8 from Alan Y. Endo, Pharm.D., FCSHP, PIH Health - #1</p> <p>Webster’s Definition of Batch: d: a quantity (as of persons or things) considered as a group.</p> <p>USP 797 refers to high-risk (non-sterile to sterile) preparations requiring sterility testing if number of items is more than 25 in a batch.</p> <p>PIH Health’s Recommendation: Define batch as medications compounded either with high-risk methods (non-sterile to sterile) or when extended dating beyond USP 797 specifications is desired.</p> |
| 1735.1 | (a) | <p>Comment #8 from Alan Y. Endo, Pharm.D., FCSHP, PIH Health - #4</p> <p>“The pharmacy shall follow its policies and procedures. Intentionally (or grossly) failing to follow these policies and procedures may be deemed unprofessional conduct.”</p> |
| 1735.1 | (a) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #2</p> <p>Dr. Blair commented recommending modifying the language to read as order entry and labeling do not require Class 8 environment:</p> <p>(a) “Anteroom” means an ISO Class 8 or better area where personnel hand hygiene and garbing procedures, staging of components, order entry, compounded sterile product labeling, and other high-particulate-generating activities are performed. It is a transition area that provides assurance that air flows from clean to dirty areas.</p> |
| 1735.1 | (a) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #5</p> <p>Dr. Sakai commented on the definition of anteroom. Dr. Sakai commented to be consistent with USP <797> definitions and eliminate confusion outlined in the chapter section “Facility Design and Environmental Controls”, are allowances for a buffered areas not physically separated from the ante area employing the principle of displacement airflow.</p> <p>Dr. Sakai’s Recommendation: Change the term “Anteroom” to Ante-Area.”</p> |
| 1735.1 | (b) | <p>Comment #3 from Romic Eskandarian, Pharm.D., Glendale Adventist Medical Center, Adventist Health – #1</p> <p>Dr. Eskandarian made the following comments on the definition of “batch”:</p> <ol style="list-style-type: none"> 1. USP 797 definition is different than the board’s definition; 2. Sterile to non-sterile preparations; and 3. Limit to only high risk purposes, and do not add low and medium risk products <p>Dr. Eskandarian further inquired as to the benefit of defining batch as a single dose.</p> |
| 1735.1 | (b) | <p>Comment #6 from Munro Bholat, Goorgen Boghossian, Tawny Bui, Theresa Lee-Yu, and</p> |

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| | | <p>Hiroyuki Nishi, Providence Health & Services Southern California - #7</p> <p>Providence Southern California commented and requested the definition of batch be changed to: “Batch” means multiple doses of sterile products combined or pooled to prepare a product that will be administered either to multiple patients or one patient on multiple occasions, or 25 or more units compounded from non-sterile ingredients.</p> <p>Providence Southern California commented more than one dose is a very small quantity to apply the term “batch” to unless other specific processes apply, such as pooling/combining ingredients into multiple doses or using non-sterile ingredients to prepare multiple doses. Hospital pharmacies typically prepare patients’ doses for the same drug at the same time but without pooling/combining ingredients. For example, hospital pharmacists could prepare patient doses for the same drug for a certain timeframe, generally 12 hours (based on 12-hour beyond use dating) or 24 hours at a time. This type of preparation is not considered batch compounding per USP or AHSP definitions.</p> |
| 1735.1 | (b) | <p>Comment #7 from Doug O’Brien, Pharm.D., and Donald Kaplan, Pharm.D., Kaiser Permanente - #2</p> <p>Kaiser comments on the following: A batch means more than one dose of a specific quantity of drug or other material that is intended to have uniform character and quality and is produced during the same continuous cycle of compounding.</p> <p>Kaiser’s Comment: There is no benefit in defining a batch for sterile to sterile transfers, whether for a single dose or multiple doses. There is already language in existing and proposed regulations that limit the risk associated with low and medium risk compounded sterile preparations (CSPs). For example: process validation is already required for personnel compounding these types of preparations (1751.7(b)). The term “batch” should only be applicable for high-risk CSPs, where end-product testing representative samples is specifically required. The use of this definition creates problems in other parts of the proposed regulations. For example, 1751(e) describes sterility testing to be performed. It states that “Products submitted for sterility testing are to include preparations from the beginning, middle, and end of each batch.” If a batch consists of two doses, it would be impossible to perform that testing without destroying all the finished product. Also, 1754(d)ii (page 14 of 23, line 3) states that cleaning and disinfecting surfaces in the ISO Class 5 hood shall occur before each batch. If a batch is defined as a single dose as described in 1735.1(b), pharmacy personnel would be required to perform hood cleaning up to several hundred times per day.</p> <p>Kaiser’s Recommendation: Define batch in the context of performing high-risk compounding only (e.g. sterile compounding using non-sterile ingredients) as described in USP <797>, and in a quantity that can be tested without destroying all the finished product.</p> <p>Batch Definition: “All high-risk level CSPs that are prepared in groups of more than 25 identical individual single-dose packages (e.g., ampules, bags, syringes, vials) or in multiple-dose vials (MDVs) for administration to multiple patients or that are exposed longer than 12 hours at 2 ° to 8 ° and longer than 6 hours at warmer than 8 ° before they are sterilized shall meet the sterility test (see Sterility Tests 71) before they are dispensed or administered.”</p> <p>Kaiser’s Identified Impact: operational inefficiency</p> |

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| 1735.1 | (b) | <p>Comment #9 from Marie Cottman, Pharm.D., Owner/PIC Pacific Compounding Pharmacy and Consultations - #2</p> <p>BOP Proposed Item: Amend 16 CCR §1735.1 to add a definition of “batch” for purposes of compounding drug products. The definition clarifies and specifies “batch” as more than one dose of a specific quantity of drug or other material that is intended to have uniform character and quality and is produced during the same continuous cycle of compounding.</p> <p>Recommendation #2 (Cottman): Change the definition of “batch” to be a unique CSP.</p> <p>Comment #2 (Cottman): USP <797> is not specific regarding the term “batch.” It is only used four unique times in the entire document! The context however, references a unique CSP regardless of the number of doses.</p> <p>Reasoning: USP <797> is not specific regarding the term “batch.” It is only used four unique times in the entire document! The context however, references a unique CSP regardless of the number of doses.</p> <p>“Cleaning and disinfecting surfaces in the ISO Class 5 hood shall occur frequently, including: at the beginning of shift; before each batch; every 30 minutes during continuous compounding of individual compounded sterile drug products; after each spill;”</p> <p>I believe the original intent of “batch” in CCR 1751.1 was to differentiate CSPs that would be dispensed to more than one patient.</p> |
| 1735.1 | (b) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #6</p> <p>Dr. Sakai commented on the definition of batch. Dr. Sakai commented the definition of batch goes beyond this proposed definition in the pharmacy setting and in particular the hospital setting. A batch is a grouping of products usually defined by a time period for when they are due to be administered. This “batch” is then prepared during a single production period. A “batch” may contain either patient specific products or non-patient specific products. A “batch” may contain similar or dissimilar products. For the hospital setting the definition would include “non-patient specific” and “prepared in anticipation of a physician’s order”. The impact of this is operational inefficiency.</p> |
| 1735.1 | (b) | <p>Comment #16 from BJ Bartleson, RN, MS, NEA-BC, CA Hospital Association (CHA) - #8</p> <p>CHA comment - <i>Remove</i> “means more than one dose of a specific quantity of the drug or other material that is intended to have uniform character and quality and is produced during the same continuous cycle of compounding”- <i>replace</i> with “multiple doses of sterile products combined or pooled to prepare a product that will be administered either to multiple patients or one patient on multiple occasions, or 25 or more units compounded from non-sterile ingredients.”</p> <p>This definition needs to match USP 797 language so that hospital pharmacies can continue to prepare patient doses for the same drug (same drug order) for a certain time frame generally 12 hours or 24 hours at a time. This type of preparation is not considered batch compounding per USP or ASHP definitions</p> |

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| | | <p>The board proposed definition does not match the USP797 or ASHP use of “batch” in reference to:</p> <ul style="list-style-type: none"> • Medium risk compounding: multiple doses of sterile products are combined or pooled to prepare a product that will be administered either to multiple patients (i.e. batching of syringes or large volumes), or one patient on multiple occasions (e.g. preparation for use over several days). • High risk compounding: only batches with more than 25 units require additional testing for sterility and endotoxins. <p>More than one dose is a very small quantity to apply the term “batch” to unless other specific processes apply such as pooling/combining ingredients into multiple doses or using non-sterile ingredients to prepare multiple doses. Hospital pharmacies typically prepare patients’ doses for the same drug (same order) at the same time but without pooling/combining ingredients.</p> <p>Hospital pharmacies typically prepare patient doses for the same drug (same order) for a certain timeframe generally 12 hours (based on 12 hour beyond-use dating) or 24 hours at a time. (e.g. a patient may receive 4-6 doses of a sterile compounded drug in a 24 hour period such as an antibiotic.) This is type of preparation is not considered batch compounding per USP or ASHP definitions.</p> |
| 1735.1 | (b) | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #5</p> <p>CSHP supports changes to compounding regulations. Most hospitals with CSP have been operating under USP guidelines and while most of the proposed language reflects USP 797, essential provisions are not reflected in the draft language that will assist hospitals in making affordable, safe, patient care changes.</p> <p>Regarding definition of “Batch,” CSHP recommends only using USP 797 “batch” definition for non-sterile to sterile compounded sterile products where there is enough time between compounding and administration for receiving test results.</p> |
| 1735.1 | (b) | <p>Comment #21 from Brian Warren, California Pharmacist Association (CPhA) - #1</p> <p>CPhA commented on the definition of “batch.” The proposed definition of “batch” in Section 1735.1 (b) should be changed to make it consistent with Chapter 797 of the United States Pharmacopeia (USP). As currently written, the definition is overly restrictive and will harm patient access to compounded drugs because requiring sterility testing for every batch, as proposed, will cause enormous increases in drug costs without a known benefit to safety.</p> <p>CPhA appreciates the efforts that the Board took in drafting these proposed regulations for consistency with Chapter 797 of the United States Pharmacopeia (USP). We recognize that the Board should not abandon its authority or responsibility for regulating the pharmacy profession by automatically deferring to an external standard or convention. However, USP represents a national professional standard. Where possible, the Board should strive for consistency with USP so as to allow for continuity in professional standards. The Board acknowledges the importance of consistency with USP throughout the Notice of Proposed Action and Initial Statement of Reasons for this rulemaking package.</p> <p>USP <797> does not require sterility testing of preparations of 25 or fewer doses. Defining</p> |

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| | | <p>“batch” as more than one dose unnecessarily places stricter sterility testing requirements on smaller preparations of compounded drugs. These requirements will increase the cost of preparing smaller preparations, making them less affordable for consumers. The stricter sterility testing requirements of batches of 25 or more doses are not necessary for smaller preparations because relying on end-product testing of randomized samples from a batch is an inferior method of ensuring quality, as compared to focusing on process validation. If the goal is to ensure the highest standards of quality and safety of sterile compounded drug products, then those promulgated regulations tailored to achieve this goal should directly promote those activities that best directly ensure attainment of the same.</p> <p>As such, we recommend the following modification to Section 1735.1 (b): (b) “Batch” means more than one dose <u>25 doses</u> of a specific quantity of drug or other material that is intended to have uniform character and quality and is produced during the same continuous cycle of compounding.</p> |
| 1735.1 | (b) | <p>Oral Testimony #2 – Dan Wills, Representing Self - #2</p> <p>Mr. Wills commented on section 1735.1 (b) where batch is defined as more than one dose. As compounding now includes eye drops and inhalation, I look at this as one dose; a multi-dose vial is now a batch. Eye drop prescriptions requiring more than one drop is now a batch and needs to be tested. Mr. Wills commented this will cause problems and access will be limited. Mr. Wills suggests he is not sure more than one bottle is appropriate. Mr. Wills commented anything more than a single prescription for a single patient to ensure safety and availability. For a single patient, it would be better for them to get the eye drops to save their eyesight than to not be able to get it to protect the rest of the public who will never get it. All questions addressed by changing definition.</p> |
| 1735.1 | (b) | <p>Oral Testimony #5 – David M. Smith, Representing Self</p> <p>Mr. Smith commented on section 1735.1 as pertains to batch. Mr. Smith followed up as his colleagues with regards to the importance to patients and in the community pharmacy addressing one patient. Mr. Smith stated he wanted to be clear in following USP that it concerns him the word batch meaning more than one does of a specific quantity of drug. Mr. Smith hopes to have this clarified so he can continue to help his patients. Mr. Smith commented he is worried as he uses all the processes and validations and performing them to serve the people. Worries me as concerned using all processes validations and performing them and want to serve the people. Mr. Smith commented his patients have metabolic syndromes and are on smaller doses of vitamins. Mr. Smith commented it is important to better understand the word batch and how it is defined. Mr. Smith thanked the board.</p> |
| 1735.1 | (b) | <p>Oral Testimony #6 – Gary Cacciatore and Richard Green, R.Ph., BCNP, Cardinal Health, Inc. - #5</p> <p>Mr. Green commented on 1735.1 regarding batches and doing cleaning every 30 minutes or between batches of different batches. Mr. Green stated as his batches only take 5 minutes, if he has to tear down sterilization of the hood, he will be doing it every 5 minutes.</p> |
| 1735.1 | (b) | <p>Oral Testimony #6 – Steve Gray Pharm.D., JD; California Society of Health-Systems Pharmacists (CSHP) - #2</p> |

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| | | <p>Dr. Gray commented on the example of batch being one dose. The reality is in a 100 bed hospital where a lot of patients need IVs, the batches made are used within 24 hours. Dr. Gray commented if you look at the simplistic definition, it doesn't fit hospital practice. Dr. Gray stated there are so many immediate adjustments especially true in California's large teaching hospitals where you have resident physicians are learning dose per individual patient. Dr. Gray commented the point is practice in hospital is different than outside hospital. Dr. Gray stated he is not saying separation solves all problems to adjust to different environments such as nuclear just heard from. Dr. Gray doesn't think these regulations should be delayed to work out be delayed for hospital. Dr. Gray reiterated the main emphasis for CHSP is for separation of hospital given the history. Dr. Gray pledged CSHP's support as well.</p> |
| 1735.1 | (b) | <p>Oral Testimony #8 – Richard Sakai, Pharm.D., FASHP, FCSHP, Children's Hospital Central California (CHCC) - #2</p> <p>Dr. Sakai commented on 1735.1 batch definition that goes beyond traditional term. Dr. Sasaki commented "made at same time" may be better. Clarification would be helpful as CHCC will batch 2 doses for the patient – same drug, dose and patient.</p> |
| 1735.1 | (b) | <p>Oral Testimony #11 – Elliot Kwok, Pharm.D., Abbotts Compounding Pharmacy – #1</p> <p>Dr. Kwok appreciates the board's work on compounding. Dr. Kwok commented on section 1735.1. Dr. Kwok stated quite a few unit dose sterile eye drops preservative free. If a dose is single dose vial, it will be very difficult to do anything more than one dose. This is impractical to do one dose at a time.</p> |
| 1735.1 | (c) | <p>Comment #3 from Romic Eskandarian, Pharm.D., Glendale Adventist Medical Center, Adventist Health – #2</p> <p>Dr. Eskandarian commented on the definition of "beyond use date" and stated the terminology should not be used. Dr. Eskandarian stated this must be parallel to the terminology of USP 797. Dr. Eskandarian suggested replacing "used" with "stored and transported."</p> |
| 1735.1 | (c) | <p>Comment #6 from Muno Bholat, Goorgen Boghossian, Tawny Bui, Theresa Lee-Yu, and Hiroyuki Nishi, Providence Health & Services Southern California - #8</p> <p>Providence Southern California commented and requested the definition of "beyond use date" be changed to: <u>"Beyond use date" means the date or time after which a compounded drug product should not be used stored or transported. The date is determined from the date or time the preparation is compounded. Administration of the drug product must be initiated prior to the beyond use date.</u></p> <p>Providence Southern California indicated the current language as written implies that the administration of the drug should not take place after the beyond use date. The definition above from USP 797 seeks to avoid any confusion or misinterpretation about the duration of administration or administration time permitted because of the beyond use dating.</p> |
| 1735.1 | (c) | <p>Comment #7 from Doug O'Brien, Pharm.D., and Donald Kaplan, Pharm.D., Kaiser Permanente - #3</p> <p>Kaiser comments on the following: "Beyond Use Date" means the date after which a</p> |

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| | | <p>compounded drug product should not be used.</p> <p>Kaiser’s Comment: The term “used” is ambiguous and unclear. It could be construed to mean “used up” or “completed”, which, in the context of sterile compounding, would mean the completion of drug administration to a patient. Some drug products are administered over several minutes; others can be infused continuously for 24 hours or more.</p> <p>Kaiser’s Recommendation: Change language to be consistent with USP <797>. “The date or time after which a compounded sterile preparation shall not be stored or transported.”</p> <p>Kaiser’s Identified Impact: High cost due to drug waste and to prevent interruption of therapy that is being administered to patients.</p> |
| 1735.1 | (c) | <p>Comment #8 from Alan Y. Endo, Pharm.D., FCSHP, PIH Health - #2</p> <p>“The date or time after which a compounded sterile preparation shall not be stored or transported”</p> |
| 1735.1 | (c) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #7</p> <p>Dr. Sakai commented on the definition of beyond use date. Dr. Sakai commented the Beyond Use Date (BUD) term deals with the compounding to ensure sterility and not stability of a product. If the Board’s intent is to incorporate both sterility and stability in the definition of (BUD), there is a significant potential for confusion. Section 1735.2 (d)(3) would have to be addressed. Currently software limitations of providing (BUD) versus expiration date may result in non-compliance until the software can be updated. An estimate to update software is between \$30-\$50K. The impact of this is high cost due to drug waste as well as an anticipated \$30-50K software upgrade.</p> <p>Dr. Sakai’s Recommendation: Change language to be consistent with USP <797>.</p> |
| 1735.1 | (c) | <p>Comment #16 from BJ Bartleson, RN, MS, NEA-BC, CA Hospital Association (CHA) - #9</p> <p>CHA comment - <i>Remove</i> “means the date after which a compounded drug product should be used.” Replace with “the date or time after which a compounded drug product should not be stored or transported. The date is determined from the date or time the preparation is compounded. Administration of the drug product must be initiated prior to the beyond-use date.” The current draft regulation implies that the administration of the drug should not take place after the beyond use date. This definition needs to align with USP 797 to avoid confusion about the duration of the administration or the administration time permitted because of beyond-use dating.</p> <p>Board proposed definition does not match USP797 definition of beyond use date: the date or time after which a CSP (compounded sterile product) shall not be stored or transported. The date is determined from the date or time the preparation is compounded.</p> <p>The current draft regulation definition implies that the administration of the drug should not take place after the beyond use date and within the USP 797 guidelines it states that administration is to begin prior to the beyond-use date. USP797 is concerned only with</p> |

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| | | <p>preparation and storage time prior to administration. USP 797 further states that it does not include limits on times or duration of clinical administration of CSPs although it does note that these properly remain professional concerns of health care personnel for the safety of patients.</p> <p>CHA recommend amending the definition to adopt the USP797 definition to avoid any confusion or misinterpretation about the duration of administration or administration time permitted because of the beyond use dating.</p> |
| 1735.1 | (c) & Lack of consistency with USP 797 | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #6</p> <p>CSHP supports changes to compounding regulations. Most hospitals with CSP have been operating under USP guidelines and while most of the proposed language reflects USP 797, essential provisions are not reflected in the draft language that will assist hospitals in making affordable, safe, patient care changes.</p> <p>Regarding definition of “Beyond Use Date,” CSHP recommends utilizing USP 797 definitions.</p> |
| 1735.1 | (c) | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #11</p> <p>CSHP commented on the definition of “beyond use date” and recommended to remove “means the date after which a compounded drug product should not be used” and replace with “the date or time after which administration of the compounded drug product should not be initiated. The date is determined from the date or time the preparation is compounded. Administration of the drug product must be initiated prior to the beyond-use date.” The current draft regulation implies that the administration of the drug should not continue after the beyond use date. This definition needs to align with USP 797 to avoid confusion about the duration of the administration or the administration time permitted because of beyond-use dating.</p> |
| 1735.1 | (c) | <p>Oral Testimony #1 – Steven Gray, Pharm.D., JD; Doug O’Brien, Pharm.D.; and Donald Kaplan, Pharm.D., Kaiser Permanente (Kaiser) - #8</p> <p>Dr. O’Brien pointed out the definition of beyond use date. The proposed definition is different than USP 797. USP 797 considers the beyond use date to be the date after which you should not continue to store or begin administration of product. This doesn’t mean if administration has begun that you have to stop using the product. USP 797 allows you to continue to use. The implications of the proposed text for nurses and others who administer medications could leave a lot of room for confusion and waste and possible harm to patients.</p> |
| 1735.1 | (c) | <p>Oral Testimony #8 – Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California (CHCC) - #3</p> <p>Dr. Sakai commented on 1735.1 (c) and 1735.5 – beyond use date (BUD) and requested clarify beyond use date is not equal to expiration. Dr. Sasaki requested clarification if BUD is when product is made vs dispensed. Dr. Sasaki commented to determine the expiration date by allowing the pharmacist to use their own cognitive expertise of the pharmacy evidence based literature rather than manufacture’s expiration date.</p> |
| 1735.1 | (c) | <p>Oral Testimony #12 – Lynn Paulsen, University of California (UC) - #4</p> |

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| | | <p>Ms. Paulsen commented the BUD definition most concerned. In some satellites some laminar flow hoods not in cleanroom and would have to make three bags where making one now.</p> |
| 1735.1 | (d) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #8</p> <p>Dr. Sakai commented on the definition of buffer areas. Dr. Sakai commented the air environment could be within a physical device such as a hood or containment isolator but also a room in operations that are more sophisticated than the typical hospital clean room (compounding procedures occur over an uncontained work surface in an ISO Class 5 air environment).</p> <p>Dr. Sakai’s Recommendation: Change the word “hood” to “air environment to be consistent with USP<797> definition.</p> |
| 1735.1 | (e) | <p>Comment #7 from Doug O’Brien, Pharm.D., and Donald Kaplan, Pharm.D., Kaiser Permanente - #4</p> <p>Kaiser comments on the following: “Cleanroom” means a separate room meeting an ISO Class 7 or better air quality.</p> <p>Kaiser’s Comment: This is a non-standard definition that appears to have been created by the Board of Pharmacy Compounding Subcommittee. According to USP <797>, a clean room for the preparation of low and medium risk level compounded products could be an ISO Class 7 buffer area where laminar flow hoods are placed, and an ISO Class 8 ante area for gowning, handwashing, and staging of ingredients and supplies. When preparing high risk compounded products or hazardous drugs, however, an ISO Class 7 clean room is required. The clean room definition should therefore consider the risk level(s) of the products being compounded.</p> <p>Kaiser’s Recommendation: Change language to be consistent with USP Chapter 797: “A room in which the concentration of airborne particles is controlled to meet a specified airborne particulate cleanliness class. Microorganisms in the environment are monitored so that a microbial level for air, surface and personnel gear are not exceeded for a specified cleanliness class.”</p> <p>Kaiser’s Identified Impact: Remodeling & construction costs: \$115 million for our organization.</p> |
| 1735.1 | (e) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #9</p> <p>Dr. Sakai commented on the definition of cleanroom. Dr. Sakai commented this is a non-standard definition that appears to have been created by the Board of Pharmacy Compounding Subcommittee. An existing, standardized definition should be used.</p> <p>Dr. Sakai’s recommendation: Change language to be consistent with USP Chapter 797: “A room in which the concentration of airborne particles is controlled to meet a specified airborne particulate cleanliness class. Microorganisms in the environment are monitored so that a microbial level for air, surface, and personnel gear are not exceeded for a specified</p> |

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| | | <p>cleanliness class.” Dr. Sakai recommends adding Compounding Barrier Isolator – a device designed to maintain an aseptic compounding environment within the isolator throughout the compounding material transfers process. Some organizations have a barrier isolator.</p> |
| 1735.1 | (e) | <p>Comment #22 from Michael Moné, R.Ph., J.D., FAPhA, Cardinal Health Nuclear Pharmacy Services (Cardinal Health) - #2</p> <p>Cardinal Health commented on the definition of “cleanroom.” The Board's proposal to add a definition of "cleanroom" has substantial impacts upon the preparation of radiopharmaceuticals and its language appears to have overlooked the special handling requirements of radiopharmaceuticals. USP 36 <797> recognizes the special handling requirements with radiopharmaceuticals where it states, "These radiopharmaceuticals shall be compounded using appropriately shielded vials and syringes in a properly functioning and certified 150 Class 5 (see Table 1) PEC located in an ISO Class 8 (see Table 1) or cleaner air environment to permit compliance with special handling, shielding, and negative air flow requirements."</p> <p>Cardinal Health proposes the following language change to add to the proposed amendments to 16 CCR §1735.1: Compounding Definitions. (e) "Cleanroom" means a separate room meeting an ISO Class 7 or better air quality. <u>For purposes of preparing radiopharmaceuticals, they shall be compounded using appropriately shielded vials and syringes in a properly functioning and certified ISO Class 5 PEC located in an ISO Class 8 or cleaner air environment to permit compliance with special handling, shielding, and negative air flow requirements.</u></p> |
| 1735.1 | (e) | <p>Oral Testimony #1 – Steven Gray, Pharm.D., JD; Doug O’Brien, Pharm.D.; and Donald Kaplan, Pharm.D., Kaiser Permanente (Kaiser) - #5</p> <p>Dr. Kaplan reviewed a specific example of this with section 1735.1 (e) regarding the definition of a cleanroom. Dr. Kaplan stated the proposed definition describes ISO Class 7 or cleaner. That definition is not used by any other standards setting organizations such as the United States Pharmacopeia nor the American Society of Health-System Pharmacists. This provision is extremely problematic. Dr. Kaplan stated in the current version of USP 797 it acknowledges a cleanroom can have two distinct areas. They can have a buffer area that would be ISO Class 7 and ante area that is less clean. There would be a sweeping of air called displacement air flow from buffer area where the hoods are to the less clean area that is ISO Class 8 for where gowning, gloving and hand washing occurs. That was designed by USP in 2004 purposefully to use displacement airflow. The board’s definition doesn’t acknowledge displacement airflow exists and a cleanroom must be ISO Class 7 only. The costs to convert a cleanroom from today’s standards that is ISO Class 7 to ISO Class 8 using displacement airflow are extraordinary. To convert the cleanroom under today’s standards to these regulations, you need to revamp the HVAC system, reconsider the heating elements, and updated a 797 cleanroom to the standards of the proposed regulations would be over \$1 million with no demonstrable benefit.</p> |
| 1735.1 | (f) | <p>Comment #7 from Doug O’Brien, Pharm.D., and Donald Kaplan, Pharm.D., Kaiser Permanente - #5</p> <p>Kaiser comments on the following: “Controlled cold temperature” means 2° to 8° C (36° to 46° F).</p> |

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| | | <p>Kaiser’s Comment: Although this proposed definition is consistent with USP <797>, it conflicts with California H&S 70263(q)(6), which states: “Drugs shall be stored at appropriate temperatures. Refrigerator temperature shall be between 2.2° C (36° F) and 7.7° C (46° F)...”</p> <p>Kaiser’s Recommendation: Change wording to read: “Controlled cold temperature” means 2.2° to 7.7° C (36° to 46° F)”</p> <p>Kaiser’s Identified Impact: Consistency with existing California statute.</p> |
| 1735.1 | (f) | <p>Comment #11 from Rita Shane, Pharm.D., FASHP, FCSHP, Cedars-Sinai Medical Center - #5</p> <p>Dr. Shane commented controlled room temperatures as defined in the proposed regulations are 20° to 25° (68° to 77° F). USP and manufactures allow for temperature excursions based on medication stability. USP allows temperatures between 15° and 30° (59° and 86° F) and transient spikes up to 40° C are permitted as long as they do not exceed 24 hours. Spikes above 40° may be permitted based upon the manufacturer package insert.</p> <p>Dr. Shane recommended languages as follows to reflect USP 797 controlled room temperatures: “Controlled room temperature” indicates 20° to 25° C (68° to 77° F); excursions between 15° and 30° (59° to 86°) or as specified in the manufacturer package insert are permitted. Dr. Shane provided an example – see Attachment A.</p> |
| 1735.1 | (g) | <p>Comment #27 from Krista Bramble - #1</p> <p>Ms. Bramble comments a request to consider allowing for freezer temperatures to go lower based on the requirements of the medications stored within.</p> |
| 1735.1 | (g) | <p>Oral Testimony #8 – Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California (CHCC) - #5</p> <p>Dr. Sakai commented on section 1735.1 (g) that the barrier isolator needs to be in negative pressure ISO Class 7. USP guidelines state if meet criteria, it can be outside ISO Class 7 environment.</p> |
| 1735.1 | (h) | <p>Comment #3 from Romic Eskandarian, Pharm.D., Glendale Adventist Medical Center, Adventist Health – #3</p> <p>Dr. Eskandarian commented on the definition of “controlled room temperature” and stated the proposed controlled room temperature of 20-25 degrees Celsius may be too warm given garbing requirements. USP 797 recommends a temperature of 20 degrees or cooler.</p> |
| 1735.1 | (h) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #10</p> <p>Dr. Sakai commented on the definition of controlled room temperature. Dr. Sakai commented the USP General Notice 27 allows for temporary excursions between 15 degrees C and 30 degrees for between 59 degrees and 86 degrees F which are experienced in pharmacies, hospitals and warehouses.</p> <p>Dr. Sakai’s Recommendations: Allow temporary excursions as per USP General Notice 27.</p> |

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| 1735.1 | (h) | <p>Comment #27 from Krista Bramble - #2</p> <p>Ms. Bramble comments a request to consider allowing for excursions under “controlled room temperature” down to 59 deg F.</p> |
| 1735.1 | (h) | <p>Oral Testimony #8 – Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California (CHCC) - #4</p> <p>Dr. Sakai commented 1735.1 (h) is so rigid to comply. Dr. Sakai recommends USP’s General notice 27 allows temporary excursions beyond a defined range and include room temperature, refrigerator temperature and freezer temperature.</p> |
| 1735.1 | (j) | <p>Comment #3 from Romic Eskandarian, Pharm.D., Glendale Adventist Medical Center, Adventist Health – #4</p> <p>Dr. Eskandarian commented on the definition of “gloved fingertip sampling” and commented the use of sterile gloves during this process as well as pointed out it must be performed in the beginning of compounding, immediately after garbing with CFU 0 and during compounding, with CFU < 3.</p> |
| 1735.1 | (j) | <p>Comment #7 from Doug O’Brien, Pharm.D., and Donald Kaplan, Pharm.D., Kaiser Permanente - #6</p> <p>Kaiser comments on the following: “Gloved fingertip sampling” means the requirement that immediately after aseptic donning of sterile gloves, compounding personnel will lightly press each fingertip and thumb onto appropriate growth media which will be incubated and then examined for growth of microorganisms.</p> <p>Kaiser’s Comment: This language is incomplete. It is important that growth media be incubated properly. This will reduce the risk of inaccurate results.</p> <p>Kaiser’s Recommendation: Use USP <797> language. “Gloved fingertip sampling” means the requirement that immediately after aseptic donning of sterile gloves, compounding personnel will lightly press each fingertip and thumb onto appropriate growth media which will be incubated at a temperature and for a time period conducive to multiplication of microorganisms, and then examined for growth of microorganisms.”</p> <p>Kaiser’s Identified Impact: operational inefficiencies.</p> |
| 1735.1 | (j) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #3</p> <p>Dr. Blair commented recommending modifying the language to read as once sterile gloves are pressed into growth media the gloves are contaminated and cannot be used:</p> <p>(j) “Gloved fingertip sampling” means the requirement that immediately after aseptic donning of sterile gloves, compounding personnel will lightly press each fingertip and thumb onto appropriate growth media which will be incubated and then examined for growth of microorganisms.</p> |

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| 1735.1 | (j) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #11</p> <p>Dr. Sakai commented on the definition of gloved fingertip sampling. Dr. Sakai commented it is important that growth media be incubated properly. This will reduce the risk of inaccurate results.</p> <p>Dr. Sakai’s Recommendation: Use USP <797> language - “Gloved fingertip sampling” means the requirement that immediately after aseptic donning of sterile gloves, compounding personnel will lightly press each fingertip and thumb onto appropriate growth media which will be incubated at a temperature and for a time period conducive to multiplication of microorganisms, and then examined for growth of microorganisms.”</p> |
| 1735.1 | (k) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #4</p> <p>Dr. Blair commented recommending modifying the language to read: (k) “Integrity” means retention of potency until the expiration <u>beyond use</u> date noted on the label.</p> |
| 1735.1 | (l) | <p>Comment #6 from Muno Bholat, Goorgen Boghossian, Tawny Bui, Theresa Lee-Yu, and Hiroyuki Nishi, Providence Health & Services Southern California - #9</p> <p>Providence Southern California commented and requested the definition of “parenteral” be changed to: Parenteral means a sterile preparation of drugs for injection through one or more layers of skin to be administered in a manner other than through the digestive tract. This includes, but is not limited to, injection through one or more layers of skin, administration into the eye and by inhalation.</p> <p>Providence Southern California commented and requested the regulatory definition should be consistent with the medical definition and SB 294 [Article 7.5, Sec. 3. 4127(a)].</p> |
| 1735.1 | (l) | <p>Comment #16 from BJ Bartleson, RN, MS, NEA-BC, CA Hospital Association (CHA) - #10</p> <p>CHA comment - <i>Remove</i> “means a sterile preparation of drugs for injection through one or more layers of skin “ <i>replace</i> with, means a preparation of drugs to be administered in a manner other than through the digestive tract. This includes, but is not limited to, injection through one or more layers of skin, administration into the eye and by inhalation.” The regulatory definitions should be consistent with the medical definition of “parenteral” and SB294 language, Article 7.5, section3. 4127(a).</p> <p>From SB294: Article 7.5, Sec 3. 4127(a) A pharmacy that compounds sterile drug products for injection, administration into the eye, or inhalation shall possess a sterile compounding pharmacy license as provided in this article.</p> <ul style="list-style-type: none"> • Definition of parenteral is outside of the alimentary canal or taken into the body or administered in a manner other than through the digestive tract, as by intravenous or intramuscular administration. (American Heritage Medical Dictionary) • Parenteral does not mean “sterile” by any definition although sterile preparations are preferred for parenteral administration • Limiting the definition of parenteral to injections through the skin only seems inconsistent |

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| | | <p>with the sterile compounding regulations from 4127(a) that include sterile compounded drugs administered into the eye and by inhalation. Sterile compounded drugs could be given by other parenteral routes, besides injections only (e.g. intravitreal, ophthalmic, inhalation, irrigation)</p> <p>CHA recommends amending the language to broaden the definition and include other parenteral routes other than injections only.</p> |
| 1735.1 | (l) | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #12</p> <p>CSHP commented on the definition of “parenteral” and recommended to remove “means a sterile preparation of drugs for injection through one or more layers of skin” and replace with, “means a preparation of drugs to be administered in a manner other than through the digestive tract. This includes, but is not limited to, injection through one or more layers of skin, administration into the eye and by inhalation.” The regulatory definitions should be consistent with the medical definition of “parenteral” and SB 294 language, Article 7.5, section 3, 4127(a). Otherwise the proposed definition is in conflict with the Business and Professions statutory language.</p> |
| 1735.1 | (m) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #6</p> <p>Dr. Blair commented recommending modifying the language to read as personal protective equipment applies to sterile and non-sterile compounding: (m) “Personal protective equipment” means clothing or devices that protect the employee from exposure to drug products and minimize the contamination of compounded sterile products and include shoe covers, head and facial hair covers, face masks, gowns, and gloves.</p> |
| 1735.1 | (m) | <p>Comment #19 from Arthur C. Whitney, R.Ph., Advantage Pharmaceuticals - #2</p> <p>Mr. Whitney comments on subsection (m) "Personal protective equipment" clothing and devices are delineated and while head and facial covers and face masks are included, there is no mention of head masks and helmets. Mr. Whitney queries the board if head masks and helmets to be included under this definition.</p> |
| 1735.1 | (n) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #7</p> <p>Dr. Blair commented recommending modifying the language to read: (n) “Potency” means active ingredient strength within +/- 10% <u>(or the range specified in the current USP NF)</u> of the labeled amount.</p> |
| 1735.1 | (n) | <p>Comment #21 from Brian Warren, California Pharmacist Association (CPhA) - #2</p> <p>CPhA commented on the definition of “potency.” The definition of “potency” in Section 1735.1 (n) should be updated for better consistency with USP. Although the Board’s proposed regulations do not currently amend this existing definition, we believe this change is consistent with the overall intent of the rulemaking. There are times where USP may define potency for a product as an active ingredient strength of greater or less than 10% of the labeled amount. Because a USP monograph represents the official standard for drug substances and is a known,</p> |

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| | | <p>citable source, deference to USP monographs should be given in regulation.</p> <p>As such, we recommend the following modification to Section 1735.1 (n): (n) "Potency" means active ingredient strength within +/- 10% of the labeled amount, <u>or as otherwise indicated by a USP monograph.</u></p> |
| 1735.1 | (o) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #8</p> <p>Dr. Blair commented recommending modifying the language to read: (o) "<u>Media fill Pprocess validation</u>" means establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications using microbiological simulation of an aseptic process with growth medium processed in a manner similar to the normal order of production and with the same container or closure. <u>The use of rational bracketing is allowed.</u></p> <p>Dr. Blair indicated "process validation" is too broad of a term. Dr. Blair also commented that the use of rational bracketing of container sizes should be allowed similar to drug manufacturing. Reference Federal Guidelines for explanation of rational bracketing.</p> |
| 1735.1 | (q) | <p>Comment #1 from Douglas Barcon, Pharm.D. - #2</p> <p>Dr. Barcon commented in regulation 1735.1 Compounding Definitions, paragraph (q) on page 3 of the draft, a segregated compounding area is defined. Dr. Barcon stated he found no issue with the definition, which is taken from USP 797. However, the draft compounding regulation does not address the "Immediate-Use CSP" section in USP 797. Since a pharmacist-in-charge is responsible for drugs throughout the facility for which he or she is listed on the Pharmacy Permit, Dr. Barcon believes the "Immediate-Use CSP" section in USP 797 should be addressed in the draft compounding regulations. Hospitals have used the term "segregated area" to describe an area where an immediate-use CSP is compounded. In this use of "segregated area," it does not meet the criteria for a "segregated compounding area" as described in USP 797. In order to describe the situation better regarding the preparation of immediate-use CSPs, without using the term "segregated compounding area," Dr. Barcon suggests describing it this way: Compounding must occur in a clean area that may not meet the definition of a segregated compounding area, in that it may have air quality worse than a controlled ISO Class 5 controlled environment. Such an area could include a specific area on a countertop that has been disinfected with 70% isopropyl alcohol in a medication room within a nursing station. A pharmacist does not directly supervise all such compounding, but a pharmacist could be present and actively involved with such compounding during a cardiopulmonary resuscitation, and the compounding could occur on a countertop or portable table. If the "Immediate-Use CSP" section of USP 797 is incorporated into the draft regulations, it should include a definition differentiating the preparation area from a segregated compounding area.</p> |
| 1735.1 | (q) | <p>Comment #7 from Doug O'Brien, Pharm.D., and Donald Kaplan, Pharm.D., Kaiser Permanente - #7</p> <p>Kaiser comments on the following: "Segregated compounding area" means a designated space, either a demarcated area or room, that is restricted to preparing sterile-to-sterile compounded sterile products with a 12-hour or less beyond use date. Such an area shall contain a device that provides unidirectional airflow of ISO Class 5 air quality for preparation of compounded sterile</p> |

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| | | <p>products and shall be void of activities and materials that are extraneous to sterile compounding.</p> <p>Kaiser’s Comment: The proposed language does not acknowledge that barrier isolators can provide ISO Class 5 air quality, even when located in a room that does not meet ISO 7 Class 7 conditions. USP <797> describes testing requirements to ensure barrier isolators function reliably in this manner (see USP <797> Section on “Placement of Primary Engineering Controls”). This could be an important strategy for preparing CSPs with beyond use dates exceeding 12 hours in medication satellites or in inpatient pharmacies that do not have a dedicated clean room.</p> <p>Kaiser’s Recommendation: Change language to support longer beyond use dating with the use of barrier isolators, provided that these primary engineering controls maintain ISO Class 5 air quality, and are tested as described in the “Placement of Primary Engineering Controls” subsection, USP <797>, page 22.</p> <p>Kaiser’s Identified Impact: Unnecessarily short beyond use dating may cause excessive drug waste. Cost impact: exceeding \$1 million/year for Kaiser organization.</p> |
| 1735.1 | (q) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #9</p> <p>Dr. Blair commented recommending modifying the language to read: (q) “Segregated compounding area” means a designated space, either a demarcated area or room, that is restricted to <u>compounding batches for aseptic filtration operations. If the compounding activities involve the dissolution of non-sterile ingredients, the mixing process will occur in no less than a Class ISO 8 area before being aseptically filtered in Class ISO 5 environment. If the segregated compounding area is for sterile-to-sterile compounding,</u> preparing sterile-to-sterile compounded sterile products with a 12-hour or less beyond use date. Such <u>This</u> area shall contain a device that provides unidirectional airflow of ISO Class 5 air quality for preparation of compounded sterile products and shall be void of activities and materials that are extraneous to sterile compounding.</p> |
| 1735.1 | (q) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #12</p> <p>Dr. Sakai commented on the definition of segregated compounding area. Dr. Sakai commented the proposed language does not acknowledge that barrier isolators can provide ISO Class 5 air quality, even when located in a room that does not meet ISO 7 Class 7 conditions. USP <797> describes testing requirements to ensure barrier isolators function reliably in this manner (see USP <797> Section on “Placement of Primary Engineering Controls). This could be an important strategy for preparing CSPs with beyond use dates exceeding 12 hours in medication satellites or in inpatient pharmacies that do not have a dedicated clean room.</p> <p>This definition also allows for the potential of “medium risk” compounding in the segregated compounding area where USP<797> limits the compounding to “low risk” in this environment. The impact is unnecessarily short beyond use dating will cause drug waste. The cost impact is difficult to estimate but the would require significant construction and/or remodel.</p> <p>Dr. Sakai’s Recommendation: Change language to support longer beyond use dating with the</p> |

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| | | use of barrier isolators, provided that these primary engineering controls maintain ISO Class 5 air quality, and are tested as described in USP <797>. Recommendation to Add ...compounded “low risk” sterile products with a 12-hours or less... |
| 1735.1 | (q) | <p>Comment #19 from Arthur C. Whitney, R.Ph., Advantage Pharmaceuticals - #3</p> <p>Mr. Whitney comments on subsection (q) "Segregated compounding area." The proposed regulations states that this means a designated space, either demarcated area or room, that is restricted to preparing sterile-to-sterile compounded sterile products with a 12-hour or less beyond use date. Such area shall contain a device that provides unidirectional airflow of ISO Class 5 air quality for preparation of compounded sterile products and shall be void of activities and materials that are extraneous to sterile compounding. Mr. Whitney queries the board if this definition also applies to physician owned infusion centers. (cf. SB 294)</p> |
| 1735.1 | (q) | <p>Oral Testimony #1 – Steven Gray, Pharm.D., JD; Doug O’Brien, Pharm.D.; and Donald Kaplan, Pharm.D., Kaiser Permanente (Kaiser) - #7</p> <p>Dr. Kaplan discussed section 1735.1 (q) that identifies a segregated compounding area. We believe this is the board’s effort to emulate USP 797 standard that describes the immediate use 12-hour or less exemption. Dr. Kaplan stated what Kaiser believes is missing is the use of barrier isolators in that environment. In order to meet the regulations, we will need to place compounding aseptic or barrier isolators in segregated compounding areas such as medication satellites or IV rooms. This is proven to provide septic compounding environments. USP 797 describes specifications and testing environments that isolators must meet in order to be present in areas that are less clean than ISO Class 7 air. The board’s proposed regulations do not acknowledge isolators can be used in these conditions. We believe the language be amended to include isolators in segregated areas per USP 797.</p> |
| 1735.1 | (r) | <p>Comment #9 from Marie Cottman, Pharm.D., Owner/PIC Pacific Compounding Pharmacy and Consultations - #3</p> <p>BOP Proposed Item: Amend 16 CCR §1735.1</p> <p>The purpose of the board’s proposal to add subdivision (r) is to add a definition of “smoke test” for purposes of compounding drug products. The definition clarifies and specifies “smoke test” as an analysis of the airflow in the ISO Class 5 hood using a smoke generating device.</p> <p>Comment #3 (Cottman): This definition is good, but it is never used in the proposed amendments. However, the inclusion of a smoke test criterion may be appropriate in Article 7 CCR 1751 Section 4 because USP <797> requires that:</p> <p>“Proper design and control prevents turbulence and stagnant air in the critical area. In situ air pattern analysis via smoke studies shall be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions.”</p> |
| 1735.1 | (r) | <p>Comment #19 from Arthur C. Whitney, R.Ph., Advantage Pharmaceuticals - #4</p> <p>Mr. Whitney comments on subsection (r) "Smoke test" means an analysis of the airflow in the ISO Class 5 hood using a generating device. Mr. Whitney requests the board please delineate what infusion centers use under this definition.</p> |

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| 1735.1 | Add definition of immediate use | <p>Comment #24 from Candace Fong, Pharm.D., and Rachelle Reyes Wenger, Dignity Health - #2</p> <p>Dignity Health recommends adding the immediate use provision with a one-hour beyond use date as stated in USP 797 to allow preparation of sterile compound products outside of an ISO Class 5 hood for emergency or immediate patient administration.</p> <p>The immediate use provision can eliminate unnecessary physical plant facility upgrade costs. Unnecessary upgrades or upgrades required that do not consider a realistic phased-in approach will run counter to transformative goals. The immediate use provision can prevent untimely patient care in fast-paced treatment areas where construction of a cleanroom is not feasible, such as emergency room departments, operating rooms, therapeutic radiology, cardiac catheterization, and respiratory therapy. Compounding in acute care hospitals requires speed and flexibility. Critical lifesaving medications in acute care hospitals are compounded in areas outside of pharmacies and cleanrooms, including the patient’s bedside. Without the immediate use exemption provision, hospitals would be unable to appropriately respond to code blues or other essential patient care therapies requiring compounding within a one hour or twelve hour time period. Regulations are needed to account for the varying environments and situations when compounding must occur to effectively provide the right care at the right time for our patients. The immediate use provision is fiscally sensible, and more importantly it is a responsive provision that will ensure public health and patient and worker safety.</p> |
| 1735.1 | Add new definition | <p>Comment #23 from William Jones, R.Ph., Central Admixture Pharmacy Services, Inc. (CAPS) - #7</p> <p>1735.1 Compounding Definitions</p> <p>The proposed regulation creates confusion with established definitions of ‘product’ and ‘preparation’. If the goal of these regulations is to create clarity for Pharmacists and harmonize with USP 797 then CAPS recommends using the terminology already established by USP. The use of the term "sterile drug product" is used throughout the document to refer to the prepared doses that result from compounding. This terminology is in direct conflict with USP Chapter 797 where "products" refer to manufactured goods while "preparations" refer to the articles/doses of drug that result from compounding. Further, the CA 4.5 document mixes the items referred to as "drug products" in section 1735(c) where a manufactured "drug product" is correctly referred to in the context of the USP definition. The document should be rewritten to substitute the term "compounded sterile preparation" or "CSP" where "sterile drug product" is used in the context of the articles/doses that result from compounding.</p> <p>CAPS recommends adding these USP definitions to 1735.1: Preparation—A preparation, or a CSP, that is a sterile drug or nutrient compounded in a licensed pharmacy or other healthcare-related facility pursuant to the order of a licensed prescriber; the article may or may not contain sterile products.</p> |
| 1735.1 | Add new definition | <p>Comment #23 from William Jones, R.Ph., Central Admixture Pharmacy Services, Inc. (CAPS) - #8</p> <p>1735.1 Compounding Definitions</p> <p>The proposed regulation creates confusion with established definitions of ‘product’ and ‘preparation’. If the goal of these regulations is to create clarity for Pharmacists and harmonize with USP 797 then CAPS recommends using the terminology already established by USP. The</p> |

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| | | <p>use of the term "sterile drug product" is used throughout the document to refer to the prepared doses that result from compounding. This terminology is in direct conflict with USP Chapter 797 where "products" refer to manufactured goods while "preparations" refer to the articles/doses of drug that result from compounding. Further, the CA 4.5 document mixes the items referred to as "drug products" in section 1735(c) where a manufactured "drug product" is correctly referred to in the context of the USP definition. The document should be rewritten to substitute the term "compounded sterile preparation" or "CSP" where "sterile drug product" is used in the context of the articles/doses that result from compounding.</p> <p>CAPS recommends adding these USP definitions to 1735.1: Product—A commercially manufactured sterile drug or nutrient that has been evaluated for safety and efficacy by the FDA. Products are accompanied by full prescribing information, which is commonly known as the FDA-approved manufacturer’s labeling or product package insert.</p> |
| 1735.1 | New definition and (k) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #5</p> <p>Dr. Blair commented recommending adding a new definition of (k) to read as follows: (k) Inhalation means via the oral route and excludes the nasal route.</p> <p>Dr. Blair commented compounders can not sterilize nasal containers/sprayers.</p> <p>(Staff Note: Addition of this definition would require the remuneration of all subsequent definitions in this section.)</p> |
| 1735.2 | | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #13</p> <p>CSHP commented on the removing the word “written” along with all other references to the word “written” throughout the regulations.</p> |
| 1735.2 | | <p>Oral Testimony #8 – Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California (CHCC) - #7</p> <p>Dr. Sakai commented on sections 1735.1, 1735.2 and 1735.3 that specific word to compound product will create delays. Master formula for every change is impossible. Dr. Sakai suggested perhaps general formal for class, 72 hours to develop. Requirement for development of master formula would delay.</p> |
| 1735.2 | (a) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #13</p> <p>Dr. Sakai commented on subsection (a) indicating this could result in delay for service which could result in patient care issues.</p> <p>Dr. Sakai’s Recommendation: Add an option (d) which should be, “the medical staff governance body of an organization on behalf of individual prescribers may authorize the compounding of drug products in the institution for patients.”</p> |

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| 1735.2 | (c) (4) | <p>Comment #19 from Arthur C. Whitney, R.Ph., Advantage Pharmaceuticals - #5</p> <p>Mr. Whitney comments under subsection (c) current regulations cite the Business and Professions Code section 4052(a) (1) when describing a "reasonable quantity" of a compounded drug product. Section 1735.2 (c) (4) reads, "does not exceed an amount the pharmacy can reasonably and safely compound." Mr. Whitney comments that while a reasonable quantity is defined under the aforementioned B&P Code; the amount a pharmacy can "safely compound" is not. Mr. Whitney requests the board please define what constitutes the amount of a safely compounded drug product.</p> |
| 1735.2 | (c)(1) | <p>Comment #27 from Krista Bramble - #3</p> <p>Ms. Bramble comments a request to include Health Care Facilities in addition to prescribers' offices.</p> |
| 1735.2 | (c)(4) | <p>Oral Testimony #2 – Dan Wills, Representing Self - #3</p> <p>Mr. Wills commented on section 1735.2 (c)(4) it looked like #3 if can't reasonably and safely compound beyond what the pharmacy can compound and are out of compliance with pharmaceutical standards.</p> |
| 1735.2 | (d) | <p>Comment #16 from BJ Bartleson, RN, MS, NEA-BC, CA Hospital Association (CHA) - #11</p> <p>CHA Comment – <i>Remove</i> the word "written" along with all other references to the word written throughout the regulations. Multiple occurrence of the word "written" throughout the regulations – <i>Remove</i> all occurrence of word "written" or "in writing" from all sections within the proposed regulations. This will allow pharmacies to be able to maintain electronic policy and procedures. Annotate all sections where "written" occurs: Sections 1735.2(d), 1735.5(a), 1751.3(a), 1751.3(b), 1751.3(c), 1751.3(d), 1751.3(d)3(1), 1751.6(e)(1), 1751.6(e)(2), and 1751.7(a)(3).</p> <p>Many pharmacies prepare and maintain documents in electronic form. Electronic documents are easily searchable and retrievable.</p> |
| 1735.2 | (d) | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #14</p> <p>CSHP commented on the removing the word "written" along with all other references to the word "written" throughout the regulations.</p> |
| 1735.2 | (d) (4) | <p>Comment #3 from Romic Eskandarian, Pharm.D., Glendale Adventist Medical Center, Adventist Health – #5</p> <p>Dr. Eskandarian commented on inactive ingredients referring to vehicle/suspension agent.</p> |
| 1735.2 | (d)(3) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children's Hospital Central California - #14</p> <p>Dr. Sakai commented on the beyond use dating requirements that the expiration date and BUD are not the same. Should the Board desire both recorded, this will require additional support by</p> |

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| | | <p>staff to support this as some organizations which utilize an electronic method to record this information do not have a place to record both expiration date and beyond use date. This will require a software update. Updates often cost between \$10-20K.</p> <p>Dr. Sakai’s Recommendation: Add: “Keep Expiration Dating Requirements” ADD “and beyond use date.”</p> <p>Dr. Sakai commented the BUD is not the same as expiration date. The Board should consider separating into two and clearly defining each to avoid confusion.</p> <p>Dr Sakai’s Recommendation: ADD Expiration date means the date after which a compounded drug product should not be used. BUD is not the same as expiration date.</p> <p>The impact is potential software costs ranging from \$10-20K.</p> |
| 1735.2 | (e) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #15</p> <p>Dr. Sakai commented on subsection (e) to allow the pharmacist to utilize their cognitive skills to evaluate the literature to determine the required information necessary to safely compound drug products.</p> <p>Dr. Sakai’s Recommendation: Add In the professional judgment of the pharmacist the care of the patient would be compromised, the written master formula may be prepared within 72 hours.</p> |
| 1735.2 | (g) | <p>Comment #19 from Arthur C. Whitney, R.Ph., Advantage Pharmaceuticals - #6</p> <p>Mr. Whitney comments under subsection (g) the proposed amendments delete the words, “chemicals and bulk substances” while maintaining the words, “drug products and other components used for drug compounding...” Mr. Whitney requests the board please explain why, in 1735.3 (b) and (c), there appears to be an inconsistency because the deleted terms in 1735.2 (g) are not deleted from 1735.3 (b) and (c), but in the latter components is deleted.</p> |
| 1735.2 | (h) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #10</p> <p>Dr. Blair commented recommending modifying the language to read: (h) Every compounded drug product shall be given an expiration date beyond use date representing the date beyond which, in the professional judgment of the pharmacist performing or supervising the compounding, it should not be used. This “beyond use date” of the compounded drug product shall not exceed 180 days from preparation or the shortest expiration date of any component in the compounded drug product, unless a longer date is supported by stability studies of finished drugs or compounded drug products using the same components and packaging. Shorter dating than set forth in this subsection may be used if it is deemed appropriate in the professional judgment of the responsible pharmacist.</p> |
| 1735.2 | (j) | <p>Comment #16 from BJ Bartleson, RN, MS, NEA-BC, CA Hospital Association (CHA) - #12</p> <p>CHA recommends that the compounding pharmacy self-assessment form be revised</p> |

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| | | <p>simultaneously with the draft regulatory amendments as licensure will depend on meeting the regulations prescribed in the self-assessment form.</p> <p>1735.2 (j) states that the compounding self-assessment must be completed prior to performing any compounding including sterile compounding (changed from sterile injectable compounding). Also from SB 294 Article 7.5 Sec 5. 4127.1(d)(2) the board must review the completed self-assessment form prior to issuing a sterile compounding license. CHA recommends that the compounding pharmacy self-assessment form be revised simultaneously with these draft changes in the compounding and sterile compounding regulations to reflect the amended laws. Licensure will depend on meeting the regulations including providing the board with the completed compounding pharmacy self-assessment. Optimally the self-assessment should match current regulations at the time of review for licensure.</p> |
| 1735.2 | (j) | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #24</p> <p>CSHP recommends that the compounding pharmacy self-assessment form be revised simultaneously with the regulatory amendments as licensure will depend on meeting the regulations prescribed in the self-assessment.</p> |
| 1735.3 | | <p>Comment #5 from Elliot Kwok, Pharm.D., Abbott’s Compounding Pharmacy, Inc. – #3</p> <p>Dr. Kwok commented Abbott’s Compounding Pharmacy’s recommendation is to amend section 1735.3. Dr. Kwok indicated “lack of supplier’s expiration date cannot be used after one year.” Dr. Kwok continued that many minerals and their salt forms are stable for a long time. Dr. Kwok provided an example: Potassium Chloride, Sodium Selenite etc. do not expire, change or degrade in one year. The expiration dates of this kind of chemical should be determined by either the pharmacist or the manufacturer based on actual nature of the substance, not just arbitrary for one year.</p> |
| 1735.3 | | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #19</p> <p>Dr. Sakai commented on the language, “container or on the receipt provided to the patient...” Dr. Sakai’s comment his concern is inpatients and outpatients being cared for in a healthcare facility currently do not receive receipts of the drugs that are prescribed during their stay. This part of the regulation appears to be of benefit for those patients receiving an actual prescription in the outpatient setting. The value for a patient receiving care from an acute care healthcare facility such as a hospital remains questionable.</p> <p>Dr. Sakai’s Recommendation: Add “...sterile injectable compounded products provided to patients in a healthcare facility are excluded.” At the end of the sentence on line 28.</p> |
| 1735.3 | | <p>Oral Testimony #8 – Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California (CHCC) - #8</p> <p>Dr. Sakai commented on sections 1735.1, 1735.2 and 1735.3 that specific word to compound product will create delays. Master formula for every change is impossible. Dr. Sakai suggested perhaps general formula for class, 72 hours to develop. Requirement for development of master formula would delay.</p> |

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| 1735.3 | (a)(6) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #16</p> <p>Dr. Sakai commented on the manufacturer, expiration date and lot number of each component. If the interpretation in this section is that a dose is not a patient specific dose as defined by a particular patient’s dose at a defined date and time, it will cost some organizations over \$144,230 annually based upon 300,000 doses taking an additional one minute to capture and record the information resulting in a need for 2.4 FTEs annually not including replacement costs nor benefits for these employees. The impact is estimated \$144,230 annually.</p> <p>Dr. Sakai’s Recommendation: Add “patient specific” before the part”...sterile products compounded...”</p> |
| 1735.3 | (a)(9)(c) | <p>Comment #7 from Doug O’Brien, Pharm.D., and Donald Kaplan, Pharm.D., Kaiser Permanente - #8</p> <p>Kaiser comments on the following: The pharmacy shall acquire and retain any available certificates of purity or analysis for chemicals, bulk drug substances, and drug products, and components used in compounding. Certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration. Certificates of purity or analysis are to be matched to the product received.</p> <p>Kaiser’s Comment: The existing regulation exempts FDA-approved drugs from the requirement to obtain certificates of purity or analysis. The proposed regulation would delete this exemption. Under the proposed regulation, if lidocaine 1% injection USP used as an ingredient during compounding, a certificate of purity or analysis would be required in the compounding record. The FDA-approved product labeling already attests to its identity, strength, and sterility.</p> <p>Kaiser’s Recommendation: “Certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration.”</p> <p>Kaiser’s Identified Impact: operational inefficiency.</p> |
| 1735.3 | (a)(9)(c) | <p>Oral Testimony #1 – Steven Gray, Pharm.D., JD; Doug O’Brien, Pharm.D.; and Donald Kaplan, Pharm.D., Kaiser Permanente (Kaiser) - #9</p> <p>Dr. Kaplan discussed section 1735.3(a)(9)(c) and observed the sentence was struck that does not require certificates of purity or analysis for drug products if approved by the if have been approved by FDA. Dr. Kaplan indicated if an FDA approved drug is used as ingredient in compounding, the proposed text would have to provide certificate of purity. There is already an abundance documentation of certificate of purity or analysis provided to the FDA in order to be FDA approved. This is unnecessary and burdensome.</p> |
| 1735.3 | (c) | <p>Comment #1 from Douglas Barcon, Pharm.D. – #6</p> <p>Dr. Barcon commented in draft regulation 1735.3 Recordkeeping of Compounded Drug Products paragraph (c) beginning on page 6, the sentence, "Certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration" was</p> |

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| | | <p>deleted. Dr. Barcon requested clarification if it is the board's intention with this change to require pharmacies to acquire certificates of purity and analysis for all drugs used in compounding, including those in vials, such as antibiotics and TPN electrolytes purchased from manufacturers direct or through wholesalers. If this is the case, Dr. Barcon suggested this could pose a problem for hospital pharmacies and compounding pharmacies if that information wasn't supplied with every package purchased from the supplier, since brands change due to changes in availability, shortages, and GPO contracts. Dr. Barcon recommended alternative text should be developed.</p> |
| 1735.3 | (c) | <p>Comment #3 from Romie Eskandarian, Pharm.D., Glendale Adventist Medical Center, Adventist Health – #6</p> <p>Dr. Eskandarian commented on the deleted lines: “Certificates of purity or analysis are not required for drug products that are approved by Food and Drug Administration.” Dr. Eskandarian commented this revision is significant for those hospitals that utilize chemicals to compound certain products. Dr. Eskandarian recommended removing the deletion of this sentence as the revision states that the chemicals used to compound drug products shall be obtained from reliable FDA-registered suppliers and clarify FDA-registered supplier as not all places where pharmacies obtain chemicals from are FDA-registered.</p> |
| 1735.3 | (c) | <p>Comment #6 from Muno Bholat, Goorgen Boghossian, Tawny Bui, Theresa Lee-Yu, and Hiroyuki Nishi, Providence Health & Services Southern California - #10</p> <p>Providence Southern California commented on the identification of “chemicals, bulk drug substances, and drug products” recommending defining these items “reliable FDA-registered suppliers.”</p> |
| 1735.3 | (c) | <p>Comment #6 from Muno Bholat, Goorgen Boghossian, Tawny Bui, Theresa Lee-Yu, and Hiroyuki Nishi, Providence Health & Services Southern California - #11</p> <p>Providence Southern California commented and requested the following change: The pharmacy shall acquire and retain certificates of purity or analysis for chemicals; and bulk drug substances, and drug products used in compounding. Certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration.</p> <p>Providence Southern California commented USP 797 requires a certificate of analysis from suppliers only when nonofficial (non-USP or NF) ingredients are used.</p> <p>Providence Southern California requests the board provide background information or evidence that supports the requirement for pharmacies to acquire/retain certificates of purity or analysis for the FDA approved drug products to help explain why the exemption was removed.</p> <p>FDA approved drugs are produced according to established GMP (good manufacturing practices) and USP/NF guidelines. Requiring pharmacies to obtain these certificates of purity or analysis does not enhance the safety of these drugs beyond FDA approved standards.</p> <p>Providence Southern California urges the board to amend this section to require manufacturers to provide these certificates to pharmacies with each of their products, rather than impose the burden on hospital pharmacies to obtain these documents from the manufacturers.</p> |

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| 1735.3 | (c) | <p>Comment #8 from Alan Y. Endo, Pharm.D., FCSHP, PIH Health - #3</p> <p>Definition of chemicals, bulk drug substances and drug products.</p> <p>PIH Health’s Recommendation: “Certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration.”</p> |
| 1735.3 | (c) | <p>Comment #9 from Marie Cottman, Pharm.D., Owner/PIC Pacific Compounding Pharmacy and Consultations - #4</p> <p>BOP Proposed Item: Amend 16 CCR §1735.3 subdivision (c) to ...require reliable suppliers of drug products for compounders to be FDA-registered. This change is necessary to add the requirement of “FDA-registered” to ensure that the supplier of drug products are adequately regulated by the Food and Drug Administration (FDA) and addressed the problem of the integrity of the purchased drug products by compounders providing compounded drug products to California consumers. The board’s proposal further clarifies by deleting “any available” and adding requirements for certificates of purity or analysis are to be matched to the product received. The requirement that all certifications of purity or analysis are to be kept and matched to the product received also includes the now required FDA-registered suppliers. This change is necessary to ensure a consolidated record for a compounded drug product that may have multiple ingredients from multiple FDA-registered suppliers. This addressed the problem of clarifying the requirements of recordkeeping for certificates of purity and analysis of drug products.</p> <p>Recommendation #4 (Cottman): This line should either a) not be removed or b) amended to include manufactured available drug products.</p> <p>Comment #4 (Cottman): There is no explanation from the Board to relative to the removal of “Certificates of purity or analysis (C of A) are not required for drug products that are approved by the Food and Drug Administration.” This is an important issue in compounding. When we compound with manufactured, FDA approved drug products (i.e. Atenolol tablets or Cefuroxime injection 750mg vials) we do not have access to a C of A and no other pharmacy is required to have a C of A to dispense these products.</p> |
| 1735.3 | (c) | <p>Comment #11 from Rita Shane, Pharm.D., FASHP, FCSHP, Cedars-Sinai Medical Center - #6</p> <p>Dr. Shane commented FDA-approved products do not have certificates of analysis. However, chemicals and bulk drug substances used in compounding may not always be FDA-approved.</p> <p>Dr. Shane recommended modifying language as follows: Products used in compounding that are not FDA-approved should have a certification of analysis.</p> |
| 1735.3 | (c) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #17</p> <p>Dr. Sakai commented on the portion that “drug products shall be obtained from reliable FDA-registered suppliers.” Dr. Sakai commented drugs approved by the Food and Drug Administration (FDA) have already passed requirements for purity as required by the FDA as well as being monitored. Pharmaceutical companies do not currently provide a certificate of purity when a healthcare facility purchases these products. Should this be part of the</p> |

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| | | <p>regulation, it is estimated that it will result in an increase of one full time equivalent (FTE) or approximately \$60K annually per organization to hire a pharmacy technician in a moderate sized hospital (350 bed facility).</p> <p>Dr. Sakai’s Recommendation: Add “...or USP quality grade products...” after the part “...FDA registered suppliers...”</p> |
| 1735.3 | (c) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #18</p> <p>Dr. Sakai commented on the proposed deleted language from subsection (c) that would remove: Certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration. Dr. Sakai commented the goal is to ensure quality products are used. USP quality grade ensures this. Products which fulfill USP standards ensure this safety. Currently organizations that utilize USP approved drugs do not acquire or maintain this information being requested. To obtain, maintain and update this information will easily require one FTE (technician) or about \$60K including benefits per organization. Dr. Sakai also notes operational inefficiency as an impact.</p> <p>Dr. Sakai’s Recommendation: Retain this language: “Certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration.”</p> <p>[Note: Dr. Sakai’s comment referenced section 1735.3(9)(c); however, the actual code section is section 1735.3(c).]</p> |
| 1735.3 | (c) | <p>Comment #16 from BJ Bartleson, RN, MS, NEA-BC, CA Hospital Association (CHA) - #13</p> <p>CHA recommends no language change and requests definitions for chemicals, bulk drug substances, drug products, and “reliable” FDA-registered supplier.</p> |
| 1735.3 | (c) | <p>Comment #16 from BJ Bartleson, RN, MS, NEA-BC, CA Hospital Association (CHA) - #14</p> <p>CHA Comment - <i>Remove</i> “the pharmacy shall acquire and retain any available certificates of purity or analysis for chemicals, bulk drug substances, and drug products. And components used in compounding” – <i>replace</i> with “The pharmacy shall acquire and retain certificates of purity or analysis for chemicals and bulk drug substances used in compounding. Certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration.” This language aligns with USP 797. FDA approved drugs are produced according to established GMP good manufacturing practices and USP/NF guidelines. Requiring pharmacies to obtain these certificates of purity or analysis does not enhance the safety of the drugs beyond FDA approved standards.</p> <p>USP 797 requires certificates of analysis from suppliers only when nonofficial (nonUSP or NF) ingredients are used.</p> <p>CHA requests background information or evidence that supports the requirement for pharmacies to acquire/retain certificates of purity or analysis for FDA approved drug products to explain why the exemption was removed from the regulation. FDA approved sterile drug products used in sterile drug compounding per the manufacturer’s approved instructions should not require certificate of analysis acquisition/retention. FDA approved drugs are produced</p> |

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| | | <p>according to established GMP good manufacturing practices and USP/NF guidelines. Requiring pharmacies to obtain these certificates of purity or analysis does not enhance the safety of these drugs beyond the FDA approved standards.</p> |
| 1735.3 | (c) | <p>Comment #17 from Tim Lopez, Pharm.D., Community Regional Medical Centers (CRMC) - #3</p> <p>CRMC commented on the verbiage, “The pharmacy shall acquire and retain certificates of purity or analysis for chemical, bulk drug substances, and drug products used in compounding.” CRMC’s concern: Certificates of analysis and purity are not readily available for RX legend drugs, They are available for bulk chemicals and drug products and should only be required for these products. This requirement could take up valuable time that our staff would otherwise be using to process recall notices and check for outdates.</p> <p>CRMC’s solution: Restore the following language to the regulation, “Certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration.”</p> |
| 1735.3 | (c) | <p>Comment #19 from Arthur C. Whitney, R.Ph., Advantage Pharmaceuticals - #7</p> <p>Mr. Whitney comments under subsection (c) Certificates of purity or analysis are required and must be matched to the product received. Mr. Whitney queries the board if there is a preference from whom the certificate of purity or analysis should be provided and how are the sterile compounding pharmacies to authenticate that the certificate is from a valid lab?</p> |
| 1735.3 | (c) | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #25</p> <p>CSHP recommends a language change using chemicals, bulk drug substances and drug products, “reliable” suppliers, not FDA-registered suppliers. Some compounding components are not supplied by FDA “registered” suppliers – e.g., sugar.</p> |
| 1735.3 | (c) | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #26</p> <p>CSHP recommends removing, “the pharmacy shall acquire and retain any available certificates of purity or analysis for chemicals, bulk drug substances, and drug products. And components used in compounding” and replace with, “The pharmacy shall acquire and retain certificates of purity or analysis for chemicals and bulk drug substances used in compounding. Certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration.”</p> <p>This language aligns with USP 797. FDA approved drugs are produced according to established GMP good manufacturing practices and USP/NF guidelines. Requiring pharmacies to obtain these certificates of purity or analysis does not enhance the safety of drugs beyond FDA approved standards.</p> |
| 1735.3 | (c) | <p>Comment #21 from Brian Warren, California Pharmacist Association (CPhA) - #3</p> <p>CPhA commented on the “certificates of purity.” The proposed changes to Section 1735.3,</p> |

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| | | <p>relating to recordkeeping, among other things, require suppliers of chemicals, bulk drug substances, and drug products to be FDA-registered, and strike an existing provision in subsection (c) that states “certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration.” CPhA believes that this sentence should not be stricken from subsection (c).</p> <p>The Board states that this change is necessary to “ensure that the supplier of drug products are adequately regulated by the Food and Drug Administration (FDA) and addressed the problem of the integrity of the purchased drug products by compounders providing compounded drug products to California consumers,” and to “ensure a consolidated record for a compounded drug product that may have multiple ingredients from multiple FDA-registered suppliers.”</p> <p>For drug products approved by the FDA, the FDA is the regulator of those products and responsible for ensuring that manufacturers ensure their products meet specification.</p> <p>As such, we recommend the following modification to Section 1735.3 (c): (c) Chemicals, bulk drug substances, and drug products used to compound drug products shall be obtained from reliable FDA-registered suppliers. The pharmacy shall acquire and retain certificates of purity or analysis for chemicals, bulk drug substances, and drug products used in compounding. Certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration. <u>Certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration.</u> Certificates of purity or analysis are to be matched to the product received.</p> |
| 1735.3 | (c) | <p>Comment #22 from Michael Moné, R.Ph., J.D., FAPhA, Cardinal Health Nuclear Pharmacy Services - #3</p> <p>Cardinal Health commented radiopharmacies prepare short lived radio tracers manufactured by FDA licensed drug manufacturers and only use FDA approved drug" kits." When all drugs sourced and procured are FDA approved commercially available drugs, there is no benefit to be achieved by requiring the manufacturer to provide certificates of purity or certificates of analysis (eGA) to be matched to the product received as the products are manufactured pursuant to cGMPs.</p> <p>Cardinal Health proposes the following language change to add to the proposed amendments to 16 CCR § 1735.3: (c) Chemicals, bulk drug substances, and drug products, used to compound drug products shall be obtained from reliable FDA-registered suppliers. The pharmacy shall acquire and retain certificates of purity or analysis for chemicals, bulk drug substances, and drug products, used in compounding. Certificates of purity or analysis are to be matched to the product received. <u>When radiopharmaceuticals are prepared from commercially available FDA-approved drugs, no certificates of purity or certificates of analysis are required.</u></p> |
| 1735.3 | (c) | <p>Comment #27 from Krista Bramble - #4</p> <p>Ms. Bramble comments this is confusing why the requirement for certificate of purity or analysis is required for FDA approved products.</p> <p>[Note: Ms. Bramble’s comment referenced section 1735.3 (9)(c); however, the actual code section is section 1735.3(c)]</p> |

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| 1735.3 | (c)(9) | <p>Oral Testimony #2 – Dan Wills, Representing Self - #4</p> <p>Mr. Wills commented on section 1735.3 (c)(9) FDA added will limit getting chemicals from another pharmacy in shortage or as Steve Gray pointed out with simple syrup will they have to go to FDA approved supplier or grocery store down the street. This will limit access.</p> |
| 1735.3 | (d) | <p>Comment #9 from Marie Cottman, Pharm.D., Owner/PIC Pacific Compounding Pharmacy and Consultations - #5</p> <p>BOP Proposed Item: Add Subdivision (d) to 16 CCR §1735.3 to specify after receipt by the pharmacy, packages of ingredients that lack a supplier’s expiration date cannot be used after one (1) year unless either appropriate inspection or testing indicates that the ingredient has retained its purity and quality for use in compounded drug products. This change is necessary to identify for the board’s regulated licensees the maximum time a drug product can be used without appropriate inspection or testing if the manufacturer failed to provide an expiration date. This addressed the problem of clarity to the board’s regulated licensees and in accordance to compounding pharmacy professional standards USP 36 <797>.</p> <p>Comment #5 (Cottman): Section §1735.3 is relative to all compounding, not just sterile compounding. The standards included for assigning expiration dating to non-dated ingredients for non-sterile compounding differ from sterile compounding. For non-sterile compounding, you can find a three year recommendations in USP <795>.</p> <p>Recommendation #5 (Cottman): CCR §1735.3 Subdivision (d) should read: (d) After receipt by the pharmacy, packages of ingredients that lack a supplier’s expiration date cannot be used after three (3) years unless either appropriate inspection or testing indicates that the ingredient has retained its purity and quality for use in non-sterile compounded drug products.</p> <p>CCR §1751.1 Sterile Compounding Recordkeeping Requirements Subdivision (c) should be added (and renumber the current Subdivision (c) to Subdivision (d)). After receipt by the pharmacy, packages of ingredients that lack a supplier’s expiration date cannot be used after one (1) year unless either appropriate inspection or testing indicates that the ingredient has retained its purity and quality for use in non-sterile compounded drug products.</p> <p>Reference USP <795>: “COMPONENT SELECTION, HANDLING, AND STORAGE sub section 6. For components that do not have expiration dates assigned by the manufacturer or supplier, the compounder shall label the container with the date of receipt and assign a conservative expiration date, not to exceed three years after receipt, to the component (see the General Notices and Requirements, Preservation, Packaging, Storage, and Labeling, Labeling, Expiration Date and Beyond-Use Date) based on the nature of the component and its degradation mechanism, the container in which it is packaged, and the storage conditions.”</p> |
| 1735.3 | (d) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #11</p> <p>Dr. Blair commented recommending modifying the language to read: (d) After receipt by the pharmacy, packages of ingredients that lack a supplier’s expiration date cannot be used after one (1) year, <u>from the date of receipt</u>, unless either appropriate inspection or testing indicates that the ingredient has retained its purity and quality for use in compounded</p> |

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| | | drug products. |
| 1735.3 | (d) | <p>Comment #21 from Brian Warren, California Pharmacist Association (CPhA) - #4</p> <p>CPhA commented on “Beyond Use Dates for Products with No Supplier’s Expiration Date.” The proposed regulations add a new subsection (d) to Section 1735.3, which would mandate a beyond use date of one year for all packages of ingredients that lack a supplier’s expiration date. CPhA believes this requirement is insufficient in that it groups active and inactive ingredients together. CPhA proposes different standards for active and non-active ingredients. When no supplier’s expiration date exists, active ingredients should not be used beyond one year from receipt and inactive ingredients should not be used beyond three years from receipt.</p> <p>As such, we recommend the following modification to Section 1735.3 (d):</p> <p>(d) After receipt by the pharmacy, packages of ingredients that lack a supplier’s expiration date cannot be used after one (1) year <u>for active ingredients or three (3) years for inactive ingredients</u>, unless either appropriate inspection or testing indicates that the ingredient has retained its purity and quality for use in compounded drug products.</p> |
| 1735.3 | (d) | <p>Oral Testimony #2 – Dan Wills, Representing Self - #5</p> <p>Mr. Wills commented on section 1735.3 (d) he is not sure moving from three to one year. Mr. Wills talked to USP who said there were more people from manufacturing and wanted to sell more products. Mr. Wills had a hard time finding the science behind this. Mr. Wills provided the example of salt at a salt flat. Some things don’t expire – salt or sulfur. Scientific definition behind this does not create more patient safety. It is a vehicle for manufactures to sell more.</p> |
| 1735.4 | (c) | <p>Comment #6 from Munro Bholat, Goorgen Boghossian, Tawny Bui, Theresa Lee-Yu, and Hiroyuki Nishi, Providence Health & Services Southern California - #4</p> <p>Providence Southern California commented and recommended amending section 1735.4 by changing “expiration date” and replace with “beyond use date” in order to be consistent through the compounding regulations.</p> <p>(c) Drug products compounded into unit-dose containers that are too small or otherwise impractical for full compliance with subdivisions (a) and (b) shall be labeled with at least the name(s) of the active ingredient(s), concentration or strength, volume or weight, pharmacy reference or lot number, and expiration date <u>beyond use date</u>.</p> <p>(Note: Section 1735.4 was not included in the original rulemaking noticed on 11/2013 and would require separate noticing and 45-day comment period.)</p> |
| 1735.4 | (c) | <p>Comment #16 from BJ Bartleson, RN, MS, NEA-BC, CA Hospital Association (CHA) - #15</p> <p>CHA Comment – Remove “expiration date” and replace with “beyond use date.” There are multiple occurrences of this throughout the draft regulations. All areas that state “expiration date” need replacement with “beyond use dating.”</p> <p>Recommend to change “expiration date” to “beyond-use date” to be consistent with other changes utilizing “beyond-use date.”</p> |

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| 1735.4 | (c) | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #27</p> <p>CSHP recommends removing “expiration date” and replacing with “beyond use date.” There are multiple occurrences of this throughout the draft regulations. All areas that state “expiration date” need replacement with “beyond use dating.”</p> |
| 1735.5 | | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #22</p> <p>Dr. Sakai commented on any revisions to the policies and procedures. Dr. Sakai commented the intent of the document revisions is to ensure staff is utilizing the most current policies and procedures. The current verbiage indicates that ALL revisions would be listed. The current method most organizations utilize is that old policies and procedures are archived and not available for staff to see to prevent the utilization of an old policy and procedure. The date of the most current revision is documented on the document alerting staff of the date the policy and procedure was reviewed and approved.</p> <p>Dr. Sakai’s Recommendation: Remove “and” and Add: “the most recent.”</p> |
| 1735.5 | | <p>Oral Testimony #8 – Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California (CHCC) - #11</p> <p>Dr. Sakai commented on section 1735.5 professional conduct is not necessary. Dr. Sakai stated he hasn’t seen a specific regulation anything listed as unprofessional conduct. Remove and use culture to determine unprofessional conduct.</p> |
| 1735.5 | (a) | <p>Comment #3 from Romic Eskandarian, Pharm.D., Glendale Adventist Medical Center, Adventist Health – #7</p> <p>Dr. Eskandarian commented on the addition of, “The pharmacy shall follow its policies and procedures and failure to follow these policies and procedures shall be deemed unprofessional conduct.” Dr. Eskandarian recommended adding <u>intentionally</u> or <u>grossly</u> or <u>willfully</u>. He suggested the word <u>shall</u> should be changed to <u>may</u>.</p> |
| 1735.5 | (a) | <p>Comment #7 from Doug O’Brien, Pharm.D., and Donald Kaplan, Pharm.D., Kaiser Permanente - #9</p> <p>Kaiser comments on the following:The pharmacy shall follow its policies and procedures and failure to follow these policies and procedures shall be deemed unprofessional conduct.</p> <p>Kaiser’s Comment: The proposed language is overly harsh, and provides no latitude if minor deviations are found in observance of policies and procedures that pose no reasonable risk to the public. There needs to be room for judgment on the part of the inspector and/or the Board.</p> <p>Kaiser’s Recommendation: “The pharmacy shall follow its policies and procedures. Intentionally (or grossly) failing to follow these policies and procedures may be deemed unprofessional conduct.”</p> |

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| | | Kaiser's Identified Impact: Draconian language; Suggest adopting concepts of "Just Culture." |
| 1735.5 | (a) | <p>Comment #9 from Marie Cottman, Pharm.D., Owner/PIC Pacific Compounding Pharmacy and Consultations - #6</p> <p>BOP Proposed Item: Amend 16 CCR §1735.5 to add to subdivision (a) the requirement that the pharmacy shall follow its policies and procedures and failure to follow these policies and procedures shall be deemed unprofessional conduct. This change is necessary to specifying the requirement of not only maintaining compounding policies and procedures but also a requirement to following the pharmacy's policies and procedures.</p> <p>Comment #6 (Cottman): In CCR §4037 "Pharmacy" means an area, place, or premises licensed by the board in which the profession of pharmacy is practiced and where prescriptions are compounded..." A Pharmacy is NOT capable of following a procedure nor can it be responsible for unprofessional conduct.</p> <p>Recommendations #6 (Cottman): Please consider changing "pharmacy" to "pharmacy compounding personnel" or "pharmacy compounding staff."</p> <p>As polices and procedures should not be carried out by non-trained pharmacy staff, the use of the term 'compounding' to describe who carries out these policies and procedures is prudent.</p> <p>Additionally, under Subdivision (b) of CCR §1735.5, please consider changing the annual review from being the sole responsibility of the PIC to include all compounding pharmacy staff. I would guess that in some pharmacy situations, the PIC is not involved in compounding at all, though I understand why that PIC should still be responsible for reviewing the policies and procedures, regardless.</p> |
| 1735.5 | (a) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #12</p> <p>Dr. Blair commented recommending modifying the language to read: (a) Any pharmacy engaged in compounding shall maintain a written policy and procedure manual for compounding that establishes procurement procedures, methodologies for the formulation and compounding of drugs, facilities and equipment cleaning, maintenance, operation, and other standard operating procedures related to compounding. The pharmacy shall follow its policies and procedures and failure to follow these policies and procedures shall be deemed <u>cause for consideration of unprofessional conduct</u>.</p> <p>Dr. Blair commented unintentional or minor failure to follow policy/procedure should not result in immediate determination of unprofessional conduct. Pattern of such failure may be considered unprofessional conduct.</p> |
| 1735.5 | (a) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children's Hospital Central California - #20</p> <p>Dr. Sakai commented on the language, "...The pharmacy shall follow its policies and procedures and failure to follow these policies and procedures shall be deemed unprofessional conduct." Dr. Sakai's concern is that the proposed language is overly harsh, and provides no latitude if minor deviations are found in observance of policies and procedures that pose no</p> |

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| | | <p>reasonable risk to the public. There needs to be room for judgment on the part of the inspector and/or the Board. Dr. Sakai identified the impact as Draconian language; use “Just Culture”.</p> <p>Dr. Sakai’s Recommendation: “The pharmacy shall follow its policies and procedures. Intentionally (or grossly) failing to follow these policies and procedures shall be deemed unprofessional conduct.”</p> <p>Dr. Sakai’s Recommendation: REMOVE the sentence “the pharmacy shall follow its policies and procedures and failure to follow these policies and procedures shall be deemed unprofessional conduct.”</p> <p>This doesn’t appear elsewhere in the regulations. The Board of Pharmacy already has the authority</p> |
| 1735.5 | (a) | <p>Comment #17 from Tim Lopez, Pharm.D., Community Regional Medical Centers (CRMC) - #4</p> <p>CRMC commented on the verbiage, “The pharmacy shall follow its policies and procedures and failure to follow these policies and procedures shall be deemed unprofessional conduct.” CRMC’s concern: The pharmacy law usually does not include disciplinary actions within regulations. Those are reserved for disciplinary sections only and this should remain the practice.</p> <p>CRMC’s solution: Delete the following language from the regulation, “The pharmacy shall follow its policies and procedures and failure to follow these policies and procedures shall be deemed unprofessional conduct.”</p> |
| 1735.5 | (a) | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #15</p> <p>CSHP commented on the removing the word “written” along with all other references to the word “written” throughout the regulations.</p> |
| 1735.5 | (a) | <p>Comment #27 from Krista Bramble - #5</p> <p>Ms. Bramble inquires can the “unprofessional conduct” piece be delineated to include specific serious failures to follow policy? The way it is written allows for unprofessional conduct no matter what the violation of policy – very broad.</p> |
| 1735.5 | (c) (7) | <p>Comment #1 from Douglas Barcon, Pharm.D. – #4</p> <p>Dr. Barcon commented that since the draft compounding regulations are inclusive of all risk levels of compounding, including the storage of bulk compounds, perhaps humidity should be added to regulation 1735.5 paragraph (c) (7) on page 8 of the draft, since it is addressed in USP 797 and USP 1079.</p> |
| 1735.5 | (c) (7) | <p>Comment #6 from Munro Bholat, Goorgen Boghossian, Tawny Bui, Theresa Lee-Yu, and Hiroyuki Nishi, Providence Health & Services Southern California - #12</p> <p>Providence Southern California commented and requested the following change:</p> |

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| | | <p>The pharmacy of compounded sterile drug products in the pharmacy and daily routine <u>monitoring and</u> documentation of room, refrigerator, and freezer temperatures. <u>If the compounding facility uses a continuous temperature recording device, compounding personnel shall verify at least once daily that the recording device itself is functioning properly.</u></p> <p>Providence Southern California recommends adding the qualifying language from USP 797 to consistently align with the national standards. Providence refrigeration units provide continuous temperature monitoring and alert systems. Daily documentation would not provide an advantage to this 24/7 monitoring nor does it increase patient safety beyond the systems already in place.</p> |
| 1735.5 | (c)(2) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #13</p> <p>Dr. Blair commented recommending modifying the language to read: (2) Documentation of a plan for recall of a dispensed compounded drug product where subsequent verification demonstrates the potential for <u>serious adverse effects events</u> with continued use of a compounded drug product.</p> <p>Dr. Blair commented “adverse effects” was too general of a term.</p> |
| 1735.5 | (c)(4) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #14</p> <p>Dr. Blair commented recommending modifying the language to read: (4) Documentation of the methodology appropriate to compounded drug products used to validate <u>verify</u> integrity, potency, quality, and labeled strength.</p> <p>Dr. Blair commented the word “validate” is too extensive of an indication.</p> |
| 1735.5 | (c)(5) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #21</p> <p>Dr. Sakai commented on expiration date being changed to beyond use dates. Dr. Sakai commented in addition of the proposed language allows the pharmacist to utilize their professional training and judgment. Also separates the expiration date of a product versus beyond use date as defined by USP<797>. Dr. Sakai indicated the impact is that it is unclear and creating confusion.</p> <p>Dr. Sakai’s Recommendation: maintain “Expiration Date” add at the end of the sentence. Drug products <u>based upon the information in the literature or supplied by the manufacturer.</u></p> |
| 1735.5 | (c)(7) | <p>Comment #7 from Doug O’Brien, Pharm.D., and Donald Kaplan, Pharm.D., Kaiser Permanente - #10</p> <p>Kaiser comments on the following: The storage of compounded sterile drug products in the pharmacy and daily documentation of room, refrigerator, and freezer temperatures.</p> <p>Kaiser’s Comment: This language, particularly the phrase “daily documentation” could be interpreted to mean that only paper logs would be acceptable. Continuous electronic</p> |

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| | | <p>monitoring technology is at least as good as, if not superior to, manual documentation on paper logs.</p> <p>Kaiser’s Recommendation: Add language that supports the use of methods other than daily logs.</p> <p>“The storage of compounded sterile drug products in the pharmacy and daily documentation of room, refrigerator, and freezer temperatures, through the use of paper logs or continuous temperature monitoring devices with appropriate alarms/alerts.</p> <p>Kaiser’s Identified Impact: operational inefficiencies.</p> |
| 1735.5 | (c)(7) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #23</p> <p>Dr. Sakai commented on the storage of compounded sterile drug products in the pharmacy and daily documentation of room, refrigerator, and freezer temperatures. This language, particularly the phrase “daily documentation” could be interpreted to mean that only paper logs would be acceptable. Continuous electronic monitoring technology is at least as good as, if not superior to, manual documentation on paper logs. The impact is operational inefficiency.</p> <p>Dr. Sakai’s Recommendation: Add language that supports the use of methods other than daily logs.</p> <p>“The storage of compounded sterile drug products in the pharmacy and daily documentation of room, refrigerator, and freezer temperatures, through the use of paper logs or continuous temperature monitoring devices with appropriate alarms/alerts.</p> |
| 1735.5 | (c)(7) | <p>Comment #21 from Brian Warren, California Pharmacist Association (CPhA) - #5</p> <p>CPhA commented on the documentation of temperature readings.</p> <p>The proposed regulations add a new required area to the policies and procedures that compounding pharmacies must maintain. The proposed Section 1735.5 (c)(7) would require compounding pharmacies to have policies and procedures on the storage of compounded sterile drug products and daily documentation of room, refrigerator, and freezer temperatures. Additionally, the proposed regulations add to the specific recordkeeping requirements imposed on sterile compounding pharmacies. The proposed Section 1751.1(a)(4) would require daily documentation of room, refrigerator, and freezer temperatures. CPhA suggests some modifications to the changes proposed in these two sections. [Also addressed in 1751.1(a)(4)]</p> <p>CPhA suggests modifying Section 1735.5 (c)(7) by striking the word “daily” from the documentation schedule. The requirement in this paragraph is intended to require policies and procedures for recordkeeping be in place, not to impose a specific recordkeeping requirement. The specific recordkeeping requirements are included in proposed Section 1751.1(a)(4), which is the appropriate location.</p> <p>As such, we recommend the following modification to Section 1735.5 (c)(7): (7) The storage of compounded sterile drug products in the pharmacy and daily documentation</p> |

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| | | of room, refrigerator, and freezer temperatures. |
| 1735.5 | (c)(7) | <p>Oral Testimony #2 – Dan Wills, Representing Self - #6</p> <p>Mr. Wills commented on the word “daily” being added: sections 1735.5 (c)(7) and 1751.1 (b)(4). There are pharmacies that don’t compound 7 days a week. Mom and pop only compound once a week helping patients as needed. By stating daily, Mr. Wills would read this to mean the pharmacist has to come in and clean every day even when not compounded or open.</p> |
| 1735.5 | (c)(7) | <p>Oral Testimony #8 – Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California (CHCC) - #12</p> <p>Dr. Sakai commented on section 1735.5 (c)(7) language to allow for electronic monitoring. Dr. Sakai commented if it has to be daily monitoring it will take 1 FTE.</p> |
| 1735.6 | | <p>Oral Testimony #8 – Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California (CHCC) - #10</p> <p>Dr. Sakai commented on section 1735.6 that unless patient specific doses are exempt CHCC will be required to collect data requiring 2 more FTE \$144,000/annual not including benefits. To collect the certificate of purity for FDA approved drugs not required by USP standard would require 1 more FTE at \$60,000/year.</p> |
| 1751/1 | (b) (6) | <p>Comment #6 from Muno Bholat, Goorgen Boghossian, Tawny Bui, Theresa Lee-Yu, and Hiroyuki Nishi, Providence Health & Services Southern California - #14</p> <p>Providence Southern California recommends adding the following language to this section: Logs of room pressure differentials <u>when applicable</u>.</p> <p>Providence Southern California commented that facilities without cleanrooms or buffer areas within anterooms cannot have pressure differentials so a log would not be required.</p> |
| 1751 | (b)(1) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #15</p> <p>Dr. Blair commented he was unable to determine what Section 1250 of Title 24, Part 2, Chapter 12 of the California Code of Regulations is and recommended deleting it and replacing it with different verbiage as indicated:</p> <p>(1) Clean Room Cleanroom and Work Station Requirements, shall be in accordance with Section 1250 of Title 24, Part 2, Chapter 12, of the California Code of Regulations <u>occur in ISO Class 8 or better</u>.</p> |
| 1751 | (b)(4) | <p>Comment #9 from Marie Cottman, Pharm.D., Owner/PIC Pacific Compounding Pharmacy and Consultations - #7</p> <p>BOP Proposed Item: Amend 16 CCR §1751 paragraph (4) of subdivision (b) to replace “be” with “The ISO environment shall be” and “annually” is replaced with “at least six months.” “Clean room” is replaced with “cleanroom.” Additionally, “and whenever the device or</p> |

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| | | <p>cleanroom is relocated, altered, or a service to the facility is performed that would impact the cleanroom or device.” is added.</p> <p>Comment #7 (Cottman): I concur with the proposed changes, but recommend that you go father for clarification. USP <797> has specific tests that need to be done in a cleanroom used to prepare CSPs. There are several ways to certify a laminar air flow hood... not all are in compliance with USP <797> and CETA.</p> <p>Recommendation #7 (Cottman): I propose that 16 CCR §1751 Paragraph b, section 4 read: The ISO environment shall be certified at least every six months by a qualified technician familiar with the methods and procedures for certifying laminar air flow hoods and cleanroom requirements for compounded sterile products as outlined in CETA Certification Guide for Sterile Compounding Facilities. Testing will be conducted under dynamic conditions as appropriate and include at a minimum smoke studies, environmental samples for viable and non-viable particles, and total particle counts (for ISO classifications).</p> |
| 1751 | (b)(4) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #16</p> <p>Dr. Blair commented recommending modifying the language to read: (4) The ISO environment shall be certified at least every six months <u>semi-annually</u> by a qualified technician who is familiar with the methods and procedures for certifying laminar air flow hoods and cleanroom requirements, in accordance with standards adopted by the United States General Services Administration and whenever the device or cleanroom is relocated, altered, or a service to the facility is performed that would impact the cleanroom or device. Certification records must be retained for at least 3 years.</p> <p>Dr. Blair commented semi-annually allows for flexibility for unforeseen occurrences.</p> |
| 1751 | (b)(6) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #17</p> <p>Dr. Blair commented recommending modifying the language to read: (6) A sink shall be included in accordance in Section 1250 of Title 24, Part 2, of the California Code of Regulations. Sinks and drains shall not be present in an ISO Class 7 or better cleanroom, in buffer area, nor adjacent to an ISO Class 5 hood in a segregated compounding area. A sink may be located in an anteroom <u>that is ISO Class 7 or better</u>.</p> |
| 1751 | (b)(6) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #25</p> <p>Dr. Sakai commented that rather than the language “A sink shall be included. ...” it should read, “<u>A sink may be located in an anteroom.</u>” Dr. Sakai commented to utilize USP<797> definition as referenced previously.</p> <p>Dr. Sakai Recommendation: Change from “anteroom” to “ante area.”</p> |
| 1751 | (b)(6) | <p>Comment #19 from Arthur C. Whitney, R.Ph., Advantage Pharmaceuticals - #8</p> <p>Mr. Whitney comments under section 1751(b) (6), the regulations add, “Sinks and drains shall</p> |

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| | | <p>not be present in an ISO Class 7 or better cleanroom, in buffer area, nor adjacent to an ISO Class 5 hood in a segregated compounding area. A sink may be located in an anteroom.” In Mr. Whitney’s opinion, a sink should be located outside of the anteroom and never located in an anteroom because of the strong potential for mold connected. In addition, in order to reduce the potential for contamination the countertops should be cleaned with acid every evening.</p> |
| 1751.1 | | <p>Comment #9 from Marie Cottman, Pharm.D., Owner/PIC Pacific Compounding Pharmacy and Consultations - #8</p> <p>BOP Proposed Item: Amend 16 CCR §1751.1 - Existing regulation at 16 CCR specifies the title of §1751.1 to be “Sterile Injectable Recordkeeping Requirements.” As a result of SB 294, the name of §1751.1 will be changed to “Sterile Compounding Recordkeeping Requirements.”</p> <p>Recommendation #8 (Cottman): I propose that this be slightly modified to be consistent with CCR §1735.3 Recordkeeping of Compounded Drug Products. “Recordkeeping of Sterile Compounded Products.”</p> |
| 1751.1 | (a)(4) | <p>Comment #21 from Brian Warren, California Pharmacist Association (CPhA) - #6</p> <p>CPhA commented on the documentation of temperature readings.</p> <p>The proposed regulations add a new required area to the policies and procedures that compounding pharmacies must maintain. The proposed Section 1735.5 (c)(7) would require compounding pharmacies to have policies and procedures on the storage of compounded sterile drug products and daily documentation of room, refrigerator, and freezer temperatures. Additionally, the proposed regulations add to the specific recordkeeping requirements imposed on sterile compounding pharmacies. The proposed Section 1751.1(a)(4) would require daily documentation of room, refrigerator, and freezer temperatures. CPhA suggests some modifications to the changes proposed in these two sections. [Also addressed in 1735.5 (c)(7)]</p> <p>CPhA suggests a slight modification to the specific recordkeeping requirement in Section 1751.1(a)(4) to reflect the fact that some compounding pharmacies are not open daily (i.e., every calendar day). Our recommended modification would clarify that documentation is only required to be recorded on days that the pharmacy is operating. This clarification is consistent with the spirit of the proposed regulation.</p> <p>As such, we recommend the following modification to Section 1751.1(a)(4): (4) Documentation of room, refrigerator, and freezer temperatures appropriate for drug preparations consistent with the temperatures listed in section 1735.1, <u>performed on a daily basis for each day the pharmacy is operating, for:-</u> (A) Controlled room temperature. (B) Controlled cold temperature. (C) Controlled freezer temperature.</p> |
| 1751.1 | (a)(6) | <p>Comment #21 from Brian Warren, California Pharmacist Association (CPhA) - #7</p> <p>CPhA commented on logs of pressure differentials. The proposed regulations add to recordkeeping requirements imposed on sterile compounding pharmacies. Proposed Section 1751.1 (a)(6) would require sterile compounding pharmacies to have logs of room pressure differentials. To provide clarity to this requirement, CPhA suggests modifying this paragraph</p> |

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| | | <p>by naming the areas that the pressure differentials must apply to (i.e., “buffer to anteroom or cleanroom to anteroom,” and “anteroom to general”).</p> <p>Additionally, we recommend that the Board adopt a standard for the pressure differentials via regulation. For consistency with USP <797>, we recommend a minimum differential positive pressure of 0.02 inAq.</p> <p>As such, we recommend the following modification to Section 1751.1 (a)(6): (6) Logs of room pressure differentials <u>between the buffer area and the anteroom or the cleanroom and the anteroom, and between the anteroom and general pharmacy area. A minimum differential positive pressure of 0.02 inch water column (inAq) shall be maintained.</u></p> |
| 1751.1 | (b) | <p>Comment #19 from Arthur C. Whitney, R.Ph., Advantage Pharmaceuticals - #9</p> <p>Mr. Whitney comments under subsection (b), in addition to the records required by section 1735.3 and subdivision (a), “for sterile compounded drug products compounded from one or more non-sterile ingredients, the following records must be made and kept by the pharmacy:” Mr. Whitney assumes this applies now to sterile to sterile compounding and requests the board please clarify.</p> |
| 1751.1 | (b) (4) | <p>Comment #1 from Douglas Barcon, Pharm.D. – #5</p> <p>Dr. Barcon commented if humidity is added to the draft regulations, it should also be added to regulation 1751.1 Sterile Compounding Recordkeeping Requirements paragraph (b) (4) on page 10.</p> |
| 1751.1 | (b) (4) | <p>Comment #6 from Munro Bholat, Goorgen Boghossian, Tawny Bui, Theresa Lee-Yu, and Hiroyuki Nishi, Providence Health & Services Southern California - #13</p> <p>Providence Southern California recommends adding the following language to this section: Daily documentation of room, refrigerator, and freezer temperatures appropriate for drug preparations consistent with the temperatures listed in section 1735.1 for...<u>If the compounding facility uses a continuous temperature recording device, compounding personnel shall verify at least once daily that the recording device itself is functioning properly.</u></p> <p>Providence Southern California recommends adding the qualifying language from USP 797 to consistently align with the national standards. Providence refrigeration units provide continuous temperature monitoring and alert systems. Daily documentation would not provide an advantage to this 24/7 monitoring nor does it increase patient safety beyond the systems already in place.</p> |
| 1751.1 | (b) (6) | <p>Comment #3 from Romic Eskandarian, Pharm.D., Glendale Adventist Medical Center, Adventist Health – #8</p> <p>Dr. Eskandarian commented on “Logs of room pressure differentials.” This should be done per policies and procedures of each hospital. Addition of “use of electronic air pressure meters with alarms and alerts to be used.” Air displacement as means of air segregation.</p> <p>(Note: Comment referenced page 11, line 5 but comment appears to address this section.)</p> |

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| 1751.1 | (b)(4) | <p>Comment #7 from Doug O'Brien, Pharm.D., and Donald Kaplan, Pharm.D., Kaiser Permanente - #11</p> <p>Kaiser comments on the following: The storage of compounded sterile drug products in the pharmacy and daily documentation of room, refrigerator, and freezer temperatures.</p> <p>Kaiser's Comment: This language, particularly the phrase "daily documentation" could be interpreted to mean that only paper logs would be acceptable. Continuous electronic monitoring technology is at least as good as, if not superior to, manual documentation on paper logs.</p> <p>Kaiser's Recommendation: Add language that supports the use of methods other than daily logs.</p> <p>"The storage of compounded sterile drug products in the pharmacy and daily documentation of room, refrigerator, and freezer temperatures, through the use of paper logs or continuous temperature monitoring devices with appropriate alarms/alerts.</p> <p>Kaiser's Identified Impact: operational inefficiencies.</p> |
| 1751.1 | (b)(4) | <p>Comment #8 from Alan Y. Endo, Pharm.D., FCSHP, PIH Health - #5</p> <p>"The storage of compounded sterile drug products in the pharmacy and the daily documentation of room, refrigerator, and freezer temperatures, through the use of paper logs or continuous temperature monitoring devices."</p> |
| 1751.1 | (b)(4) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children's Hospital Central California - #24</p> <p>Dr. Sakai commented on the storage of compounded sterile drug products in the pharmacy and daily documentation of room, refrigerator, and freezer temperatures. This language, particularly the phrase "daily documentation" could be interpreted to mean that only paper logs would be acceptable. Continuous electronic monitoring technology is at least as good as, if not superior to, manual documentation on paper logs. The impact is operational inefficiency.</p> <p>Dr. Sakai's Recommendation: Add language that supports the use of methods other than daily logs.</p> <p>"The storage of compounded sterile drug products in the pharmacy and daily documentation of room, refrigerator, and freezer temperatures, through the use of paper logs or continuous temperature monitoring devices with appropriate alarms/alerts.</p> |
| 1751.1 | (b)(4) | <p>Oral Testimony #2 – Dan Wills, Representing Self - #7</p> <p>Mr. Wills commented on the word "daily" being added: sections 1735.5 (c)(7) and 1751.1 (b)(4). There are pharmacies that don't compound 7 days a week. Mom and pop only compound once a week helping patients as needed. By stating daily, Mr. Wills would read this to mean the pharmacist has to come in and clean every day even when not compounded or open.</p> |

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| 1751.1 | (b)(6) | <p>Comment #7 from Doug O'Brien, Pharm.D., and Donald Kaplan, Pharm.D., Kaiser Permanente - #12</p> <p>Kaiser comments on the following: Logs of pressure differentials.</p> <p>Kaiser's Comment: This statement could imply that a log of pressure differentials would be required in a cleanroom that does not have a physical separation between the buffer area and the ante area, in which airflow displacement method is used as a means of separation. This would be inappropriate. There is no requirement in USP <797> to maintain a log when airflow displacement is used in this manner.</p> <p>Kaiser's Recommendation: Change language to be consistent with the context of USP <797>: "Logs of pressure differentials for rooms providing a physical separation through the use of walls, doors, and pass-throughs. A minimum differential positive pressure of 0.02- to 0.05-inch water column is required. This can be achieved by using paper logs or continuous pressure monitoring devices with appropriate alarms/alerts."</p> <p>In addition, we propose the use of displacement airflow adopted in USP Chapter 797 be added to the proposed regulations:</p> <p>"For rooms providing a physical separation through the use of walls, doors, and pass-throughs, a minimum differential positive pressure of 0.02- to 0.05-inch water column is required. For buffer areas not physically separated from the ante-areas, the principle of displacement airflow shall be employed. This concept utilizes a low pressure differential, high airflow principle. Using displacement airflow typically requires an air velocity of 40 ft per minute or more from the buffer area across the line of demarcation into the ante-area."</p> <p>Kaiser's Identified Impact: Remodeling & construction costs: \$115 million for our organization.</p> |
| 1751.1 | (b)(6) | <p>Comment #8 from Alan Y. Endo, Pharm.D., FCSHP, PIH Health - #6</p> <p>PIH Health's Recommendation: Pressure gauge OR air velocity meter to monitor the pressure differential or airflow between the buffer area and ante-area in cleanrooms (not segregated compounding areas).</p> |
| 1751.1 | (b)(6) | <p>Comment #11 from Rita Shane, Pharm.D., FASHP, FCSHP, Cedars-Sinai Medical Center - #4</p> <p>Dr. Shane commented current draft language requires monitoring of pressure differentials. This can only be done when there is a physical barrier or separate room. USP 797 states for buffer areas not physically separated from ante-areas, displacement airflow (measured by air velocity) shall be used instead of pressure differential monitoring.</p> <p>Dr. Shane recommended modifying the language as follows to reflect USP 797: 1751.1 Sterile Compounding Recordkeeping Requirements (b) – In addition to the records required by section 1735.3 and subdivision (a) for sterile compounding drug products, the following records must be made and kept by the pharmacy: (6) Logs of room pressure differentials OR air flow velocity measurements as described in USP 797.</p> |
| 1751.1 | (b)(6) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children's Hospital Central</p> |

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| | | <p>California - #26</p> <p>Dr. Sakai commented on records requirement for logs of pressure differential. This statement could imply that a log of pressure differentials would be required in a cleanroom that does not have a physical separation between the buffer area and the ante area, in which airflow displacement method is used as a means of separation. This would be inappropriate. There is no requirement in USP <797> to maintain a log when airflow displacement is used in this manner. The impact would be operational inefficiency.</p> <p>Dr. Sakai's Recommendation: Change language to be consistent with the context of USP <797>:</p> <p>"Logs of pressure differentials for rooms providing a physical separation through the use of walls, doors, and pass-throughs. A minimum differential positive pressure of 0.02- to 0.05-inch water column is required. This can be achieved by using paper logs or continuous temperature monitoring devices with appropriate alarms/alerts."</p> |
| 1751.1 | (b)(6) | <p>Comment #22 from Michael Moné, R.Ph., J.D., FAPhA, Cardinal Health Nuclear Pharmacy Services - #4</p> <p>Cardinal Health commented on the new recordkeeping requirement for logs of room pressure differentials. In radio pharmacy practice the ante and buffer rooms are both ISO Class 8 air quality.</p> <p>Cardinal Health proposes the following language change to add to the proposed amendments to 16 CCR §1751.1: (6) Logs of room pressure differentials.</p> <p>(6) Logs of room pressure differentials. <u>For the preparation of radiopharmaceuticals where the ante and buffer rooms are both ISO Class 8 air quality or better, no logs of room pressure differentials are required.</u></p> |
| 1751.1 | (d) | <p>Comment #19 from Arthur C. Whitney, R.Ph., Advantage Pharmaceuticals - #12</p> <p>Mr. Whitney comments under subsection (b) where personnel competency validation is amended from at least every twelve months, "for sterile to sterile compounding and at least every six months for individuals compounding sterile products from non-sterile ingredients," please consider consistency by simply amending to at least months for sterile to sterile compounding and the same for non-sterile to sterile compounding. The standard of practice in sterile compounding is six months.</p> <p>Similarly, Mr. Whitney suggests that the amended verbiage in 1751.1 (d) is consistent with the above recommendation. That is, that the re-evaluation of garbing and gloving competency occurs at least every six months for personnel compounding sterile to sterile products and for personnel compounding non-sterile to sterile products.</p> |
| 1751.2 | (b) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #18</p> <p>Dr. Blair commented recommending modifying the language to read:</p> <p>(b) Name and concentrations of <u>each active pharmaceutical</u> ingredients contained in the sterile drug product.</p> |

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| 1751.3 | | <p>Comment #8 from Alan Y. Endo, Pharm.D., FCSHP, PIH Health - #7</p> <p>PIH Health’s Recommendation: Endotoxin/pyrogen testing is to be done for high-risk preparations (non-sterile to sterile) or for extended dating beyond USP 797 storage specifications.</p> |
| 1751.3 | | <p>Oral Testimony #10 – Rheta Sandoval, Pharm.D., Kaweah Delta Medical Center - #1</p> <p>Dr. Sandoval thanked the board for the opportunity and commented on section 1751.3 for policies and procedures. There is a conflict 1751.3 and 1751.4 and recommended removing the work “daily.”</p> |
| 1751.3 | (a) | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #16</p> <p>CSHP commented on the removing the word “written” along with all other references to the word “written” throughout the regulations.</p> |
| 1751.3 | (a)(4) | <p>Oral Testimony #2 – Dan Wills, Representing Self - #8</p> <p>Mr. Wills comment on section 1751.3 (a)(4) that staff not defined.</p> |
| 1751.3 | (a)(5) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #27</p> <p>Dr. Sakai commented on the added text of, <u>“Training of staff in the cleaning and maintenance of an ISO environment and segregated compounding areas.”</u></p> <p>Dr. Sakai commented on the correction of this technical term.</p> <p>Dr. Sakai’s Recommendation: Add “classified air” in between the words ISO and ENVIRONMENT.</p> |
| 1751.3 | (a)(6) | <p>Comment #7 from Doug O’Brien, Pharm.D., and Donald Kaplan, Pharm.D., Kaiser Permanente - #13</p> <p>Kaiser comments on the following: A viable and nonviable sampling plan.</p> <p>Kaiser’s Comment: The language is unclear and ambiguous.</p> <p>Kaiser’s Recommendation: “Viable and nonviable environmental airborne particle testing plan.”</p> <p>Kaiser’s Identified Impact: clarity.</p> |
| 1751.3 | (a)(7) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #28</p> <p>Dr. Sakai commented on the added text of, <u>For barrier isolators, documentation of the</u></p> |

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| | | <p><u>manufacturer’s recommended purge time.”</u></p> <p>Dr. Sakai commented on the use of a barrier isolator and the purge time is just one element of the proper use of the device and in some cases the purge time is incorporated into the mechanism and use is prevented until the process is completed. Thus documentation of the purge time is not helpful.</p> <p>Dr. Sakai’s Recommendation: For barrier isolator use, manufacturer standards shall comply with USP<797> guidelines.</p> |
| 1751.3 | (a)(8) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #19</p> <p>Dr. Blair commented recommending modifying the language to read: (8) Procedures for handling cytotoxic agents <u>if cytotoxic agents are compounded</u>.</p> |
| 1751.3 | (b) | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #17</p> <p>CSHP commented on the removing the word “written” along with all other references to the word “written” throughout the regulations.</p> |
| 1751.3 | (c) | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #18</p> <p>CSHP commented on the removing the word “written” along with all other references to the word “written” throughout the regulations.</p> |
| 1751.3 | (d) | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #19</p> <p>CSHP commented on the removing the word “written” along with all other references to the word “written” throughout the regulations.</p> |
| 1751.3 | (d) | <p>Oral Testimony #8 – Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California (CHCC) - #13</p> <p>Dr. Sakai commented on section 1751.3 (d) that sterility and endotoxin testing are not required in USP 797. If the board implement non-sterile to sterile testing, Dr. Sakai anticipates \$100/\$150 batch plus a machine costing approximately \$100,000. Dr. Sakai stated this was quite expensive.</p> |
| 1751.3 | (d) (3) (I) | <p>Comment #3 from Romic Eskandarian, Pharm.D., Glendale Adventist Medical Center, Adventist Health – #9</p> <p>Dr. Eskandarian commented on “sterility and bacterial endotoxin testing.” Dr. Eskandarian commented it only needs to be done for <u>high risk</u> preparations.</p> |
| 1751.3 | (d) (3) (I) | <p>Comment #6 from Muno Bholat, Goorgen Boghossian, Tawny Bui, Theresa Lee-Yu, and Hiroyuki Nishi, Providence Health & Services Southern California - #15</p> |

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| | | <p>Providence Southern California recommends adding the following language to this section: (I) For sterile batch compounding, written policies and procedures must be established for the use of master formulas and work sheets, appropriate documentation, and for sterility and bacterial endotoxin testing <u>for non-sterile compounding or extending beyond use dating past specifications from section 1751.8.</u></p> <p>Providence Southern California recommends amending language for sterility and bacterial endotoxin testing to be done when non-sterile ingredients are used or when extended dating beyond USP 797 storage specifications is desired (as in draft language section 1751.8).</p> |
| 1751.3 | (d) (3) (J) | <p>Comment #6 from Muno Bholat, Goorgen Boghossian, Tawny Bui, Theresa Lee-Yu, and Hiroyuki Nishi, Providence Health & Services Southern California - #16</p> <p>Providence Southern California recommends adding the following language to this section: (J) For non-sterile to sterile compounding: (i) Sterilization (ii) End-product evaluation and testing <u>including sterility and bacterial endotoxin testing.</u></p> <p>Providence Southern California commented and recommended to remove sterility and endotoxin testing verbiage from section 1751.3 (d)(3)(I) and move it to section 1751.3 (d)(3)(J) on non-sterile to sterile compounding. USP 797 guidelines require sterility and bacterial endotoxin testing only for high-risk level (i.e. non-sterile to sterile) compounding prepared in groups of more than 25 individual single-dose packages. Low-risk and medium-risk preparations would only require sterility testing if extended beyond use dating was being used per USP 797.</p> |
| 1751.3 | (d)(2) | <p>Comment #9 from Marie Cottman, Pharm.D., Owner/PIC Pacific Compounding Pharmacy and Consultations - #9</p> <p>Comment #9 (Cottman): Existing regulations at 16 CCR §1751.3 specify requirements for sterile compounding policies and procedures. Subparagraph 2 of Subdivision d. “All personnel involved must read the policies and procedures...”</p> <p>Recommendation #9 (Cottman): There should be a similar paragraph in the non-sterile compounding section of the pharmacy law, CCR §1735.5 Subdivision (b) could possibly be amended to: “All personnel involved in compounding must read the policies and procedures before compounding non-sterile drug products and at least annually ongoing. The Pharmacist In Charge is responsible for reviewing the policies and procedures at least annually.”</p> |
| 1751.3 | (d)(2)(G) | <p>Comment #19 from Arthur C. Whitney, R.Ph., Advantage Pharmaceuticals - #10</p> <p>Mr. Whitney comments under (d)(2)(G), he recommends that instead of Regular Daily cleaning and disinfection schedule for the controlled area and any equipment ... that it reads, “Regular Clean Daily <u>cleaning and disinfect daily</u> when in use or anticipation of use and disinfection schedule for of the controlled area and any equipment....”</p> |
| 1751.3 | (d)(3)(1) | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #20</p> |

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| | | <p>CSHP commented on the removing the word “written” along with all other references to the word “written” throughout the regulations.</p> |
| 1751.3 | (d)(3)(D) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #20</p> <p>Dr. Blair commented recommending modifying the language to read: (D) <u>Media fill</u> Pprocess validation.</p> |
| 1751.3 | (d)(3)(F) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #29</p> <p>Dr. Sakai commented on Class 100 cleanrooms, and barrier isolator workstations. Dr. Sakai commented this is old terminology. This is not a cleanroom so this is not applicable.</p> <p>Dr. Sakai’s Recommendation: Remove “Class 100 cleanroom.”</p> |
| 1751.3 | (d)(3)(I) | <p>Comment #7 from Doug O’Brien, Pharm.D., and Donald Kaplan, Pharm.D., Kaiser Permanente - #14</p> <p>Kaiser comments on the following: For sterile batch compounding, written policies and procedures must be established for the use of master formulas and work sheets, appropriate documentation, and for sterility and bacterial endotoxin testing.</p> <p>Kaiser’s Comment: This language appears to imply that all sterile batch compounding must have some sterility and bacterial endotoxin testing. If that is the intention, it is not reasonable or appropriate for low or medium-risk CSPs. It is not in alignment with USP <797>, which routinely requires this type of testing ONLY for high-risk compounded sterile preparations (e.g. non-sterile to sterile compounding), if the batch size is greater than or equal to 25 units.</p> <p>Kaiser’s Recommendation: This language could be acceptable if the policy could be that sterility and endotoxin testing are only required on high risk level preparations or preparations suspected to be contaminated. Otherwise move the sterility and bacterial endotoxin testing language to 1751.3(d)(J)(ii).</p> <p>Kaiser’s Identified Impact: High cost due to unnecessary testing; wasting finished drug product.</p> |
| 1751.3 | (d)(3)(I) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #30</p> <p>Dr. Sakai commented his concern is the purpose is to ensure products are being compounded safely. The greatest risk is for non-sterile to sterile product compounding. The impact is high cost due to unnecessary testing and wasting finished drug product.</p> <p>Dr. Sakai’s Recommendation: Add “for non-sterile to sterile compounding” after “endotoxin testing.”</p> <p>[Note: Dr. Sakai’s comment referenced section 1751.3(d)(I); however, the actual code section is section 1751.3(d)(3)(I).]</p> |

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| 1751.3 | (d)(3)(I) | <p>Comment #16 from BJ Bartleson, RN, MS, NEA-BC, CA Hospital Association (CHA) - #16</p> <p>CHA Comment - <i>Remove</i> “For sterile batch compounding, written policies and procedures must be established for the use of master formulas and work sheets, appropriate documentation, and for sterility and bacterial endotoxin testing, (j) Sterilization. For non-sterile to sterile compounding, (i) Sterilization, (k) end-product evaluation and testing. (ii) End-product evaluation and testing”, <i>replace</i>, “For sterile batch compounding, written policies and procedures must be established for the use of master formulas and work sheets, appropriate documentation, and for sterility and compounding or extending beyond-use dating past specifications from Section 1751.8, (j) for non-sterile to sterile compounding: (i)Sterilization, (ii) End-product evaluation and testing including sterility and bacterial endotoxin testing.” Language needs to be amended for sterility and bacterial endotoxin testing to be done when non-sterile ingredients are used or when extended dating beyond USP 797 storage specifications is desire, and align with USP 797 guidelines for high-risk level and low-risk, medium risk preparations.</p> <p>CHA requests amending language for sterility and bacterial endotoxin testing to be done when non-sterile ingredients are used or when extended dating beyond USP 797 storage specifications is desired (as in draft section 1751.8).</p> <p>CHA request to remove sterility and endotoxin testing verbiage from 1751.3(d)(3)(I) and add it to 1751.3(d)(3)(J) section on non-sterile to sterile compounding:</p> <ul style="list-style-type: none"> • USP797 guidelines require sterility and bacterial endotoxin testing only for high-risk level (i.e. non-sterile to sterile) compounding prepared in groups of more than 25 individual single-dose packages. • Low-risk and medium-risk preparations would only require sterility testing if extended beyond-use dating was being used per USP 797. |
| 1751.3 | (d)(3)(I) | <p>Comment #17 from Tim Lopez, Pharm.D., Community Regional Medical Centers (CRMC) - #5</p> <p>CRMC commented on the verbiage, “For sterile batch compounding, written policies and procedures must be established for the use of master formulas and work sheets, appropriate documentation, and for sterility and bacterial endotoxin testing.” CRMC’s concern: USP <797> does not require sterility or bacterial endotoxin testing for products that adhere to the expiration dates in the chapter. These requirements are only for high-risk, non-sterile to sterile compounding or if the facility is using a beyond use date greater than risk level standard. Section 1751.8 describes these two instances and specifies the required sterility testing.</p> <p>CRMC’s solution: Delete the following, “and for sterility and bacterial endotoxin testing.” and add, “For non-sterile to sterile and extended beyond use dating compounding:”</p> |
| 1751.3 | (d)(3)(I) | <p>Oral Testimony #7 –Doug O’Brien, Pharm.D., Kaiser Permanente (Kaiser) - #1</p> <p>Dr. O’Brien added an additional comment on section 1751.3 (d)(3)(I) the way it is written it implies that you have to do sterility and endotoxin on all sterile batches. USP 797 bases on sound science, don’t require sterility and bacteria endotoxin unless high risk (non-sterile to sterile). Dr. O’Brien stated the regulation looks like it will require testing for all batches while USP 797 doesn’t require testing for sterile to sterile. Dr. O’Brien agrees on testing from non-sterile to sterile. Process validation used for sterile to sterile compounding. Dr. O’Brien</p> |

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| | | thanked the board. |
| 1751.4 | | <p>Comment #1 from Douglas Barcon, Pharm.D. – #7</p> <p>Dr. Barcon commented in draft regulation 1751.4 Facility and Equipment Standards for Sterile Compounding [from Non-Sterile Ingredients] beginning at the bottom of page 13, the addition of "from non-sterile ingredients" has rendered this important regulation applicable only to the preparation of non-sterile-to-sterile compounding. Dr. Barcon states this section of the draft needs to address non-sterile-to-sterile and sterile-to-sterile compounding. Dr. Barcon further comments that it could be addressed in the title of the regulation and the text.</p> |
| 1751.4 | | <p>Comment #5 from Elliot Kwok, Pharm.D., Abbott’s Compounding Pharmacy, Inc. – #4</p> <p>Dr. Kwok commented Abbott’s Compounding Pharmacy’s recommendation is to amend section 1751.4. Dr. Kwok commented on “Cleaning and disinfecting...every 30 minutes during continuous compounding of individual compounded sterile drug products...” Dr. Kwok indicated the 30 minute rule is totally unsafe and impractical. Dr. Kwok has patients who require 20 to 40 vials of a product and it requires 45 to 60 minutes to prepare. Dr. Kwok indicated he cannot remove these vials in the middle of compounding to do a thorough cleaning after 30 minutes. Such a practice will increase the risk of contamination, error as well as adding to the cost of the product. Abbott’s Compounding Pharmacy, Inc. agrees with the other provisions within this regulation.</p> |
| 1751.4 | | <p>Comment #6 from Muno Bholat, Goorgen Boghossian, Tawny Bui, Theresa Lee-Yu, and Hiroyuki Nishi, Providence Health & Services Southern California - #17</p> <p>Providence Southern California recommends striking the following language to this section’s title: Facility and Equipment Standards for Sterile Compounding [from Non-Sterile Ingredients].</p> <p>Providence Southern California recommends removing “from non-sterile ingredients” from the title since the contents of the section related exclusively to non-sterile ingredients. This section pertains to all sterile compounding and the title is not clear.</p> |
| 1751.4 | | <p>Comment #7 from Doug O’Brien, Pharm.D., and Donald Kaplan, Pharm.D., Kaiser Permanente - #15</p> <p>Kaiser comments on the following: 1751.4. Facility and Equipment Standards for Sterile Injectable Compounding [from Non-Sterile Ingredients].</p> <p>Kaiser’s Comment: This title appears to state that the section below would apply when compounding from non-sterile Ingredients. The language of the section should apply to all sterile compounding activities. This looks like an error.</p> <p>Kaiser’s Recommendation: Clarify whether this section would ONLY apply to sterile compounding from non-sterile ingredients.</p> <p>Kaiser’s Identified Impact: operational inefficiency.</p> |
| 1751.4 | | Comment #8 from Alan Y. Endo, Pharm.D., FCSHP, PIH Health - #9 |

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| | | <p>Location of BSC or isolator in ISO 7 area, with min negative pressure of 0.01-inch water column and minimum of 12 air changes per hour.</p> <p>PIH Health’s Recommendation: Include timeframe (ex. 5 years) to allow facility changes to be made before enforcing.</p> <p>Proposed language:</p> <p>Location of BSC or isolator in ISO 7 area with:</p> <p>1) min negative pressure of 0.01-inch water column and minimum of 12 air changes per hour; OR</p> <p>2) air velocity measurement (minimum 40 feet per minute) between ante and buffer areas if the BSC or isolator isn’t in a dedicated negative pressure room.</p> |
| 1751.4 | | <p>Comment #11 from Rita Shane, Pharm.D., FASHP, FCSHP, Cedars-Sinai Medical Center - #1</p> <p>Dr. Shane commented the words “from Non-Sterile Ingredients” were added to “Facility and Equipment Standards” in the proposed language revision. It is unclear if this section only pertains to items made from non-sterile ingredients.</p> <p>Dr. Shane recommended removing “from Non-Sterile Ingredients” from the title of 1751.4 or clarify whether this section applies to sterile products.</p> |
| 1751.4 | | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #31</p> <p>Dr. Sakai commented on the title of section 1751.4 - Facility and Equipment Standards for Sterile Injectable Compounding [from Non-Sterile Ingredients]. This title appears to state that the section below would apply when compounding from non-sterile Ingredients. The language of the section should apply to all sterile compounding activities. This looks like an error. The impact is operational inefficiency.</p> <p>Dr. Sakai’s Recommendation: Clarify whether this section would ONLY apply to sterile compounding from non-sterile ingredients.</p> |
| 1751.4 | | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #32</p> <p>Dr. Sakai commented on the “Cleaning shall include the periodic use of sporicidal agent. Dr. Sakai indicated USP 797 does not use this.</p> <p>Dr. Sakai’s Recommendation: Remove the sentence.</p> |
| 1751.4 | | <p>Oral Testimony #8 – Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California (CHCC) - #14</p> |

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| | | Dr. Sakai commented on section 1751.4 as USP does not require sporicidal agent and recommends removing it. If it is kept, Dr. Sakai requests the board to define periodic. |
| 1751.4 | | <p>Oral Testimony #10 – Rheta Sandoval, Pharm.D., Kaweah Delta Medical Center - #2</p> <p>Dr. Sandoval thanked the board for the opportunity and commented on section 1751.3 for policies and procedures. There is a conflict 1751.3 and 1751.4 and recommended removing the work “daily.”</p> |
| 1751.4. | | <p>Oral Testimony #11 – Elliot Kwok, Pharm.D., Abbotts Compounding Pharmacy – #2</p> <p>Dr. Kwok commented on section 1751.4. It is impractical to do this every 30 minutes. Patients require over 1 hour compounding - patient 1 hour to mix his/her vials. This is more dangerous for patient. Dr. Kwok asked the board to consider change it to after each compounding or as needed.</p> |
| 1751.4 | (a) – (d) | <p>Comment #3 from Romic Eskandarian, Pharm.D., Glendale Adventist Medical Center, Adventist Health – #12</p> <p>Dr. Eskandarian commented on “cleaning the surfaces.” Dr. Eskandarian indicated according to the revisions of BOP AND USP: cleaning and disinfecting surfaces in the ISO class 5 hood shall occur frequently, including: at the beginning of each shift, before each batch, every 30 minutes during continuous compounding of individual compounded sterile drug products, after each spill, when surface contamination is known or suspected, and when switching between cytotoxic and non-cytotoxic ingredients. Dr. Eskandarian’s concern is specifically how do we interrupt compounding in order to clean surface every 30 minutes and record accordingly?</p> |
| 1751.4 | (d) (iii) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #21</p> <p>Dr. Blair commented recommending modifying the language to read: (iii) every 30 minutes during continuous compounding of individual compounded sterile drug products <u>at the end of each batch</u>;</p> <p>Dr. Blair commented manually intervening an aseptic process with cleaning poses a greater risk of cross-contamination.</p> |
| 1751.4 | (d) (vi) (f) | <p>Comment #1 from Douglas Barcon, Pharm.D. – #8</p> <p>Dr. Barcon commented in draft regulation 1751.4, paragraph (f) beginning on page 14, the regulation states "The hood shall be decontaminated when switching between cytotoxic and non-cytotoxic ingredients." Since cytotoxic products should be compounded in a compounding aseptic isolator designed for cytotoxic compounding or in a vertical airflow biological safety cabinet designed for cytotoxic agents, and both are generally in a negative pressure room relative to the surrounding ante-room, this sentence seems to conflict with paragraph (g) and with regulation 505.5.1 in the 2013 California Pharmacy Law Book. This is also repeated in regulation 1751.4, paragraph (d) (vi). Dr. Barcon stated he checked with GermFree regarding their LFGI compounding aseptic isolator. Those units can be switched between cytotoxic compounding and non-cytotoxic compounding, but it requires cleaning, modification, and recertification when making the change-it cannot be done on the fly. Dr. Barcon stated in today's environment, he would hope that facilities are not switching back and forth between</p> |

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| | | cytotoxic compounding and non-cytotoxic compounding in the same biological safety cabinet or compounding aseptic isolator. |
| 1751.4 | (e) | <p>Comment #3 from Romic Eskandarian, Pharm.D., Glendale Adventist Medical Center, Adventist Health – #10</p> <p>Dr. Eskandarian commented on “Cleaning shall include the periodic use of sporicidal agent.” Dr. Eskandarian indicated the use of sporicidal agent is not recommended by USP 797.</p> |
| 1751.4 | (e) | <p>Comment #6 from Munro Bholat, Goorgen Boghossian, Tawny Bui, Theresa Lee-Yu, and Hiroyuki Nishi, Providence Health & Services Southern California - #18</p> <p>Providence Southern California recommends striking the following language to this section: Counters, cleanable work surfaces and floors shall be cleaned and disinfected daily. Walls, ceiling, storage shelving, tables and stools are to be cleaned and disinfected monthly. Cleaning shall occur after any unanticipated event that could increase the risk of contamination. Cleaning shall include the periodic use of a sporicidal agent.</p> <p>Providence Southern California recommends striking the requirement of a sporicidal cleaning agent. USP 797 does not require the use of a sporicidal agent. USP 797 does require careful consideration of compatibilities, effectiveness, and inappropriate or toxic residues. Sporicidal agents may not be appropriate in all cases.</p> |
| 1751.4 | (e) | <p>Comment #8 from Alan Y. Endo, Pharm.D., FCSHP, PIH Health - #8</p> <p>USP 797 does not require the use of a sporicidal agent.</p> <p>PIH Health’s Recommendation: Eliminate reference to sporicidal agent.</p> |
| 1751.4 | (e) | <p>Comment #16 from BJ Bartleson, RN, MS, NEA-BC, CA Hospital Association (CHA) - #18</p> <p>CHA Comment - <i>Remove</i> “cleaning shall include the periodic use of sporicidal agent.” USP 797 does not require use of a sporicidal cleaning agent but does require careful consideration of compatibilities, effectiveness, and inappropriate or toxic residues. Sporicidal agents may not be appropriate in all cases.</p> |
| 1751.4 | (e) | <p>Comment #21 from Brian Warren, California Pharmacist Association (CPhA) - #8</p> <p>CPhA commented on sterile compounding facility cleaning requirements. The proposed regulations amend the cleaning and disinfection requirements applicable to sterile compounding facilities. The requirements specify that cleaning shall be done at certain intervals (e.g., daily). CPhA suggests modifying section 1751.4 (e) to clarify that these requirements are minimum standards and that cleaning can occur more frequently.</p> <p>As such, we recommend the following modification to Section 1751.4 (e): (e) Counters, cleanable work surfaces and floors shall be cleaned and disinfected daily. Walls, ceiling, storage shelving, tables and stools are to be cleaned and disinfected monthly. Cleaning shall occur after any unanticipated event that could increase the risk of contamination. Cleaning shall include the periodic use of a sporicidal agent. <u>The cleaning requirements specified in this subsection are intended to establish minimum standards and shall not be interpreted to prevent</u></p> |

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| | | <u>cleaning at more frequent intervals.</u> |
| 1751.4 | (f) | <p>Comment #11 from Rita Shane, Pharm.D., FASHP, FCSHP, Cedars-Sinai Medical Center - #8</p> <p>Dr. Shane commented current draft language references NSF International Standard/American National Standard for Biosafety Cabinetry – Biosafety Cabinetry: Design, Construction, Performance, and Field Certification [NSF/ANSI 49-2012], as revised July 7, 2012, related to certifying laminar air flow hoods and cleanrooms, as well as compounding aseptic containment isolators. This standard does not apply to laminar air flow hoods or compounding aseptic containment isolators.</p> <p>Dr. Shane recommended replace NSF reference with CETA Certification Guide for Sterile Compounding Facilities CAG-003-2006-11, revised January 31, 2012.</p> |
| 1751.4 | (f) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #22</p> <p>Dr. Blair commented recommending modifying the language to read:</p> <p>(f) Pharmacies preparing sterile cytotoxic agents shall do so in accordance with Section 505.12.1 of Title 24, Chapter 5, of the California Administrative Code, requiring a laminar air flow hood. The hood must be certified every six months <u>semi-annually</u> by a qualified technician who is familiar with the methods and procedures for certifying laminar air flow hoods and cleanroom requirements, in accordance with NSF International Standard/American National Standard for Biosafety Cabinetry – Biosafety Cabinetry: Design, Construction, Performance, and Field Certification [NSF/ANSI 49-2012], as revised July 7, 2012 (available from the Chair, Joint Committee on Biosafety Cabinetry c/o NSF International, P.O. Box 130140, 789 N. Dixboro Road, Ann Arbor, MI 48105, USA, phone number (734) 769-8010) or manufacturer’s specifications. The hood shall be decontaminated when switching between cytotoxic and non-cytotoxic ingredients.</p> |
| 1751.4 | (g) | <p>Comment #6 from Munro Bholat, Goorgen Boghossian, Tawny Bui, Theresa Lee-Yu, and Hiroyuki Nishi, Providence Health & Services Southern California - #19</p> <p>Providence Southern California recommends adding the following language to this section: Pharmacies preparing sterile cytotoxic agents shall use a biological safety cabinet or compounding aseptic containment isolator that provides an ISO Class 5 environment during dynamic compounding conditions which is maintained in accordance with the manufacturer’s recommendations and which is certified every six months. If a compounding aseptic containment isolator meeting the above criteria is located outside of an ISO Class 7 area, the compounding area shall maintain a minimum negative pressure of 0.01-inch water column and have a minimum of 12 air changes per hour. <u>The use of a closed-system vial-transfer device within the ISO Class 5 barrier isolator or compounding aseptic containment isolator located in a non-negative pressure room is acceptable.</u></p> <p>Providence Southern California urges the board to amend this section to allow for sterile compounding of cytotoxic agents in a non-negative pressure room when closed-system vial-transfer devices (CSTDs) are used within a BSC or a CACI in a non-negative pressure room as deemed acceptable per USP 797 guidelines (referred to as two-tiers of containment).</p> |

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| | | <p>USP 797 guidelines allow for facilities that prepare a low volume of hazardous drugs to utilize CSTDs within BSC/CACI's as two-tiers of containment in a non-negative pressure room.</p> <p>Closed systems vial-transfer devices are approved by NIOSH (National Institute for Occupational Safety and Health) guidelines. FDA created product code, ONB, specific for closed antineoplastic and hazardous drug reconstitution and transfer system devices that require data to prove a system is closed for use with hazardous drugs and reduces exposure.</p> |
| 1751.4 | (g) | <p>Comment #7 from Doug O'Brien, Pharm.D., and Donald Kaplan, Pharm.D., Kaiser Permanente - #16</p> <p>Kaiser comments on the following: Pharmacies preparing sterile cytotoxic agents shall use a biological safety cabinet or compounding aseptic containment isolator that provides an ISO Class 5 environment during dynamic compounding conditions which is maintained in accordance with the manufacturer's recommendations and which is certified every six months. If a compounding aseptic containment isolator meeting the above criteria is located outside of an ISO Class 7 area, the compounding area shall maintain a minimum negative pressure of 0.01-inch water column and have a minimum of 12 air changes per hour.</p> <p>Kaiser's Comment: The proposed language does not acknowledge that barrier isolators can provide ISO Class 5 air quality, even when located in a room that does not meet ISO 7 Class 7 conditions. USP <797> describes testing requirements to ensure barrier isolators function reliably in this manner (see USP <797> Section on "Placement of Primary Engineering Controls). This could be an important strategy for preparing CSPs with beyond use dates exceeding 12 hours in medication satellites or in inpatient pharmacies that do not have a dedicated clean room.</p> <p>Kaiser's Recommendation: Change language to support longer beyond use dating with the use of barrier isolators, provided that these primary engineering controls maintain ISO Class 5 air quality, and are tested as described in USP <797>.</p> <p>Kaiser's Identified Impact: Limits the flexibility in selecting the appropriate engineering control for sterile compounding of cytotoxic agents.</p> |
| 1751.4 | (g) | <p>Comment #11 from Rita Shane, Pharm.D., FASHP, FCSHP, Cedars-Sinai Medical Center - #2</p> <p>Dr. Shane commented if a Compounding Aseptic Containment Isolator is used, the proposed regulation requires having a separate negative pressure room and 12 air changes per hour.</p> <p>Dr. Shane recommended clarifying if this section is limited to isolators.</p> |
| 1751.4 | (g) | <p>Comment #11 from Rita Shane, Pharm.D., FASHP, FCSHP, Cedars-Sinai Medical Center - #3</p> <p>Dr. Shane commented if the intent is to require the same standards for Biologic Safety Cabinets as Compounding Aseptic Containment Isolators, hospitals that have not been recently renovated may not be able to meet these requirements by July 1, 2014, due to the need for facility changes. These changes require Office of Statewide Health Planning and Development (OSHPD) approval. Economic Impact: The cost of remodeling one sample facility to meet this requirement is significant. (Source: Facilities Management Department) 1. Venting BSC to outside: \$2 million; 2. Wind dilution/exhaust studies: \$55,000; and 3. Remaining</p> |

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| | | <p>construction (not including above) cost estimate \$3.6 million.</p> <p>Dr. Shane recommended if Biologic Safety Cabinets are to be included, hospitals may not be able to meet the July 1, 2014, deadline due to renovation required. In order to ensure that cancer patients do not have their chemotherapy treatments disrupted, consider a timeframe for meeting these requirements, i.e., 3 years.</p> |
| 1751.4 | (g) | <p>Comment #14 from Hank Rahe, BSIM, MSE, Containment Technology Group, Inc. - #2</p> <p>Mr. Rahe commented that existing regulations at section 1751.4 (g)* “the compounding area shall maintain a minimum negative pressure of 0.01-inch water column and have a minimum of 12 air changes per hour.”</p> <p>Mr. Rahe’s commented that placing an aseptic compounding isolator in a negative pressure room does not protect the compounded preparation (patient safety) or the worker in a negative pressure room. It does have a significant negative economic impact on health care cost in the State of California and should be removed from the proposed regulations.</p> <p>Creating a negative pressure environment will increase the bio burden of the area by drawing in contamination from unseal and contaminated environments such as behind walls through electrical outlets, switches and other penetrations in the walls and ceilings. Contamination could include mold and spores which are common in these areas and the root cause or the many deaths reported from compounded preparations. The contamination will settle on surfaces and could transfer to components placed into the ISO class 5 compounding environment.</p> <p>The worker in the area is not protected from either potential dermal or inhalation exposure. They would be in the area of highest concentration of the hazardous drug. The proposed change does not protect worker safety and would place the worker in a work environment of higher bioburden and potential exposure to the compounded hazardous drug.</p> <p>As an alternative for added protection during transport use secondary containment with a simple zip lock bag or carrier if the vial is dropped and broken the spill is contained. If a spill does occur the spill is a liquid and not vapor or aerosol and can be cleaned up with appropriate emergency spill kit containing proper PPE. This will result in minimal worker exposure.</p> <p>The proposed change fails to meet the criteria of a real benefit to the people of the State of California particularly where the protection of public health and safety and worker safety are involved. The proposed change does not protect the public health and has the opposite effect of increasing the potential for contaminated preparations. The proposal does add to healthcare cost because it would require construction and maintenance of a negative pressure room. Estimated cost range from \$20,000 upwards per facility. The requirement for a negative pressure room does appear in USP 797 but was added without the benefit of a comment period. USP unlike the State of California has no consideration for the cost of compliance.</p> <p>[*Note: Mr. Rahe’s comment referenced section 1751.4 (f); however, the actual code section is section 1751.4 (g)]</p> |
| 1751.4 | (g) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #33</p> |

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| | | <p>Dr. Sakai commented on the following portion of subsection (g), "...If a compounding aseptic containment isolator meeting the above criteria is located outside of an ISO Class 7 area; the compounding area shall maintain a minimum negative pressure of 0.01-inch water column and have a minimum of 12 air changes per hour." Dr. Sakai commented the proposed language does not acknowledge that barrier isolators can provide ISO Class 5 air quality, even when located in a room that does not meet ISO 7 Class 7 conditions. USP <797> describes testing requirements to ensure barrier isolators function reliably in this manner (see USP <797> Section on "Placement of Primary Engineering Controls). This could be an important strategy for preparing CSPs with beyond use dates exceeding 12 hours in medication satellites or in inpatient pharmacies that do not have a dedicated clean room. The impact would be remodeling and construction costs exceeding \$10 million.</p> <p>Dr. Sakai's Recommendation: Change language to support longer beyond use dating with the use of barrier isolators, provided that these primary engineering controls maintain ISO Class 5 air quality, and are tested as described in USP <797>.</p> |
| 1751.4 | (g) | <p>Comment #16 from BJ Bartleson, RN, MS, NEA-BC, CA Hospital Association (CHA) - #19</p> <p>CHA Comment - <i>Add to this section 1751.4(g):</i> "the use of a closed system vial-transfer device within the ISO Class 5 barrier isolator or compounding aseptic containment isolator located in a non-negative pressure room is acceptable." Need to align this section with USP 797 guidelines to allow facilities to prepare a low volume of hazardous drugs to utilize CSTD's within BSC/CACI's as two-tiers of containment in a non-negative pressure room.</p> <p>Request that this section be further amended to allow sterile compounding of cytotoxic agents in a non-negative pressure room when closed-system vial-transfer devices (CSTDs) are used within a BSC or a CACI in a non-negative pressure room as deemed acceptable per USP797 guidelines (referred to as two-tiers of containment). USP797 guidelines allow for facilities that prepare a low volume of hazardous drugs to utilize CSTDs within BSC/CACI's as two-tiers of containment in a non-negative pressure room. Closed-system vial-transfer devices are approved by NIOSH (National Institute for Occupational Safety and Health) guidelines. FDA created a product code, ONB, specific for closed antineoplastic and hazardous drug reconstitution and transfer system devices that requires data to prove a system is closed for use with hazardous drugs and reduces exposure.</p> |
| 1751.4 | (g) | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #28</p> <p>CSHP recommends adding to (g), "the use of a closed system vial-transfer device within the ISO Class 5 barrier isolator or compounding aseptic containment isolator located in a non-negative pressure room is acceptable." Need to align this section with USP 797 guidelines to allow facilities to prepare a low volume of hazardous drugs to utilize CSTD's within BSC/CACI's as two-tiers of containment in a non-negative pressure room.</p> |
| 1751.4 | (h) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #23</p> <p>Dr. Blair commented recommending modifying the language to read: (h) Viable surface and volumetric air sampling by impaction shall occur at least every six months <u>monthly</u> by a qualified technician who is familiar with the methods and procedures for</p> |

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| | | <p>surface testing and air sampling. Viable air sampling is to be performed under dynamic conditions that simulate actual production. Exceeded action levels shall prompt an immediate investigation of cleaning and compounding operations and facility management.</p> <p>Dr. Blair continued to comment that microbial monitoring should occur routinely on no less than a monthly basis. The reason is microbial growth can bloom quickly and become a problem well within a six month period.</p> |
| 1751.4 | (i) (add) | <p>Comment #1 from Douglas Barcon, Pharm.D. – #3</p> <p>Dr. Barcon commented although USP General Chapter 797 addresses facility design and environmental controls that directly impact the staff performing the sterile compounding, some parts of it may be overlooked during the dynamic operation of a cleanroom or a room housing a compounding aseptic isolator. For example, a cleanroom in one such facility was built in a section of the building that had no air conditioning and had ambient room air temperatures around 90 degrees Fahrenheit during the summer months. The temperature in the cleanroom was even warmer, making work difficult. The cleanroom was cooled with a portable air conditioner placed inside that decreased the ambient temperature to 83 degrees Fahrenheit, which was still excessive for staff garbed to compound sterile products. USP 797 includes a statement that controlled sterile compounding facilities shall provide a comfortable and well-lighted working environment, which typically includes a temperature of 20 degrees centigrade (68 degrees Fahrenheit) or cooler to maintain comfortable conditions for compounding personnel to perform flawlessly when attired in the required aseptic compounding garb. According to Dr. Barcon, this section from USP 797 should be included in the draft compounding regulations to ensure it is not overlooked during cleanroom design and certification. A good location would be adding it as paragraph (i) to regulation 1751.4 on page 15.</p> |
| 1751.4 | (i) [add] | <p>Comment #1 from Douglas Barcon, Pharm.D. – #9</p> <p>Dr. Barcon commented in section 1751.4, there is no reference to temperature monitoring. Dr. Barcon suggested perhaps a paragraph (i) could be added to address monitoring cleanroom temperature to address storage of drugs on carts within the cleanroom and personnel comfort in the cleanroom.</p> |
| 1751.4 | (i) Adding a new sub- section | <p>Comment #22 from Michael Moné, R.Ph., J.D., FAPhA, Cardinal Health Nuclear Pharmacy Services - #5</p> <p>Cardinal Health commented on the facility and equipment standards for sterile compounding (from non-sterile ingredients).</p> <p>The nature of the preparation of radiopharmaceuticals is unique. It takes an authorized licensed Nuclear Pharmacist less than 2 minutes to prepare an FDA approved vial of Tc-99m medronate for imaging skeletal metastases. It is prepared by aseptically adding sterile Tc-99m sodium pertechnetate and sterile normal saline to the kit vial (all FDA approved sterile ingredients).</p> <p>Cardinal Health proposes the following language change to add to the proposed amendments to 16 CCR §1751.4: <u>(i) When preparing radiopharmaceuticals the nuclear pharmacist shall be responsible for cleaning and disinfecting surfaces in the ISO Class 5 hood frequently, including: at the</u></p> |

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| | | <u>beginning of each shift; after each spill; when surface contamination is known or suspected and prior to each unique radiopharmaceutical preparation cycle.</u> |
| 1751.4 | Title | <p>Comment #16 from BJ Bartleson, RN, MS, NEA-BC, CA Hospital Association (CHA) - #17</p> <p>CHA Comment - <i>Remove</i> “from Non-sterile ingredients.” Remove this since the contents do not only pertain to non-sterile ingredients. The title is unclear since it pertains to all sterile compounding.</p> |
| 1751.5 | | <p>Comment #5 from Elliot Kwok, Pharm.D., Abbott’s Compounding Pharmacy, Inc. – #5</p> <p>Dr. Kwok commented Abbott’s Compounding Pharmacy’s recommendation is to amend section 1751.5. Dr. Kwok commented on “gloves are to be routinely disinfected with sterile 70 percent isopropyl alcohol after contact with non-sterile objects.” Dr. Kwok asks the board clarify “routinely” as it is unclear if it means “every time” or “as necessary”? If it means “every time”, Dr. Kwok commented it is impractical because most exterior of vials, syringes and bottles are non-sterile. Even the exterior of the 70 percent isopropyl alcohol bottle is non-sterile.</p> |
| 1751.5 | | <p>Oral Testimony #6 – Gary Cacciatore and Richard Green, R.Ph., BCNP, Cardinal Health, Inc. - #3</p> <p>Mr. Green commented on section 1751.5 requiring sterility testing sample at 3 stages: beginning, middle, and end. Any patient who has breast cancer and needs bone scan, take raw drug and add it to the drug vial and will take two minutes but will now have to and add to drug vial takes 2 minutes but have to do 14 days sterility and testing for beginning, middle and end.</p> |
| 1751.5 | | <p>Oral Testimony #9 – Jeffrey Nehira, Pharm.D., Dignity Health – Mercy General Hospital - #4</p> <p>Dr. Nehira commented on section 1751.5 requirements for sterile gloves to have gloves tested for alcohol compatibility. Dr. Nehira suggests writing this out.</p> |
| 1751.5 | | <p>Oral Testimony #11 – Elliot Kwok, Pharm.D., Abbotts Compounding Pharmacy – #3</p> <p>Dr. Kwok commented on section 1751.5. After contact with non-sterile objects, wrapping on needle is non-sterile. Dr. Kwok stated you have to be careful on how to mix product and how sterile airflow rather than disinfect everything.</p> |
| 1751.5 | (a)(1) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #34</p> <p>Dr. Sakai commented on cleanroom garb consisting of a non-shedding gown, head cover, face mask, and shoe covers must be worn inside the designated area at all times. Dr. Sakai commented this section describes sterile compounding (not compounding hazardous drugs). Face masks are not necessary for non-hazardous sterile compounding.</p> <p>Dr. Sakai’s Recommendation is to use this language instead: “Cleanroom garb consisting of a non-shedding gown, head cover, and shoe covers must be worn inside the designated area at all times.”</p> |

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| 1751.5 | (a)(3) | <p>Comment #14 from Hank Rahe, BSIM, MSE, Containment Technology Group, Inc. - #4</p> <p>Mr. Rahe commented to add the word “sterile” after percent and before isopropyl in the last sentence.</p> |
| 1751.5 | (a)(3) | <p>Comment #21 from Brian Warren, California Pharmacist Association (CPhA) - #9</p> <p>CPhA commented on the use of alcohol antiseptic. The proposed regulations amend existing standards for cleanroom garb, cleansing, and personal protective equipment in Section 1751.5. We suggest a slight modification to paragraph (3) of subsection (a). That paragraph contains a standard that “cleansing with a persistently active alcohol-based product followed by the donning of sterile gloves must occur within the buffer area, not prior to entering.” We suggest adding the word “waterless” to the term “alcohol-based product.” The word “cleansing” could be interpreted to mean cleansing using water, and addition of the word “waterless” will help avoid any confusion regarding the cleansing process.</p> <p>As such, we recommend the following modification to Section 1751.5 (a) (3):</p> <p>(3) Personnel shall don personal protective equipment in an order that proceeds from those activities considered the dirtiest to those considered the cleanest. The donning of shoe covers or dedicated shoes, head and facial hair covers and face masks shall be followed by the washing of hands and forearms up to the elbows for 30 seconds with soap and water and then the donning of a non-shedding gown. Cleansing with a persistently active <u>waterless</u> alcohol-based product followed by the donning of sterile gloves must occur within the buffer area, not prior to entering. Gloves are to be routinely disinfected with sterile 70 percent isopropyl alcohol after contact with non-sterile objects.</p> |
| 1751.5 | (a)(3) | <p>Comment #23 from William Jones, R.Ph., Central Admixture Pharmacy Services, Inc. (CAPS) - #3</p> <p>CAPS commented on sterile compounding attire. The proposed regulation lists a specific order of gowning. This order of gowning would not be appropriate in all pharmacy models. CAPS continuously modifies and enhances gowning procedures based on FDA input. Our current gowning procedure, although compliant with FDA inspectional observations, would not meet the letter of the proposed CA 1751 standards. CAPS recommends allowing for an alternate order of gowning if it is shown to be equivalent or superior to the proposed gowning method.</p> <p>CAPS proposed language for 1751.5 (a) (3):</p> <p>(a) When compounding sterile drug products from one or more non-sterile ingredients the following standards must be met:</p> <p>(1) Cleanroom garb consisting of a low non-shedding coverall gown, head cover, face mask, and shoe covers must be worn inside the designated area at all times.</p> <p>(2) Cleanroom garb must be donned and removed in an anteroom or outside the designated area in a designated area immediately outside the segregated compounding area.</p> <p>(3) Personnel shall don personal protective equipment in an order that proceeds from those activities considered the dirtiest to those considered the cleanest. <u>The following order is to be followed unless the pharmacy has a procedure in place that documents a method equivalent to or is superior to the method described here.</u> The donning of shoe covers or dedicated shoes, head and facial hair covers and face masks shall be followed by the washing of hands and forearms up to the elbows for 30 seconds with soap and water and then the donning of a non-</p> |

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| | | shedding gown. Cleansing with a persistently active alcohol-based product followed by the donning of sterile gloves must occur within the buffer area, not prior to entering. Gloves are to be routinely disinfected with sterile 70 percent isopropyl alcohol after contact with non-sterile objects. |
| 1751.5 | (a)(4) | <p>Comment #22 from Michael Moné, R.Ph., J.D., FAPhA, Cardinal Health Nuclear Pharmacy Services - #6</p> <p>Cardinal Health commented on the proposed changes have removed the pharmacist's ability granted under USP 36 <797> to validate alternate technologies. USP 36 <797> provides for "The use of technologies, techniques, materials, and procedures other than those described in this chapter are not prohibited so long as they have been proven to be equivalent or superior with statistical significance to those described herein." This might include the non-use of shoe covers, head & facial covers face masks, gown, sterile gloves, sterile isopropyl alcohol. Where such alternate technologies have been demonstrated to be equivalent or superior to the requirements in USP <797> the USP authors have contemplated and in fact approved their use. Additionally, the Board's proposal when applied to an authorized licensed nuclear pharmacist would place that nuclear pharmacist in conflict with requirements of the Nuclear Regulatory Commission and the Radiologic Health Branch of the California Department of Health who require nuclear pharmacists to wear ring dosimeters to monitor the amount of extremity exposure received by occupational workers.</p> <p>Cardinal Health proposes the following language change to add to the proposed amendments to 16 CCR §1751.5: 1751.5. Sterile Compounding Attire. (4) With respect to the preparation of radio pharmaceuticals, an authorized licensed nuclear pharmacist may employ the use of technologies, techniques, materials, and procedures other than those described in USP 36 <797> that are not prohibited so long as they have been proven to be equivalent or superior with statistical significance to those described therein. [Note: The addition of (4) would require the renumbering of following sections in 1751.5]</p> <p>(4 <u>5</u>) Hand, finger, or wrist jewelry. If jewelry cannot be removed then it must be thoroughly cleaned and covered with a sterile glove. <u>This section does not apply to ring dosimeters.</u></p> |
| 1751.5 | (a)(5) | <p>Comment #14 from Hank Rahe, BSIM, MSE, Containment Technology Group, Inc. - #5</p> <p>Mr. Rahe commented to add the word “sterile” after with and before isopropyl.</p> |
| 1751.5 | (a)(6) | <p>Comment #13 from Dennis Lau, Pharmacist - #1</p> <p>Dr. Lau comments that the new Section 1751.5(a)(6) states: Individuals experiencing rashes, sunburn, weeping sores, conjunctivitis, active respiratory infections, or those wearing cosmetics shall be excluded from working in ISO Class 5 and ISO Class 7 compounding areas until their conditions are remedied. Dr. Lau queries the board to consider specifying the cosmetic types or formulations not allowed (shedding of flakes and particles) in ISO Class 5 and ISO Class 7 compounding areas similar to the FDA cosmetic product categories?</p> <p>Dr. Lau comments he is pursuing this specific issue on behalf of the many women in the pharmacy profession and the unpredictability of staffing levels inherent in hospital work.</p> |

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| | | <p>FDA Product category code = 03 [Eye Makeup Preparations] a.) Eyebrow Pencil; b.) Eyeliner; c.) Eye Shadow; d.) Eye Lotion; e.) Eye Makeup Remover; f.) Mascara; and g.) Other Eye Makeup Preparations</p> <p>FDA Product category code = 07 [Makeup Preparations (not eye)] a.) Blushers (all types); b.) Face Powders; c.) Foundations; d.) Leg and Body Paints; e.) Lipstick; f.) Makeup Bases; g.) Rouges; h.) Makeup Fixatives; and i.) Other Makeup Preparations</p> |
| 1751.5 | (a)(6) | <p>Comment #13 from Dennis Lau, Pharmacist - #2</p> <p>Dr. Lau queries the board to see if the board would consider surgery face shields with cosmetics in the ISO Class 5 and 7 compounding areas?</p> <p>Dr. Lau comments he is pursuing this specific issue on behalf of the many women in the pharmacy profession and the unpredictability of staffing levels inherent in hospital work.</p> |
| 1751.5 | (a)(6) | <p>Comment #13 from Dennis Lau, Pharmacist - #3</p> <p>Dr. Lau queries the board to see if the board would consider cosmetic “sealers” used by professional makeup artists as a possible way to prevent shedding of “flakes and particles.” Dr. Lau comments that at any given time, any pharmacist or pharmacy technician on staff in a hospital pharmacy may be called upon to compound a sterile IV, such as in an emergency or unexpected staffing shortage.</p> <p>Dr. Lau comments he is pursuing this specific issue on behalf of the many women in the pharmacy profession and the unpredictability of staffing levels inherent in hospital work.</p> |
| 1751.5 | (a)(6) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #35</p> <p>Dr. Sakai commented on the requirement in (a)(6) that individuals experiencing rashes, sunburn, weeping sores, conjunctivitis, active respiratory infections....” Dr. Sakai commented the goal is to prevent the flaking of skin which could result in contamination of the compounded product. Covering a mild sunburn (which often does not flake) as it heals will prevent the sloughing of skin to the ambient air minimizing the risk of contamination. Inclusion of this section would result in the need to bring in additional staff to replace those employees with mild sunburns.</p> <p>Dr. Sakai’s Recommendation: Add the word “exposed” before sunburn.</p> |
| 1751.5 | (c) | <p>Comment #21 from Brian Warren, California Pharmacist Association (CPhA) - #10</p> <p>CPhA commented barrier isolator hoods are considered to be a self-contained cleanroom and as such usually do not have preparation and anterooms consistent with cleanrooms. Given the unique nature and prolific use in hospital pharmacies of barrier isolator hoods, we believe the regulations should clarify differences in cleaning and garbing.</p> <p>As such, we recommend the following modification to Section 1751.5 to add subsection (c): (c) The requirements of subdivision (a) and (b) shall not apply if a barrier isolator is used to</p> |

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| | | <p><u>compound sterile products from one or more non-sterile ingredients, except when cleaning the barrier isolator or at any time the barrier isolator hood is open and as such breaks positive air flow rendering an ISO 5 environment.</u></p> |
| 1751.5 | (e) | <p>Comment #22 from Michael Moné, R.Ph., J.D., FAPhA, Cardinal Health Nuclear Pharmacy Services - #7</p> <p>Cardinal Health commented in the preparation of radiopharmaceuticals where all drugs sourced and prepared are FDA approved commercially available sterile drugs, the performance of sterility and pyrogen testing is performed by the manufacturer as a component of its cGMP process. Applying this requirement to the preparation of radiopharmaceuticals from FDA - approved commercially available pharmaceuticals creates an impractical situation with the dispensing of a radiopharmaceutical: the sterility test takes 14 days to complete, whereas the radiopharmaceutical has a half-life of 6 hours and a beyond-use date of 12 hours. For example: it takes less than 2 minutes to prepare an FDA approved vial of Tc-99m medronate for imaging skeletal metastases. It is prepared by aseptically adding sterile Tc-99m sodium pertechnetate and sterile normal saline to the kit vial (all FDA approved sterile ingredients).</p> <p>Cardinal Health proposes the following language change to add to the proposed amendments to 16 CCR §1751.5:</p> <p>(e) Batch-produced sterile drug products compounded from one or more non-sterile ingredients shall be subject to documented end product testing for sterility in accordance with methodologies and processes found in Chapter 71 of the United States Pharmacopeia - National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), and pyrogens in accordance with the methods of Chapters 85 and 151 of the United States Pharmacopeia - National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), hereby incorporated by reference, and shall be quarantined until the end product testing confirms sterility and acceptable levels of pyrogens before dispensing. Products submitted for sterility testing are to include preparations from the beginning, middle, and end of each batch. This requirement of end product testing confirming sterility and acceptable levels of pyrogens prior to dispensing shall apply regardless of any sterility or pyrogen testing that may have been conducted on any ingredient or combination of ingredients that were previously non-sterile. <u>Nuclear pharmacies that prepare and dispense only FDA-approved commercially available pharmaceuticals shall perform quarterly random representative retrospective sterility testing.</u></p> |
| 1751.6 | (e) | <p>Oral Testimony #8 – Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California (CHCC) - #15</p> <p>Dr. Sakai commented on section 1751.6 (e) and agrees with mimic the complexity of validation but this would be a problem as they make stock bank that they use to pull out and use to fill syringes. If validation is required, the cost to mimic validations is expensive. Dr. Sakai stated the problem if have to validate the process, cost to mimic validation expensive eliminate the word volume. CHCC has 80 individuals expect cost \$10,000-12,000/annual.</p> |
| 1751.6 | (e) (1) (J) (2) | <p>Comment #1 from Douglas Barcon, Pharm.D. – #10</p> <p>Dr. Barcon commented on section 1751.6 entitled Training of Sterile Compounding Staff, Patient, and Caregiver paragraph (1)(J)(2) on page 18 of the draft, that states, "Each person who handles compounded sterile drug products ... ," that this is not clear. Dr. Barcon further</p> |

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| | | commented a delivery driver in a long term care pharmacy or delivery staff in other environments would not be expected to be trained on aseptic technique. Delivery staff, however, do need training on the proper storage of compounded sterile products in transit between the pharmacy and the final destination. Policies and procedures should address this and require documentation of training. Dr. Barcon stated he believes this paragraph in 1751.6 needs clarification, and perhaps delivery should be addressed somewhere in the draft regulation. |
| 1751.6 | (e) (2) | <p>Comment #6 from Muno Bholat, Goorgen Boghossian, Tawny Bui, Theresa Lee-Yu, and Hiroyuki Nishi, Providence Health & Services Southern California - #20</p> <p>Providence Southern California recommends striking the following language to this section: Each person who handles <u>prepares</u> compounded sterile drug products must successfully complete practical skills training in aseptic technique and aseptic area practices. Evaluation must include written testing and a written protocol of periodic routine performance checks involving adherence to aseptic area policies and procedures. Each person’s proficiency and continuing training needs must be reassessed every 12 months. Results of these assessments must be documented and retained in the pharmacy for three years.</p> <p>Providence Southern California recommends changing the words from “handles” to “prepares.” Personnel who do not perform compounding but transport or handle compounded sterile drug products for restocking, transportation, or dispensing should not be required to undergo aseptic technique training.</p> |
| 1751.6 | (e)(1) | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #21</p> <p>CSHP commented on the removing the word “written” along with all other references to the word “written” throughout the regulations.</p> |
| 1751.6 | (e)(1)(E) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #36</p> <p>Dr. Sakai commented on Aseptic preparation procedures using media fill tests which are as complicated as the most complex manipulations performed by staff and which contain the same amount of volume transferred during the compounding process. Dr. Sakai commented the volume transfers may vary in amount depending upon the final amount to be produced. If the Board wants to mimic every variation in volume possible during the compounding process, the number can be infinite and is not practical.</p> <p>Dr. Sakai’s Recommendation: Period after staff and eliminate the rest.</p> |
| 1751.6 | (e)(1)(J) (2) | <p>Comment #7 from Doug O’Brien, Pharm.D., and Donald Kaplan, Pharm.D., Kaiser Permanente - #17</p> <p>Kaiser comments on the following: Each person who handles compounded sterile drug products must successfully complete practical skills training in aseptic technique and aseptic area practices. Evaluation must include written testing and a written protocol of periodic routine performance checks involving adherence to aseptic area policies and procedures...</p> |

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| | | <p>Kaiser’s Comment: This language is unclear. It could mean that a person who merely delivers compounded sterile drug products to patient care areas would be required to complete specific training and testing.</p> <p>Kaiser’s Recommendation: Use this language instead: “Each person who compounds sterile drug products must successfully complete practical skills training...”</p> <p>Kaiser’s Identified Impact: Clarification.</p> |
| 1751.6 | (e)(2) | <p>Comment #9 from Marie Cottman, Pharm.D., Owner/PIC Pacific Compounding Pharmacy and Consultations - #10</p> <p>BOP Proposed Item: Amend 16 CCR §1751.6 paragraph (2) of subdivision (e) to add additional information to the requirement outlining who of the compounding personnel must complete practical skills training in aseptic technique and aseptic area practices. Specifically, the board’s proposal strikes “assigned to the controlled area” and replaces with “who handles compounded sterile drug products” so that the paragraph will read as “Each person who handles compounded sterile drug products must successfully complete practical skills training in aseptic technique and aseptic area practices...”</p> <p>Comment #10 (Cottman): “Handles” is a very broad term which may be interpreted as “touching” the product. I do not believe that it is the intent of this proposal that the retail cashier or the hospital pharmacy clerk who is “handling” the product when it is dispensed to the patient or the floor is required to be trained and tested on the methods of aseptic techniques or aseptic area practices.</p> <p>Recommendation #10 (Cottman): Change the term “handles” to “participates in the preparation of”</p> |
| 1751.6 | (e)(2) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #24</p> <p>Dr. Blair commented recommending modifying the language to read: (2) Each person who handles compounded sterile drug products <u>performs aseptic processing</u> must successfully complete practical skills training in aseptic technique and aseptic area practices. Evaluation must include written testing and a written protocol of periodic routine performance checks involving adherence to aseptic area policies and procedures. Each person’s proficiency and continuing training needs must be reassessed every 12 months <u>annually</u>. Results of these assessments must be documented and retained in the pharmacy for three years.</p> |
| 1751.6 | (e)(2) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #37</p> <p>Dr. Sakai commented on the added verbiage “who handles compounded sterile drug products” that the term “handles” is too broad of a term in that other individuals “handle” the drug products such as nurses, couriers, respiratory care practitioners, physicians, nurse practitioners, Physician Assistants. Most, if not all, are not involved in the preparations of these products. The impact is training of everyone who “handles” these compounded medications would be an astronomical expense.</p> |

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| | | Dr. Sakai's Recommendation: leave verbiage as is. |
| 1751.6 | (e)(2) | <p>Comment #16 from BJ Bartleson, RN, MS, NEA-BC, CA Hospital Association (CHA) - #20</p> <p>CHA Comment - <i>Remove</i> "handles" and replace with "prepares." Personnel who do not perform compounding but transport or handle compounded sterile drug products for restocking, transportation or dispensing should not be required to undergo aseptic technique training.</p> |
| 1751.6 | (e)(2) | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #22</p> <p>CSHP commented on the removing the word "written" along with all other references to the word "written" throughout the regulations.</p> |
| 1751.6 | (e)(2) | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #29</p> <p>CSHP recommends removing "handles" and replace with "prepares." Personnel who do not perform compounding but transport or handle compounded sterile drug products for restocking, transportation or dispensing should not be required to undergo aseptic technique training.</p> <p>(Note: CSHP's comment referenced section 1751.6 9e)(2); however, the actual code section is section 1751.6 (e)(2).]</p> |
| 1751.7 | | <p>Comment #5 from Elliot Kwok, Pharm.D., Abbott's Compounding Pharmacy, Inc. – #6</p> <p>Dr. Kwok commented Abbott's Compounding Pharmacy's recommendation is to amend section 1751.7. Dr. Kwok commented on "Requires samples for sterility testing to be taken at the beginning, middle and end of the compounding process." Dr. Kwok asks the board clarify what volume is required for all three samples. Additionally, Dr. Kwok requests the board clarify if all three samples are to be put in a single dose vial or three different vials for sterility testing. Dr. Kwok stated we need to test the end product dispensed to patients not testing the process. Dr. Kwok stated testing a process is for complicated manufacturing and not necessarily applicable for a simple drug compound.</p> |
| 1751.7 | | <p>Oral Testimony #6 – Gary Cacciatore and Richard Green, R.Ph., BCNP, Cardinal Health, Inc. - #2</p> <p>Mr. Green commented on section 1751.7 states that after you compound a batch you have to do a 14 day sterility and pyrogen testing before distributing to a patient. Mr. Green stated that statement negates nuclear pharmacy. Californians will not have access to nuclear pharmacy as the drugs have 9 minute half-life, 6 hour half-life, and 13 hours half-life. Ethical nuclear pharmacies use FDA approved. In nuclear, prescriptions have to be prepared at time of use. Mr. Green acknowledges use of term "compounding" but prefers the term "preparation." Mr. Green stated if there is no call out for nuclear, the regulations will shut down nuclear pharmacy in California.</p> |
| 1751.7 | | <p>Oral Testimony #11 – Elliot Kwok, Pharm.D., Abbotts Compounding Pharmacy – #4</p> |

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| | | <p>Dr. Kwok commented on section 1751.7 and inquired what kind of volume is desired. Dr. Kwok stated the cost of testing is \$150 plus transportation which would mean \$178 passed to the patient.</p> |
| 1751.7 | (a) (3) | <p>Comment #6 from Muno Bholat, Goorgen Boghossian, Tawny Bui, Theresa Lee-Yu, and Hiroyuki Nishi, Providence Health & Services Southern California - #21</p> <p>Providence Southern California recommends striking the following language to this section: Written justification <u>Documentation justifying</u> of the chosen beyond use dates for compounded sterile drug products.</p> <p>Providence Southern California recommends amending the language to remove the word “written” while still requiring documentation to justify appropriate beyond use dating.</p> |
| 1751.7 | (a)(3) | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #23</p> <p>CSHP commented on the removing the word “written” along with all other references to the word “written” throughout the regulations.</p> |
| 1751.7 | (b) | <p>Comment #1 from Douglas Barcon, Pharm.D. – #11</p> <p>Dr. Barcon commented on section 1751.7 entitled Sterile Compounding Quality Assurance and Process that the validation paragraph (b) on page 19 of the draft mentions, "validation process on technique." Dr. Barcon stated that he believes the intent was to address "validation process on aseptic technique," but it is not clear.</p> |
| 1751.7 | (b) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #</p> <p>Dr. Blair commented recommending modifying the language to read: (b) Each individual involved in the <u>aseptic</u> preparation of sterile drug products must first successfully complete a validation <u>qualification</u> process on technique before being allowed to prepare sterile drug products. The validation <u>qualification</u> process shall be carried out in the same manner as normal production, except that an appropriate microbiological growth medium is used in place of the actual product used during sterile preparation. The validation <u>qualification</u> process shall be as complicated as the most complex manipulations performed by staff and which contain the same amount of volume transferred during the compounding process. The same personnel, procedures, equipment, and materials must be involved. Completed medium samples must be incubated in a manner consistent with the manufacturer’s recommendations and demonstrated to promote growth. If microbial growth is detected, then the sterile preparation process must be evaluated, corrective action taken, and the validation <u>qualification</u> process repeated. Personnel competency must be revalidated <u>requelified</u> at least every twelve months <u>annually</u> for sterile to sterile compounding and at least every six months <u>semi-annually</u> for individuals compounding sterile products from non-sterile ingredients, whenever the quality assurance program yields an unacceptable result, when the compounding process changes, equipment used in the compounding of sterile drug products is repaired or replaced, the facility is modified in a manner that affects airflow or traffic patterns, or whenever improper aseptic techniques are observed. Revalidation <u>Requelification</u> must be documented.</p> |

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| 1751.7 | (b) | <p>Comment #14 from Hank Rahe, BSIM, MSE, Containment Technology Group, Inc. - #6</p> <p>Mr. Rahe commented the word “medium” is used in several places in the section. Mr. Rahe thinks the correct word is “media” and should be corrected.</p> |
| 1751.7 | (b) | <p>Comment #19 from Arthur C. Whitney, R.Ph., Advantage Pharmaceuticals - #11</p> <p>Mr. Whitney comments under subsection (b) where personnel competency validation is amended from at least every twelve months, “for sterile to sterile compounding and at least every six months for individuals compounding sterile products from non-sterile ingredients,” please consider consistency by simply amending to at least months for sterile to sterile compounding and the same for non-sterile to sterile compounding. The standard of practice in sterile compounding is six months.</p> <p>Similarly, Mr. Whitney suggests that the amended verbiage in 1751.1 (d) is consistent with the above recommendation. That is, that the re-evaluation of garbing and gloving competency occurs at least every six months for personnel compounding sterile to sterile products and for personnel compounding non-sterile to sterile products.</p> |
| 1751.7 | (b) | <p>Oral Testimony #8 – Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California (CHCC) - #16</p> <p>Dr. Sakai commented on section 1751.7 (b) that states there is a national accepted validation process. Dr. Sakai is not aware of validation process for non-injectable. If aware please include.</p> |
| 1751.7 | (c) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #38</p> <p>Dr. Sakai commented on the proposed addition of subsection (c): All compounding personnel must successfully complete an initial competency evaluation. In addition, immediately following the hand hygiene and garbing procedure, all compounding personnel must successfully complete a gloved fingertip sampling procedure (zero colony forming units) at least three times before initially being allowed to compound sterile drug products. Dr. Sakai commented repeated exposures yield a 3 colony count versus USP797. Initial per USP797 is zero.</p> <p>Dr. Sakai’s Recommendation: Add the word “initial” before hand hygiene.</p> |
| 1751.7 | (d) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #27</p> <p>Dr. Blair commented recommending modifying the language to read: (d) Re-evaluation of garbing and gloving competency shall occur at least annually <u>semi-annually</u> for personnel compounding products made from sterile ingredients and at least every six months for personnel compounding products from non-sterile ingredients.</p> |
| 1751.7 | (e) | <p>Comment #1 from Douglas Barcon, Pharm.D. – #12</p> |

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| | | <p>Dr. Barcon commented on section 1751.7 paragraph (e) on page 20 that the regulation addresses tests for sterility and presence of pyrogens per USP General Chapters 71, 85, and 151 for batch-produced sterile products. Pyrogen testing as per USP General Chapter 51 specifies the rabbit pyrogen test, which poses problems if used. Dr. Barcon further stated it is quite expensive and would be beyond the capacity of a compounding pharmacy that is not compounding large batch quantities of non-sterile-to-sterile products where costs could be amortized over many doses. Such a batch size could fall under manufacturing and not pharmacy. Additionally, some medications cannot be tested on rabbits because they are harmful to the rabbit. Further, the rabbit pyrogen test is not 100% accurate (some pyrogens are only pyrogens in humans) and it does cause pain and suffering to the rabbits. Dr. Barcon stated an alternate test used for presence of pyrogens is the Bacterial Endotoxin Test, as discussed in USP General Chapter 85, even though endotoxin appears not to be categorized as a pyrogen in USP.</p> <p>Dr. Barcon further commented Bacterial Endotoxin Testing using Limulus Amebocyte Lysate (LAL) clotting is affordable and has replaced rabbit pyrogen testing in many instances, but it generally only responds to gram-negative bacteria, which is the source of endotoxin. The LAL test can also respond to fungal glucans. Non-endotoxin pyrogens, such as gram-positive organisms and fungal organisms, are a problem, and have been reported in published papers. Depending on the capabilities of the sterile compounding pharmacy and whether it is in a hospital or not, these testing procedures may need to be outsourced.</p> <p>Dr. Barcon continued to comment that Associates of Cape Cod, Inc., a company in Massachusetts, specializes in products to test for endotoxin and glucans, using the LAL test. Their Pyros Kinetix Flex product is capable of using LAL with and without an endotoxin blocker to test for the quantified presence of bacterial endotoxin and fungal glucans as pyrogens. Dr. Barcon suggested such a product could be used to track a source of pyrogens by separating fungal from bacterial. QI Medical, in Nevada City, California, is another source for sterility, pyrogen, and aseptic technique validation products.</p> <p>Dr. Barcon added there is also a new pyrogen test that is sensitive to all of these pyrogens. The monocyte activation test (MAT) uses whole human blood, which will be an issue. It is also an expensive test (around \$500) per test sample and uses an ELISA antibody response. It is not a standalone process and would likely require sending samples to an outside lab. Information on the MAT test can be found in the following journal article: Hasiwa N, Daneshian M, Bruegger P, et al. Evidence for the detection of non-endotoxin pyrogens by the whole blood monocyte activation test. AL TEX. 2013; 30(2):169-208. A kit product for the MAT test is available in the U.S., but it is expensive, even when it does not include the lab equipment.</p> <p>Dr. Barcon continued to comment dehydrogenation of glassware or glass vials by heating per USP 151 is affordable, but validating such depyrogenation would be an expensive process if rabbits were used. Of course, endotoxin testing is an alternative, as stated. Dr. Barcon noted that USP 797 also states that sterility tests for autoclaved high-risk CSPs are not required unless they are prepared in batches of more than 25 units. The current draft regulations [1751.7 (3)(e)] on page 20 do not specify the type of sterilization or batch size, which prevents pharmacies from compounding any size batch of non-sterile to sterile products without performing sterility testing. If the Board of Pharmacy was to specify a limit to the batch size of non-sterile to sterile autoclaved CSPs where sterility testing is not required, it would allow pharmacies to do small batches affordably and more timely. Dr. Barcon indicated the Board would have to define a small batch. If there is still concern about the safety of not doing a sterility test on a small</p> |

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| | | <p>batch, the CSP solution (not suspension) could be filtered through a 0.22 micron or smaller pyrogen-free filter into the final containers prior to autoclaving.</p> <p>Dr. Barcon further commented in section 751.7 paragraph (e), on page 20, the quarantine period specifies sterility and pyrogen levels, but does not address endotoxin levels, which are specified in USP monographs and in General Chapter 85. This is confusing because the text of USP 797 intimates that pyrogens and endotoxin are considered one and the same, and in some sense, they are. Dr. Barcon reiterated as he stated earlier, USP 151 addresses the pyrogen test. Levels of pyrogens themselves are not measured. It is the number of febrile responses to the product injected into rabbits that is measured to be within an acceptable level. In the section on depyrogenation by dry heat, USP 797 states, "The effectiveness of the dry heat depyrogenation cycle shall be verified using endotoxin challenge vials (ECVs). The bacterial endotoxin test should be performed on the ECV s to verify that the cycle is capable of achieving a 3-log reduction in endotoxin (see <i>Sterilization and Sterility Assurance of Compendial Articles</i> (1211) and <i>Bacterial Endotoxins Test</i> (85)." USP 151 addresses all pyrogens regardless of the type. Any changes to this paragraph of the draft regulation should include the addition of endotoxin levels. Since filtration is another form of sterilization, Dr. Barcon suggested perhaps adding a sentence addressing filtration of the final product through a bacterial-retentive sterile pyrogen-free 0.22 micron or smaller pore filter and validating the integrity of the filter with a bubble-point test after the transfer should be added to this regulation and other regulations addressing non-sterile-to-sterile compounding for terminal sterilization of those products. Dr. Barcon continued commenting likewise, USP 797 specifies that CSP <i>solutions</i> sterilized by autoclaving are filtered through a sterile pyrogen-free 1.2 micron or smaller pore filter prior to sterilization or during the transfer to the final container to remove particulate matter. Filtration of the final product cannot be done on suspensions such as those produced by the New England Compounding Center. Suspensions would require alternative processes and procedures for filtration as specified in USP and the literature to ensure sterility. These processes may be beyond the capability of a compounding pharmacy. A review article discussing such methods was found with a Google.com search on November 11, 2013, entitled <u>Parenteral Suspension: An Overview</u> by Patel RM in the International Journal of Current Pharmaceutical Research, Vol. 2, Issue 3, 2010, 4-13. This foreign journal is not indexed through PubMed.</p> <p>Dr. Barcon added the Board may wish to add a list of sterilization processes as specified in USP General Chapter 797 and USP General Chapter 1211 (Sterilization and Sterility Assurance of Compendial Articles), which includes filtration, bubble point testing of filters for validation of filter integrity following filtration, autoclaving with steam, and dry heat to the draft regulations versus just stating, "sterilization" within the text. Ionizing radiation and ethylene oxide sterilization processes could also be included in the list.</p> |
| 1751.7 | (e) | <p>Comment #9 from Marie Cottman, Pharm.D., Owner/PIC Pacific Compounding Pharmacy and Consultations - #12</p> <p>BOP Proposed Item: Amend 16 CCR §1751.7. Sterile Compounding Quality Assurance and Process Validation. Subdivision (c) (e). Batch-produced sterile drug products... shall be quarantined until the end product testing confirms sterility and acceptable levels of pyrogens before dispensing.</p> <p>Comment #12 (Cottman): Batch is defined in these amendments as “more than one dose...” which results in this section applying to ALL CSPs yet it is in direct conflict with the proposed CCR §1751.8 Beyond Use Dating for Sterile Compounded Drug Products.</p> |

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| | | <p>Recommendation #12(Cottman): Remove the phrase “Batch-produced”</p> |
| 1751.7 | (e) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #28</p> <p>Dr. Blair commented recommending modifying the language to read:</p> <p>(e) Batch-produced sterile drug products compounded from one or more non-sterile ingredients shall be subject to documented end product testing for sterility in accordance with methodologies and processes found in Chapter 71 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), and pyrogens <u>endotoxins</u> in accordance with the methods of Chapters 85 and 151 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), hereby incorporated by reference, and shall be quarantined until the end product testing confirms sterility and acceptable levels of pyrogens <u>endotoxins</u> before dispensing. Products submitted for sterility testing are to include preparations from the beginning, middle, and end of each batch. This requirement of end product testing confirming sterility and acceptable levels of pyrogens <u>endotoxins</u> prior to dispensing shall apply regardless of any sterility or pyrogen testing that may have been conducted on any ingredient or combination of ingredients that were previously non-sterile.</p> <p>Dr. Blair also commented There should be concessions made for test method validation of each compounded preparation. For Ch <71>, concession should be to use maximum rinse indicated in USP <71> for membrane filtration sterility testing method. There should be concessions made for test method validation of each compounded preparation. For Ch <85>, concession should be to test for inhibition only and allow to use 4 lamda positive product control and eliminate full scope of individual inhibition/enhancement testing. USP Ch <151> is the pyrogens testing in rabbits. This test is not practical and should be removed.</p> |
| 1751.7 | (e) | <p>Comment #16 from BJ Bartleson, RN, MS, NEA-BC, CA Hospital Association (CHA) - #21</p> <p>CHA Comment - <i>Remove</i> “Batch-produced sterile drug products compounded from one or more non-sterile ingredients shall be subject to documented end product testing...and shall be quarantined until the end product testing confirms sterility and acceptable levels of pyrogens before dispensing” <i>and replace with</i> “batch-produced sterile drug products compounded from one or more non-sterile ingredients that are exposed longer than 12 hours at 2 to 8 degrees and longer than 6 hours at warmer than 8 degrees before they are sterilized shall meet the sterility test in accordance with methodologies and processes... and shall be quarantined until the end product testing confirms sterility and acceptable levels of pyrogens before dispensing.” This wording aligns with USP 797 language for end product testing.</p> <p>Recommend using USP 797 language for end product testing of high risk compounded sterile products:</p> <ul style="list-style-type: none"> • “All high risk level CSP’s that are prepared in groups of more than 25 identical individual single –dose packages (eg., ampuls, bags, syringes, vials) or in multiple-dose vials (MDV’s) for administration to multiple patients or that are exposed longer than 12 hours at 2°-8° and longer than 6 hours at warmer than 8° before they are sterilized shall meet the sterility test (see Sterility Tests <71> before they are dispensed or administered..... • “When high risk level compounded sterile products are dispensed before receiving the |

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| | | <p>results of their sterility tests, there shall be a written procedure requiring daily observation of the incubating test specimens and immediate recall of the dispensed CSP's when there is any evidence of microbial growth in the test specimens.”</p> |
| 1751.7 | (e) | <p>Comment #19 from Arthur C. Whitney, R.Ph., Advantage Pharmaceuticals - #13</p> <p>Mr. Whitney comments in subsection (e), there is proposed amended language that requires [p]roducts submitted for sterility testing are to include preparations from the beginning, middle, and end of batch.... This is impractical and inconsistent and should not be amended into the proposed language.</p> |
| 1751.7 | (e) | <p>Comment #21 from Brian Warren, California Pharmacist Association (CPhA) - #11</p> <p>CPhA commented on sterility testing of batch-produced sterile drug products. The proposed regulations amend existing standards for sterile compounding quality assurance and process validation. In particular, Section 1751.7 (e) mandates that products submitted for sterility testing include preparations from the beginning, middle, and end of each batch. We suggest a few modifications to this subsection.</p> <p>First, where the draft regulation would require sterility testing at the beginning, middle, and end of each batch, we suggest a modification to have sterility testing apply to the finished preparation. No evidence shows that testing each ingredient that is part of a finished preparation increases the likelihood of sterility or increases patient safety. Sterility testing conducted at the beginning, middle, and end of each batch only increases the cost of sterile compounding, without any clear consumer benefit.</p> <p>If the goal is to ensure the highest standards of quality and safety of sterile compounded drug products, then those promulgated regulations tailored to achieve this goal should directly promote those activities that best directly ensure attainment of the same. Industry best practices recommended by the federal Food and Drug Administration call for personnel and process validation as the key components to ensuring patient sterility. These best practices call for finished preparation testing as a means of verifying personnel and process validation.</p> <p>Second, the wording of the requirement could be misinterpreted, as it is unclear whether sterility testing requirements are intended to apply to both active and inactive ingredients that are part of the finished preparation or to the various solutions resulting from manipulation during the compounding of the finished preparation. We recommend referring to “active ingredients”</p> <p>As such, we recommend the following modification to Section 1751.7 (e): (e) Batch-produced sterile drug products compounded from one or more non-sterile ingredients shall be subject to documented end product testing for sterility in accordance with methodologies and processes found in Chapter 71 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), and pyrogens in accordance with the methods of Chapters 85 and 151 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), hereby incorporated by reference, and shall be quarantined until the end product testing confirms sterility and acceptable levels of pyrogens before dispensing. Products submitted for sterility testing are to include <u>finished</u> preparations from the beginning, middle, and end of each batch. This requirement of end product testing confirming sterility and acceptable levels of pyrogens prior to dispensing shall apply regardless</p> |

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| | | <p>of any sterility or pyrogen testing that may have been conducted on any active ingredient or combination of <u>active</u> ingredients that were previously non-sterile <u>outside of the Beyond-Use-Dating guidelines in USP <797> or autoclaved as the terminal sterilization process.</u></p> |
| 1751.7 | (e) | <p>Comment #23 from William Jones, R.Ph., Central Admixture Pharmacy Services, Inc. (CAPS) - #2</p> <p>CAPS commented on quality assurance and process validations. The proposed requirement in 1751.7 (e) requires quarantining for non sterile to sterile batch compounded CSPs while the preparation is undergoing sterility and pyrogen testing. Further, the requirement includes any compounds made from components that were previously rendered sterile through a non sterile to sterile compounding process. This requirement creates an obstacle for patient care as well as a possible conflict with proposed federal regulations. The Drug Quality and Security Act may become law before these rules are implemented. The new federal law permits "outsourcing facilities" to compound drug shortage items under certain circumstances with the conditional blessing of the FDA. The practice of pharmacies making drug shortage items has been happening apart from this regulation and the new federal statute will now sanction it under the regulation of the FDA. If the proposed 1751.7(e) was in place, pharmacies who have been relying on compounded drug shortage items coming from outsourcing facilities would now be required to sterility test, pyrogen test, and quarantine finished prescriptions made from drug shortage items despite these tests having been performed by the outsourcing facility. An example of this would be magnesium sulfate injection for compounding TPNs, unavailable as an FDA approved drug, but sanctioned by FDA through an outsourcing facility. If this drug were obtained to compound TPN solutions by a hospital in California the TPNs would need to be quarantined until sterility and pyrogen testing was completed. Quarantining and testing thousands of TPN solutions is impractical and this new rule would have the affect of exacerbating the drug shortage issues facing pharmacies.</p> <p>CAPS agrees that non sterile to sterile preparations should be quarantined and released for use if sterility testing indicates that the sample was sterile. CAPS recommends an exemption placed in the sterility and pyrogen testing provisions of section 1751.7(e) that exempts CSPs used as components that were obtained from federally registered entities that have already passed a sterility and pyrogen test and are packaged with a certificate of analysis.</p> <p>CAPS proposed language for 1751.7 (e): (e) Batch-produced sterile drug products compounded from one or more non sterile ingredients shall be subject to documented end product testing for sterility in accordance with methodologies and processes found in Chapter 71 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), and pyrogens in accordance with the methods of Chapters 85 and 151 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), hereby incorporated by reference, and shall be quarantined until the end product testing confirms sterility and acceptable levels of pyrogens before dispensing. Products submitted for sterility testing are to include preparations from the beginning, middle, and end of each batch. This requirement of end product testing confirming sterility and acceptable levels of pyrogens prior to dispensing shall apply regardless of any sterility or pyrogen testing that may have been conducted on any ingredient or combination of ingredients that were previously non-sterile <u>unless the component that was compounded from non-sterile ingredients was compounded by an entity registered with the State of California and the FDA and they provide a Certificate of Analysis with the component documenting that it</u></p> |

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| | | <u>was tested for sterility, pyrogens, and chemistry and was within specification.</u> |
| 1751.7 | (e) | <p>Oral Testimony #2 – Dan Wills, Representing Self - #9</p> <p>Mr. Wills commented on section 1751.7 (e) that all testing has to be in compliance with USP 71. Mr. Wills talked to the previous chairman of USP. USP 71 was designed with industrial compounding. An example you must test 4 items if you are making a batch of anything less than 100. Now, if you need 2 items, you will need to make at least six because USP 71 requires at least four. It makes more sense to adjust based on the amount made. If stay with USP 71 limiting opportunities for compounding.</p> |
| 1751.7 | (f) | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #29</p> <p>Dr. Blair commented recommending modifying the language to read:</p> <p>(f) Batch-produced sterile to sterile transfers shall be subject to periodic testing through <u>media fill</u> process validation for sterility as determined by the pharmacist-in-charge and described in the written policies and procedures.</p> |
| 1751.7 | € | <p>Comment #9 from Marie Cottman, Pharm.D., Owner/PIC Pacific Compounding Pharmacy and Consultations - #16</p> <p>Recommendation #12 (Cottman): I recommend that you approve the addition of Section 1751.8 Beyond Use Dating for Sterile Compounded Drug Products (as noted above) and reword section 1751.7 Subdivision (e) to the following:</p> <p>Sterile drug products compounded from one or more non-sterile ingredients in groups of more than 25 identical individual single-use packages, in MDV's for administration to multiple patients, or with beyond use dating exceeding that stated in CCR 1751.8 shall be tested for sterility in accordance with standards for sterility testing found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), hereby incorporated by reference. For sterile drug products (except ophthalmic drops and inhalations) compounded from one or more non-sterile ingredients in groups of more than 25 identical individual single-use packages or in MDV's for administration to multiple patients shall be tested for pyrogens in accordance with in accordance with standards for sterility testing found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), hereby incorporated by reference. Whenever possible, relative to patient therapy and pharmaceutical stability, CSPs will be quarantined until the results of sterility and pyrogen testing are complete.</p> <p>Reasoning: Referenced USP <797> High Risk Sterile Compounds Sterility Testing and Bacterial Endotoxin (Pyrogen) Testing.</p> |
| 1751.7 | Title | <p>Comment #12 from William Blair, Pharm.D., MBA, McGuff Compounding Pharmacy Services, Inc. - #25</p> <p>Dr. Blair commented recommending modifying the language to read: 1751.7. Sterile Compounding Quality Assurance and <u>Media Fill</u> Process Validation.</p> |

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| 1751.8 | | <p>Comment #9 from Marie Cottman, Pharm.D., Owner/PIC Pacific Compounding Pharmacy and Consultations - #16</p> <p>Recommendation #12 (Cottman): I recommend that you approve the addition of Section 1751.8 Beyond Use Dating for Sterile Compounded Drug Products (as noted above) and reword section 1751.7 Subdivision (e) to the following:</p> <p>Sterile drug products compounded from one or more non-sterile ingredients in groups of more than 25 identical individual single-use packages, in MDV's for administration to multiple patients, or with beyond use dating exceeding that stated in CCR 1751.8 shall be tested for sterility in accordance with standards for sterility testing found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), hereby incorporated by reference. For sterile drug products (except ophthalmic drops and inhalations) compounded from one or more non-sterile ingredients in groups of more than 25 identical individual single-use packages or in MDV's for administration to multiple patients shall be tested for pyrogens in accordance with in accordance with standards for sterility testing found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), hereby incorporated by reference. Whenever possible, relative to patient therapy and pharmaceutical stability, CSPs will be quarantined until the results of sterility and pyrogen testing are complete.</p> <p>Reasoning: Referenced USP <797> High Risk Sterile Compounds Sterility Testing and Bacterial Endotoxin (Pyrogen) Testing.</p> |
| 1751.8 | | <p>Comment #7 from Doug O'Brien, Pharm.D., and Donald Kaplan, Pharm.D., Kaiser Permanente - #20</p> <p>Kaiser comments on the following: Missing language in this section.</p> <p>Kaiser's Comment: The current proposed regulations do not contain beyond use dating requirements for "immediate use" preparations</p> <p>Kaiser's Recommendation: To be more consistent with USP <797>, we recommend that this language be used:</p> <p>" „Immediate use" is when administration is expected to begin no later than one hour following the start of the preparation of the compounded sterile preparation. The immediate use provision is intended only for those situations where there is a need for immediate administration of a compounded sterile preparation. Preparations that are medium-risk level, high-risk level, or hazardous drug compounded sterile preparations shall not be prepared as immediate-use compounded sterile preparations. Immediate use preparations are exempt from the requirements of low-risk level preparations and may be compounded in a less stringent environment than ISO Class 5 conditions."</p> <p>Kaiser's Identified Impact: operational inefficiency.</p> |
| 1751.8 | | <p>Comment #8 from Alan Y. Endo, Pharm.D., FCSHP, PIH Health - #10</p> <p>Medium Risk beyond use date at controlled cold temperature is 7 days.</p> |

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| | | PIH Health’s Recommendation: 9 days at controlled cold temperature (USP 797). |
| 1751.8 | | <p>Comment #9 from Marie Cottman, Pharm.D., Owner/PIC Pacific Compounding Pharmacy and Consultations - #11</p> <p>BOP Proposed Item: Add 16 CCR §1751.8 Beyond Use Dating for Sterile Compounded Drug Products.</p> <p>Comment #11 (Cottman): This is a good addition to CA BOP Regulations! It is directly from USP <797>.</p> <p>Recommendation #11(Cottman): I recommend that you approve the addition of Section 1751.8 Beyond Use Dating for Sterile Compounded Drug Products and reword section 1751.7 Subdivision (e) as indicated below.</p> |
| 1751.8 | | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #44</p> <p>Dr. Sakai commented on missing language in this section. Dr. Sakai commented the current proposed regulations do not contain beyond use dating requirements for “immediate use” preparations. The impact is operational inefficiency.</p> <p>Dr. Sakai’s Recommendation: Add language to be consistent with USP Chapter 797 - “The immediate use provision is intended only for those situations where there is a need for immediate administration of a compounded sterile preparation. Preparations that are medium-risk level, high-risk level, or hazardous drug compounded sterile preparations shall not be prepared as immediate-use compounded sterile preparations. Administration begins not later than 1 hour following the start of the preparation of the compounded sterile preparation. Immediate use preparations are exempt from the requirements of low-risk level preparations and may be compounded in worse than ISO Class 5 conditions.”</p> |
| 1751.8 | | <p>Comment #21 from Brian Warren, California Pharmacist Association (CPhA) - #12</p> <p>CPhA commented on beyond use dating for sterile compounded drug products. The proposed regulations amend existing Section 1571.8, inserting entirely new text to establish minimum requirements for beyond use dating for sterile compounded drug products. The requirements are based on the standards contained in USP <797>.</p> <p>We are supportive of consistency between USP <797> and California regulations, and the Board’s proposed regulations make much progress toward this goal. This consistency helps prevent conflict between a nationally recognized professional standard and the state’s legal practice requirements. However, it is important to note that there is a difference between a standard and a rule. Whereas a standard such as those contained in USP <797> represents a generally accepted model, a rule established by the Board is a specific requirement with the force of law. A professional standard should be followed in most cases, but a rule is strictly enforced in every instance. Regulations based on standards need to be written with this in mind. The standards in USP <797> should guide the Board’s regulations, but cannot always be verbatim copied into a regulation.</p> <p>The standards for beyond use dating are an area where regulatory language should reflect that</p> |

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| | | <p>exceptions to the model do exist. USP <797> standards should generally be followed, but there are times where these standards are not applicable. Some products should be given a shorter beyond use date than the general standard and some products can safely be given a longer beyond use date.</p> <p>We suggest modifying the proposed regulation to allow for exceptions to the beyond use dating formula when a different standard is provided for in scientific literature or specified by the manufacturer. This would not result in a different standard, but would ensure that the USP <797> standards applying to all sterile compounding, except when specific information justifies operating outside of the general standard.</p> <p>As such, we recommend the following modification to Section 1751.8: 1751.8. Beyond Use Dating for Sterile Compounded Drug Products. In addition to the requirements and limitations of section 1735.2, subdivision (h), every sterile compounded drug product shall be given and labeled with a beyond use date as follows, <u>unless otherwise provided for in scientific literature or specified by the manufacturer.</u></p> |
| 1751.8 | | <p>Comment #23 from William Jones, R.Ph., Central Admixture Pharmacy Services, Inc. (CAPS) - #4</p> <p>CAPS commented on beyond use dating for sterile compounded drug products. USP <797> uses risk levels to classify different levels of compounding and the corresponding standard beyond use dates associated with these risk levels. The proposed compounding regulation does not use these risk levels which have become a standard and this creates confusion when reading section 1751.8 Beyond Use Dating for Compounded Sterile Products. Without the use of the risk level classifications or an alternative classification, Pharmacist are left with no method to reference the compounding process and the associated dating and/or testing requirements. CAPS recommends the use of the USP <797> risk levels to clarify section 1751.8 Beyond Use Dating for Sterile Compounded Drug Products.</p> |
| 1751.8 | | <p>Oral Testimony #8 – Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California (CHCC) - #17</p> <p>Dr. Sakai commented on section 1751.8 recommended changes from 7 to 9 days. If it is only 7 days, CHCC anticipates additional \$83,200/annually.</p> |
| 1751.8 | (a) | <p>Comment #6 from Muno Bholat, Goorgen Boghossian, Tawny Bui, Theresa Lee-Yu, and Hiroyuki Nishi, Providence Health & Services Southern California - #22</p> <p>Providence Southern California recommends adding the following language to this section: Compounding involved only transfer, measuring, and mixing manipulations using not more than three commercially manufactured packages of sterile products and not more than two entries into any one sterile container or package of sterile products or administration container/device to prepare the drug product. Manipulations are limited to aseptically opening ampuls, penetrating disinfected stoppers on vials with sterile needles and syringes, and transferring sterile liquids in sterile syringes to sterile administration devices, package containers of other sterile products, and containers for storage and dispensing.</p> <p>Providence Southern California recommends adding in all three criteria to quality compounded sterile products that should have beyond use dating matching the USP 797 low-risk category.</p> |

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| | | <p>Excluding all criteria for each category allows for looser interpretation and permits some compounded sterile products to be dated in different risk level categories and with different beyond use dating from established USP 797 guidelines.</p> |
| 1751.8 | (a) | <p>Comment #16 from BJ Bartleson, RN, MS, NEA-BC, CA Hospital Association (CHA) - #22</p> <p>CHA Comment - <i>Add to 1751.8(a)</i>: “Compounding involved only transfer, measuring, and mixing manipulations using not more than three commercially manufactured packages of sterile products and not more than two entries into any one sterile container or package of sterile products or administration container/device to prepare the drug product. Manipulations are limited to aseptically opening ampules, penetrating disinfected stoppers on vials with sterile needles and syringes, and transferring sterile liquids in sterile syringes to sterile administration devices, package containers of other sterile products, and containers for storage and dispensing.”</p> <p>Only one of three criteria are included in these regulations. All three criteria need to be added to prevent misinterpretation and the ability for some compounded sterile products to be dated different risk categories and with different beyond-use dating from established USP guidelines.</p> <p>General comment on Section 1751.8: This section has adopted the low, medium, and high risk level compounding beyond-use dating and some of the criteria for categorizing the risk level as listed in USP797.</p> <ul style="list-style-type: none"> • Not including all criteria for each category allows for looser interpretation and permits some compounded sterile products to be dated in different risk level categories and with different beyond-use dating from established USP797 guidelines. <p>CHA Requests adding in all 3 criteria (only 1 of 3 is currently in proposed draft language) to qualify compounded sterile products that should have beyond use dating matching USP797 low-risk category.</p> <ul style="list-style-type: none"> • Without limiting the number and types of transfers during preparation, complex products like TPN with multiple ingredients can be prepared under the board regulations and meet this lower level of beyond use dating wherein under USP797 it would be medium risk (which should align with 1751.8(b)). <p>USP 797 states: “CSPs compounded under all the following conditions are at a low risk of contamination. Low Risk Conditions</p> <ol style="list-style-type: none"> 1. The CSPs are compounded with aseptic manipulations entirely within ISO Class 5 or better air quality using only sterile ingredients, products, components, and devices. 2. The compounding involved only transfer, measuring, and mixing manipulations using not more than three commercially manufactured packages of sterile products and not more than two entries into any one sterile container or package (e.g. bag, vial) of sterile product or administration container/device to prepare the CSP. 3. Manipulations are limited to aseptically opening ampuls, penetrating disinfected stoppers on vials with sterile needles and syringes, and transferring sterile liquids in sterile syringes to sterile administration devices, package containers of other sterile products, and containers for storage and dispensing.” <p>(Then the 4th condition is included verbatim in 1751.8(a)(1-3))</p> |
| 1751.8 | (a) | <p>Comment #18 from Michael Moore, R.Ph. - #2</p> |

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| | | <p>Mr. Moore comments that subsections (a), (b), and (d) all state that the maximum beyond use date respective to their manner of preparation when they are prepared "...in the absence of passing a sterility test in accordance with standards for sterility testing found in Chapter 797...."</p> <p>Mr. Moore queries the board, what about "WITH" sterility testing? Is there going to be a maximum, or will that be left up to the individual pharmacies with the expectation that they would be able to provide justification for that dating? Should there be a requirement that EVERY batch prepared be tested? If sterility samples are submitted in an attempt to extend the dating, will a pharmacy be able to use product while waiting for the results?</p> |
| 1751.8 | (b) | <p>Comment #3 from Romic Eskandarian, Pharm.D., Glendale Adventist Medical Center, Adventist Health – #11</p> <p>Dr. Eskandarian commented on "7 days at controlled cold temperatures BUD for low risk preparations." Dr. Eskandarian indicated this should be changed from 7 to 9 days.</p> <p>(Note: Comment referenced page 20, line 14 but comment appears to address this section.)</p> |
| 1751.8 | (b) | <p>Comment #7 from Doug O'Brien, Pharm.D., and Donald Kaplan, Pharm.D., Kaiser Permanente - #18</p> <p>Kaiser comments on the following: (b) Where the sterile compounded drug product was compounded solely with aseptic manipulations entirely within an ISO Class 5 hood located in an ISO Class 7 buffer area with an anteroom, using multiple individual or small doses of sterile products combined or pooled to prepare a compounded sterile product that will be administered either to multiple patients or to one patient on multiple occasions, in the absence of passing a sterility test in accordance with standards for sterility testing found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1,2013), hereby incorporated by reference, the beyond use date shall specify that storage and exposure periods for the sterile compounded drug product cannot exceed the following:</p> <ol style="list-style-type: none"> (1) 30 hours at controlled room temperature (2) 7 days at controlled cold temperature (3) 45 days at controlled freezer temperature <p>Kaiser's Comment: This section appears to have been extracted from the medium-risk category definition in USP <797>. The bolded text appears to have been changed by the Board of Pharmacy subcommittee. The current version of USP <797> specifies a beyond use date for medium-risk level compounded sterile preparations of nine (9) days at controlled cold temperature. Nine days is more appropriate and practical, as it supports the ability of home infusion pharmacies to prepare and distribute weekly supplies of total parenteral nutrition solutions. It should be noted that the original version of USP <797> listed a beyond use date of seven days for medium-risk level CSPs, and changed the BUD to nine (9) days for that reason.</p> <p>Kaiser's Recommendation: Change to nine (9) days at controlled cold temperature.</p> <p>Kaiser's Identified Impact: Operational inefficiency; higher costs for drug delivery to home infusion patients.</p> |

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| 1751.8 | (b) | <p>Comment #11 from Rita Shane, Pharm.D., FASHP, FCSHP, Cedars-Sinai Medical Center - #7</p> <p>Dr. Shane commented current draft language states that sterile compounded drug products from multiple individual or small doses of sterile products combined or pooled to prepare a compounded sterile product that will be administered either to multiple patients or to one patient on multiple occasions, in the absence of passing a sterility test in accordance with USP 797, storage and exposure cannot exceed 7 days stored at controlled cold temperatures.</p> <p>Dr. Shane recommended modifying the language as follows to reflect USP 797 for medium risk preparations: Storage and exposure period cannot exceed more than 9 days at controlled cold temperature.</p> |
| 1751.8 | (b) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #39</p> <p>Dr. Sakai commented that subsection (b) appears to have been extracted from the medium-risk category definition in USP <797>. The following text, “(2) 7 days at controlled cold temperature,” appears to have been changed by the Board of Pharmacy subcommittee. The current version of USP <797> specifies a beyond use date for medium-risk level compounded sterile preparations of nine (9) days at controlled cold temperature. Nine days is more appropriate and practical, as it supports the ability of home infusion pharmacies to prepare and distribute weekly supplies of total parenteral nutrition solutions. It should be noted that the original version of USP <797> listed a beyond use date of seven days for medium-risk level CSPs, and changed the BUD to nine days for that reason. The impact is operational inefficiency and higher costs for drug delivery to home infusion patients.</p> <p>Dr. Sakai’s Recommendation: Change to nine (9) days at controlled cold temperature.</p> |
| 1751.8 | (b) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #40</p> <p>Dr. Sakai commented on the verbiage of “(2) 7 days at controlled cold temperature.” USP797 utilizes 9 days.</p> <p>Home Care rationale: USP797 BUD of 9 days allows for once weekly deliveries enabling CHC to serve a widespread geographic area and fulfill a need for an underserved population.</p> <ul style="list-style-type: none"> -TPN set up of BAXA Compounder \$60.00 -Technician 1 hour \$20.00 -Pharmacist 30 minutes \$35.00 -Distribution/Driver \$60.00 -Gas/Vehicle \$25.00 <p>Total \$200.00 per patient Average of 8 patients - \$1600.00 per week or \$83,200.00 per year</p> <p>The reduction of Beyond Use Data could also result in Home Care restricting its service area or declining referrals in order to continue to provide service for the existing patients. The impact is approximately \$83,200 annually.</p> |

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| | | Dr. Sakai's Recommendation: use "9" days at controlled cold temperature. |
| 1751.8 | (b) | <p>Comment #16 from BJ Bartleson, RN, MS, NEA-BC, CA Hospital Association (CHA) - #23</p> <p>CHA Comment - <i>Add to 1751.8 (b):</i> "or where the process includes complex aseptic manipulations other than the single-volume <i>transfer, or requires unusually long duration such as that required to complete dissolution or homogenous mixing.</i> This language provides consistency with USP 797 by providing examples of conditions that would qualify a compounded sterile product.</p> <p>CHA recommends adding in the other two examples of conditions which would qualify a compounded sterile product to be consistent with the beyond-use dating in this section that matches USP797 medium-risk level.</p> <p>USP797 states: "When CSPs are compounded aseptically under low-risk conditions and one or more of the following conditions exists, such CSPs are at a medium risk of contamination. 1. Multiple individual or small doses of sterile products are combined or pooled to prepare a CSP that will be administered either to multiple patients or to one patient on multiple occasions. 2. The compounding process includes complex aseptic manipulations other than the single-volume transfer. 3. The compounding process requires unusually long duration, such as that required to complete dissolution or homogenous mixing." (Then the 4th condition is included verbatim in 1751.8(b)(1-3))</p> |
| 1751.8 | (b) | <p>Comment #18 from Michael Moore, R.Ph. - #3</p> <p>Mr. Moore comments that subsections (a), (b), and (d) all state that the maximum beyond use date respective to their manner of preparation when they are prepared "...in the absence of passing a sterility test in accordance with standards for sterility testing found in Chapter 797...."</p> <p>Mr. Moore queries the board, what about "WITH" sterility testing? Is there going to be a maximum, or will that be left up to the individual pharmacies with the expectation that they would be able to provide justification for that dating? Should there be a requirement that EVERY batch prepared be tested? If sterility samples are submitted in an attempt to extend the dating, will a pharmacy be able to use product while waiting for the results?</p> |
| 1751.8 | (b) | <p>Comment #18 from Michael Moore, R.Ph. - #5</p> <p>Mr. Moore comments this section describes the environment present at most home infusion pharmacy providers that compound TPN products. It spells out that the maximum BUD for these products without sterility testing will be 30 hours at controlled room temperature, 7 days at controlled cold temperature, and 45 days at controlled freezer temperature.</p> <p>A 7 day expiration date for this class of medications is not practical and will result in massive expense associated with provision of care to this patient population. Most medications in home infusion are prepared a week at a time. The maximum expiration dating we can even get for a</p> |

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| | | <p>certain formula of TPN is 9 days. Many patients are not within a practical delivery distance of a pharmacy. Their medications require overnight shipment via UPS or Fed-Ex. With a 7 day BUD, pharmacies will be forced to ship these patients twice weekly without sterility testing; and he does not believe sterility testing would be practical in this situation either. There would be a significant financial impact of carrying out this regulation.</p> <p>Currently, he believes providers of this category of medications (TPN) are using a 9 day expiration dating. Eric Kastango, an expert in this field, has argued that the BUD for “Medium Risk” medications (including TPN) should be 9 days. The January 15th 2014 AJHP (ASHP Guidelines on Compounding Sterile Preparations) also reiterates this 9 day BUD.</p> |
| 1751.8 | (b) & (b) (2) | <p>Comment #6 from Muno Bholat, Goorgen Boghossian, Tawny Bui, Theresa Lee-Yu, and Hiroyuki Nishi, Providence Health & Services Southern California - #23</p> <p>Providence Southern California recommends adding the following language to this section: (b) Where the sterile compounded drug product was compounded solely with aseptic manipulations entirely within an ISO Class 5 hood located in an ISO Class 7 buffer area with an anteroom, using multiple individual or small doses of sterile products combined or pooled to prepare a compounded sterile product that will be administered either to multiple patients or to one patient on multiple occasions or where the process includes complex aseptic manipulations other than the single-volume transfer, <u>or requires unusually long duration such as that required to complete dissolution or homogenous mixing</u>, in the absence of passing a sterility test in accordance with standards for sterility testing found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), hereby incorporated by reference, the beyond use date shall specify that storage and exposure periods for the sterile compounded drug product cannot exceed the following: (1) 30 hours at controlled room temperature (2) 7 <u>9</u> days at controlled cold temperature (3) 45 days at controlled freezer temperature</p> <p>Providence Southern California recommends adding in the other two examples of conditions which would qualify a compounded sterile product to be consistent with the beyond use dating in this section that aligns with the USP 797 medium-risk level.</p> <p>Providence Southern California recommends changing the cold temperature beyond use date to 9 days to match conditions that correlate with USP 797 medium-risk level.</p> |
| 1751.8 | (b)(2) | <p>Comment #17 from Tim Lopez, Pharm.D., Community Regional Medical Centers (CRMC) - #1</p> <p>CRMC commented on the verbiage, “7 days at controlled cold temperatures.” CRMC’s concern is the proposed dating described above is not consistent with the dating for medium risk products described in USP <797> (USP-36, NF-31). This section in USP <797> states that medium risk products are sterile for 9 days at controlled room temperature and this is how many institutions, including ours, currently practice.</p> <p>CRMC’s solution: Change the proposed regulation to "9 days at controlled cold temperatures" to be consistent with USP <797> and current practice.</p> |

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| 1751.8 | (b)(2) | <p>Comment #23 from William Jones, R.Ph., Central Admixture Pharmacy Services, Inc. (CAPS) - #5</p> <p>CAPS commented on beyond use dating for sterile compounded drug products. The refrigerated beyond use date for this ‘medium risk’ process in the absence of a sterility test is 7 days. This creates an obstacle for homecare patients who would be required to be available for multiple deliveries of their medium risk medications each week. CAPS recommends a refrigerated beyond use date of 9 days which is the USP <797> standard beyond use dating in the absence of a sterility test.</p> <p>CAPS proposed language for 1751.8 (b) (2) (b) Where the sterile compounded drug product was compounded solely with aseptic manipulations entirely within an ISO Class 5 hood located in an ISO Class 7 buffer area with an anteroom, using multiple individual or small doses of sterile products combined or pooled to prepare a compounded sterile product that will be administered either to multiple patients or to one patient on multiple occasions, in the absence of passing a sterility test in accordance with standards for sterility testing found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), hereby incorporated by reference, the beyond use date shall specify that storage and exposure periods for the sterile compounded drug product cannot exceed the following: (1) 30 hours at controlled room temperature (2) 9 days at controlled cold temperature (3) 45 days at controlled freezer temperature</p> |
| 1751.8 | (b)(3) | <p>Comment #16 from BJ Bartleson, RN, MS, NEA-BC, CA Hospital Association (CHA) - #24</p> <p>CHA Comment - <i>Remove 7 and replace with 9 days at controlled cold temperatures. Change to 9 days to match conditions that correlate with USP 797 Medium-Risk Level.</i></p> |
| 1751.8 | (c) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #41</p> <p>Dr. Sakai commented on the verbiage from subsection (c), “or where the sterile compounded drug product lacks effective antimicrobial preservatives.” This section appears to have been extracted from the high-risk category definition in USP <797>. The above mentioned text appears to have been added by the Board of Pharmacy subcommittee. It appears to say that if sterile ingredients without preservatives are used or if a preservative is not added during aseptic manipulations within an ISO Class 5 hood located in an ISO Class 7 buffer area, then these short beyond use dates would apply. This scenario occurs commonly in hospital pharmacies, and is normally associated with low and medium risk level compounded sterile preparations. It is inappropriate to place this language in a high-risk section. The issue of anteroom versus ante area has been previously discussed. The impact is unnecessarily short beyond use dating will cause drug waste and cost impact exceeding \$1 million/year.</p> <p>Dr. Sakai’s Recommendation: Delete the above mentioned text. Change “anteroom” to “ante area.”</p> |
| 1751.8 | (c) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #42</p> |

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| | | <p>Dr. Sakai commented on the verbiage, “anteroom, using non-sterile.”</p> <p>Dr. Sakai’s Recommendations: Change “anteroom” to “ante area.”</p> |
| 1751.8 | (c) | <p>Comment #23 from William Jones, R.Ph., Central Admixture Pharmacy Services, Inc. (CAPS) - #6</p> <p>CAPS commented on beyond use dating for sterile compounded drug products. Section 1751.7(e) and 1751.8(c) appear to conflict. 1751.7(e) requires sterility and pyrogen testing and quarantining for non sterile to sterile batch compounded CSPs. Section 1751.8(c) permits assigning a BUD date for compounds made from non sterile to sterile components "in the absence of passing a sterility test." Assuming the assignment of BUD also indicates that it is permissible to dispense, these two sections are conflicting. The language in section 1751.8(c) appears to mimic USP <797> for High Risk Level CSPs, however, USP 797 included a provision that indicates a sterility test is not required for batch sizes of no more than 25 units. The 1751 language does not include this provision and in fact insists on a sterility and pyrogen test in all cases for non sterile to sterile compounding. Did the board inadvertently leave the 25 unit limit out of the rule? These two sections need to be edited to eliminate the conflict.</p> <p>1751.8 (c):</p> <p>(c) Where the sterile compounded drug product was compounded solely with aseptic manipulations entirely within an ISO Class 5 hood located in an ISO Class 7 buffer area with an anteroom, using non-sterile ingredients, including manufactured products not intended for sterile routes of administration, or non-sterile devices, before terminal sterilization, or where the sterile compounded drug product lacks effective antimicrobial preservatives, in the absence of passing a sterility test in accordance with standards for sterility testing found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), hereby incorporated by reference, the beyond use date shall specify that storage and exposure periods for the sterile compounded drug product cannot exceed the following:</p> <ol style="list-style-type: none"> (1) 24 hours at controlled room temperature (2) 3 days at controlled cold temperature (3) 45 days at controlled freezer temperature <p>1751.7 (e):</p> <p>(e) Batch-produced sterile injectable drug products compounded from one or more non sterile ingredients shall be subject to documented end product testing for sterility in accordance with methodologies and processes found in Chapter 71 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), and pyrogens in accordance with the methods of Chapters 85 and 151 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), hereby incorporated by reference, and shall be quarantined until the end product testing confirms sterility and acceptable levels of pyrogens before dispensing. Products submitted for sterility testing are to include preparations from the beginning, middle, and end of each batch. This requirement of end product testing confirming sterility and acceptable levels of pyrogens prior to dispensing shall apply regardless of any sterility or pyrogen testing that may have been conducted on any ingredient or combination of ingredients that were previously non-sterile.</p> |
| 1751.8 | (c) | <p>Oral Testimony #8 – Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California (CHCC) - #18</p> <p>Dr. Sakai commented on section 1751.8 (c) in order to comply with this section would have to get a machine that costs over \$1 million and \$130,000/annual service contract.</p> |

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| 1751.8 | (d) | <p>Comment #1 from Douglas Barcon, Pharm.D. – #13</p> <p>Dr. Barcon commented in section 1751.8 entitled Beyond Use Dating for Sterile Compounded Products paragraph (d) on page 22 of the draft, he believed this was adapted from USP 797 but misquoted. Dr. Barcon stated it could use clarification, so there is no misunderstanding. As currently written it appears to conflict with other paragraphs. If Dr. Barcon understands the intent of this paragraph, he believes it should state, "Where the sterile compounded drug product was compounded solely with aseptic manipulations entirely within an ISO Class 5 hood not located within an ISO Class 7 buffer room with an anteroom or is an ISO Class 5 barrier isolator not located within an ISO Class 7 buffer room with an anteroom and documentation from the manufacturer of the barrier isolator does not permit operation in an environment that exceeds ISO Class 7 in the absence of passing a sterility test in accordance with standards for sterility testing found in Chapter 797 of the United States Pharmacopeia-National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013) hereby incorporated by reference, the beyond use date shall be 12 hours." Dr. Barcon stated if his understanding was incorrect, requests clarification as to whether or not this current paragraph of the draft addressing sterile-to-sterile low-risk CSPs with a 12-hour or less BUD where the placement of primary engineering controls did not meet specified criteria (ISO class 5 hood within ISO Class 7 buffer room) for a longer beyond-use date. Alternatively, if the current paragraph is meant for a <i>non-hatched</i> sterilized high-risk sterile compound in USP 797, the beyond-use date of a preparation without sterility testing is 24 hours; and if it meant for a <i>hatched</i> sterilized high-risk sterile compounds, the beyond-use date would generally be 12 hours, depending on storage conditions.</p> <p>Dr. Barcon further commented designing and building sterile compounding facilities in hospitals and health-systems is an extremely expensive process that makes it difficult for many health facilities to comply in a manner that optimizes their productivity, due to the delays, costs, and requirements of the Office of Statewide Health Planning and Development (OSHPD). Facilities often opt for \$20,000 barrier isolators rather than build one or more cleanrooms that can cost upwards of \$100,000 each. Sterile compounding regulations have gotten to the point that it has become very time-consuming and expensive to do sterile compounding, when one considers all the documentation, process validations, equipment, supplies, testing, and training required. NECC, as a worst-case scenario, and several other sterile compounding pharmacies, show that we need these regulations to ensure patient safety. Outsourcing of compounding and validation testing will likely increase, due to the costs. Dr. Barcon continued, unfortunately, without sufficient reimbursement, many sterile compounding pharmacies will be unable to continue to compound at previous levels and provide the level of service necessary to service their customers, and some will cut corners to remain profitable.</p> |
| 1751.8 | (d) | <p>Comment #6 from Muno Bholat, Goorgen Boghossian, Tawny Bui, Theresa Lee-Yu, and Hiroyuki Nishi, Providence Health & Services Southern California - #24</p> <p>Providence Southern California recommends adding the following language to this section: (d) Where the sterile compounded drug product was compounded solely with aseptic manipulations entirely within an ISO Class 5 hood <u>that is located in a segregated compounding area and restricted to sterile compounding activities, using only sterile ingredients, components, and devices, by personnel properly cleansed and garbed,</u> in the absence of passing a sterility test in accordance with standards for sterility testing found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision,</p> |

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| | | <p>Effective August 1, 2013) hereby incorporated by reference, the beyond use date shall be 12 hours.</p> <p>Providence Southern California recommends adding in criteria to qualify conditions that would meet the beyond use dating. Without qualifiers non-sterile (high-risk level) products could be prepared in this manner which would be very unsafe.</p> <p>This section is meant to include the provisions from USP 797 for Low-Risk Level CSPs with 12-hour or less beyond use dating – when an ISO Class 5 hood cannot be located within an ISO Class 7 buffer area. Providence Southern California comments many hospitals operate under this provision safely and meet the USP 797 criteria.</p> |
| 1751.8 | (d) | <p>Comment #7 from Doug O’Brien, Pharm.D., and Donald Kaplan, Pharm.D., Kaiser Permanente - #19</p> <p>Kaiser comments on the following: The section addresses sterile preparations compounded in ISO Class 5 hoods not located in ISO Class 7 areas.</p> <p>Kaiser’s Comment: An additional statement needs to be added that if the sterile preparations are compounded in an ISO Class 5 compounding aseptic containment isolator (not located in an ISO Class 7 area), the beyond use date will be the same as if the CACI was located in an ISO Class 7 area.</p> <p>Kaiser’s Recommendation: Change language to support longer beyond use dating with the use of barrier isolators, provided that these primary engineering controls maintain ISO Class 5 air quality, and are tested as described in USP <797>.</p> <p>Kaiser’s Identified Impact: Unnecessarily short beyond use dating will cause drug waste. Cost impact: exceeding \$1 million/year for our organization.</p> |
| 1751.8 | (d) | <p>Comment #7 from Doug O’Brien, Pharm.D., and Donald Kaplan, Pharm.D., Kaiser Permanente - #21</p> <p>Kaiser comments on the following: Where the sterile compounded drug product was compounded solely with aseptic manipulations entirely within an ISO Class 5 hood in the absence of passing a sterility test in accordance with standards for sterility testing found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013) hereby incorporated by reference, the beyond use date shall be 12 hours.</p> <p>Kaiser’s Comment: This language is inconsistent with the other parts of 1751.8.</p> <p>Kaiser’s Recommendation: “Where the sterile compounded drug product was compounded solely with aseptic manipulations entirely within an ISO Class 5 hood in the absence of passing a sterility test in accordance with standards for sterility testing found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013) hereby incorporated by reference, the beyond use date cannot exceed 12 hours.”</p> <p>Kaiser’s Identified Impact: operational inefficiencies.</p> |

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| 1751.8 | (d) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #43</p> <p>Dr. Sakai commented on the section addresses sterile preparations compounded in ISO Class 5 hoods not located in ISO Class 7 areas. Dr. Sakai commented an additional statement needs to be added that if the sterile preparations are compounded in an ISO Class 5 compounding aseptic containment isolator (not located in an ISO Class 7 area), the beyond use date will be the same as if the CACI was located in an ISO Class 7 area. The impact is potentially significant for facilities with a barrier isolator.</p> <p>Dr. Sakai’s Recommendation: Change language to support longer beyond use dating with the use of barrier isolators, provided that these primary engineering controls maintain ISO Class 5 air quality, and are tested as described in USP <797>. Unnecessarily short beyond use dating will cause drug waste.</p> |
| 1751.8 | (d) | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #45</p> <p>Dr. Sakai commented on “...hereby incorporated by reference, the beyond use date shall be 12 hours.” Dr. Sakai commented his concern is the current verbiage indicates all products will be 12 hours regardless of the data.</p> <p>Dr. Sakai’s Recommendation: Replace “shall be” to “shall not exceed.”</p> |
| 1751.8 | (d) | <p>Comment #16 from BJ Bartleson, RN, MS, NEA-BC, CA Hospital Association (CHA) - #25</p> <p>CHA Comment - <i>Add in:</i> “that is located in a segregated compounding area and restricted to sterile compounding activities, using only sterile ingredients, components, and devices, by personnel properly cleansed and garbed,” Criteria need to be added to qualify conditions that would meet this beyond-use dating. Without the qualifiers, non-sterile (high-risk level) products could be prepared in an unsafe manner. Regulations need to match USP 797 so that hospitals without the means to construct costly cleanrooms can operate safe operations under ISO Class 5 conditions.</p> <p>CHA recommends adding in criteria to qualify conditions that would meet this beyond-use dating. Without qualifiers non-sterile (high-risk level) products could be prepared in this manner which would be very unsafe.</p> <ul style="list-style-type: none"> - This section is meant to include the provision from USP797 for Low-Risk Level CSPs with 12-Hour or Less BUD – when an ISO Class 5 hood cannot be located within an ISO Class 7 buffer area. - It does not include the 4 criteria listed in USP797 that need to be met to qualify a sterile compound for this exception to preparation within a cleanroom environment. - Many hospitals without the means to construct costly cleanrooms operate under this provision and meet the USP797 criteria. - Without the criteria, if left as stated above, any compound can be prepared under this regulation and be given a 12-hour beyond use date. It does not stipulate sterile to sterile compounding only nor the requirement of a segregated sterile compounding area. Segregated sterile compounding area is defined and discussed in other sections: 1735.1(q), 1751.5(a)(2) |

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| | | <p>USP797 states that all of the following four criteria must be met in order for compounded sterile products to be prepared inside an ISO Class 5 hood that cannot be located in an ISO 7 buffer room:</p> <ol style="list-style-type: none"> 1. PEC's (Primary engineering controls = LAFW, BSC, CACI, CAI) shall be certified and maintain ISO Class 5 and shall be in a segregated compounding area restricted to sterile compounding activities that minimize the risk of CSP contamination. 2. The segregated compounding area shall not be in a location that has unsealed windows or doors that connect to the outdoors or high traffic flow, or that is adjacent to construction sites, warehouses, or food preparation. Note that this list is not intended to be all inclusive. 3. Personnel shall follow the procedures described in Personnel Cleansing and Garbing and Additional Personnel Requirements prior to compounding. Sinks should not be located adjacent to the ISO Class 5 PEC. Sinks should be separated from the immediate area of the ISO Class 5 PEC device. 4. The specifications in Cleaning and Disinfecting the Sterile Compounding Areas, Personnel Training and Competency Evaluation of Garbing, Aseptic Work Practices and Cleaning/Disinfection Procedures, and Nonviable Environmental Sampling Testing shall be followed as described in the chapter. |
| 1751.8 | (d) | <p>Comment #18 from Michael Moore, R.Ph. - #4</p> <p>Mr. Moore comments that subsections (a), (b), and (d) all state that the maximum beyond use date respective to their manner of preparation when they are prepared "...in the absence of passing a sterility test in accordance with standards for sterility testing found in Chapter 797...."</p> <p>Mr. Moore queries the board, what about "WITH" sterility testing? Is there going to be a maximum, or will that be left up to the individual pharmacies with the expectation that they would be able to provide justification for that dating? Should there be a requirement that EVERY batch prepared be tested? If sterility samples are submitted in an attempt to extend the dating, will a pharmacy be able to use product while waiting for the results?</p> |
| 1751.8 | (d) | <p>Comment #18 from Michael Moore, R.Ph. - #6</p> <p>Mr. Moore comments that this section describes the environment where a medication is prepared in a class 5 hood, but without a class 7 room environment. It assigns a BUD of 12 hours to everything regardless of storage.</p> <p>Mr. Moore is aware of at least one rural district facility that still does not have a compounding room or a barrier-isolator; they compound low-risk products in a class 5 hood. Mr. Moore is not sure why medication BUDs are restricted to 12 hours regardless of storage conditions. If they follow all the proper aseptic technique and they prepare a single, patient-specific dose of an IV preparation from sterile components, why is there a huge chasm between the BUDs? A product compounded from non-sterile components gets 24 hours at room temperature? In a hospital setting with limited pharmacy services, a 24 hour expiration dating would be more practical, and he does not believe that patient safety would be compromised with the additional 12 hours. Perhaps a second BUD of 24 hours could be included in the regulations for storage under refrigeration.</p> |

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| 1751.8 | (e) [add] | <p>Comment #6 from Muno Bholat, Goorgen Boghossian, Tawny Bui, Theresa Lee-Yu, and Hiroyuki Nishi, Providence Health & Services Southern California - #25</p> <p>Providence Southern California recommends adding the following language to this section: (e) Where the sterile compounded drug product was compounded solely with aseptic manipulations in conditions worse than ISO Class 5, involving simple transfer using only sterile ingredients and components, the beyond use dates shall be one hour. These preparations are limited to situations where there is a need for emergency or immediate patient administration of a compounded sterile product where preparation inside an ISO Class 5 environment would subject the patient to additional risk due to delays in therapy. If administration has not begun within one hour from the start of preparation, the compounded sterile product must be discarded appropriately.</p> <p>Providence Southern California recommends adding the immediate-use provision, with a 1-hour beyond use date, as per USP 797 to allow for preparation of sterile compounded products outside of an ISO Class hood for emergency or immediate patient administration. Critical medications are compounded for emergent situations and direct patient administration including code blues, heart attacks, and strokes, and preparation inside an ISO 5 hood within an ISO 7 buffer zone with cleansing and garbing would cause significant delays to patient therapy and risk patient harm. Hospital pharmacists mix or “compound” sterile drug products at the patient bedside during code blue to provide life sustaining medications to patients.</p> <p>Providence Southern California comments that lack of immediate-use provision, with a 1-hour beyond use date, for compounding sterile products outside of an ISO Class 5 hood for emergency or immediate patient administration where preparation inside an ISO 5 hood within an ISO 7 buffer room or cleanroom would cause delays and risk patient harm.</p> |
| 1751.8 | (e) | <p>Comment #16 from BJ Bartleson, RN, MS, NEA-BC, CA Hospital Association (CHA) - #26</p> <p>CHA Comment - <i>Add (e)</i>: “Where the sterile compounded drug product was compounded solely with aseptic manipulations in conditions worse than ISO Class 5, involving simple transfer using only sterile ingredients and components, the beyond use date shall be one hour. These preparations are limited to situations where there is a need for emergency or immediate patient administration of a compounded sterile product where preparation inside an ISO Class 5 environment would subject the patient to additional risk due to delays in therapy. If administration has not begun within one hour from the start of preparation, the compounded sterile product must be discarded appropriately. The addition of the immediate-use provision , with a one-hour beyond-use date, as per USP Chapter 797 must be incorporated to allow for preparation of sterile compounded products to be prepared outside of an ISO Class 5 hood for emergency or immediate patient administration where preparation inside an ISO 5 hood within an ISO 7.</p> <p>CHA requests addition of immediate-use provision, with a 1 hour beyond-use date, as per USP Chapter 797 to allow for preparation of sterile compounded products to be prepared outside of an ISO Class 5 hood for emergency or immediate patient administration where preparation inside an ISO 5 hood within an ISO 7 buffer room or cleanroom would cause delays and risk patient harm.</p> <ul style="list-style-type: none"> • Critical medications in hospitals are compounded for emergent situations and direct patient administration including code blues, heart attacks, and strokes, and preparation inside an ISO 5 hood within an ISO 7 buffer room with cleansing and garbing would cause significant delays to |

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| | | <p>patient therapy.</p> <ul style="list-style-type: none"> • Also at our facilities pharmacists mix or “compound” sterile drug products at the patient bedside during code blues to provide life sustaining intravenous (IV) medication to patients requiring cardiopulmonary resuscitation. • Pursuant to section 1751, compounding sterile drug products must conform to section 1735 et seq. Section 1735 (a) defines “compounding” as “occurring in a licensed pharmacy, by or under the supervision of a licensed pharmacist”. • The practice of pharmacists mixing sterile compounded drugs, at the bedside or outside of ISO Class 5 environments, during emergencies or for direct patient administration, is preferred to drug preparation or mixing performed by nursing or other healthcare staff less familiar with drugs, drug properties, and sterile compounding techniques and guidelines. <p>Without amending the regulations to include immediate-use beyond-use dating, hospital pharmacies would not be able to prepare critical emergency drugs outside of a cleanroom environment and delays in preparation of therapy could cause patient harm.</p> <p>USP797 includes 6 criteria for compounded sterile products to meet in order for the Immediate-Use provision to apply:</p> <ol style="list-style-type: none"> 1. The compounding process involves simple transfer of not more than three commercially manufactured packages of sterile nonhazardous products or diagnostic radiopharmaceutical products from the manufacturers’ original containers and not more than two entries into any one container or package (e.g. bag, vial) of sterile infusion solution of administration container/device. For example, antineoplastics 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 non-sterile 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 beyond use date 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 safety discarded. |
| 1751.9 | | <p>Comment #18 from Michael Moore, R.Ph. - #7</p> <p>Mr. Moore comments he can appreciate that the idea of a single-dose medication contains no preservative. He would draw the board’s attention to the recent emergent shortage of many injectable products often packaged as single-dose such as the electrolytes like potassium and calcium used for preparation of TPN. If facilities had been forced to comply with the proposed regulations he is CERTAIN that the shortage would have been considerably more severe and patient lives put at significant risk. Pharmacists became very creative in extending the dates of expiration after entering single-dose medication vials. There was fear among pharmacists that they were pushing the envelope of what was safe by using vials beyond a “single-dose”, but there was an even greater fear that their patients could die without them. By mandating 1 to 6 hours, pharmacists will have no choice. Mr. Moore urges the board to consider that this</p> |

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| | | <p>shortage was not a one-time event and is likely to be seen again in some form at some point in the future.</p> |
| 1751.9 | (a)(1) | <p>Comment #21 from Brian Warren, California Pharmacist Association (CPhA) - #13</p> <p>CPhA commented on time limitations on use of opened containers. The proposed regulations add a new Section 1571.9, establishing limitations on use for opened or needle-punctured sterile drug products and compounded sterile products in single-dose and multiple-dose containers. These limitations are based on the standards contained in USP <797>.</p> <p>As stated above, we support consistency between USP <797> and California regulations but stress that because the Board’s regulations have the force of law the regulatory language often needs to be written slightly differently than USP <797>.</p> <p>The standards for use of opened or needle-punctured single-dose and multiple-dose containers are another area where regulatory language should reflect that exceptions to the model do exist. USP <797> standards should generally be followed, but there are times where these standards are not applicable. It is possible that some products should be discarded sooner than provided for in the standard and others may be safe to use for a period longer than provided for in the standard.</p> <p>The proposed regulation already includes an exception for multi-use containers when a manufacturer specifies a use date of longer than the general standard (in subsection (c) of Section 1751.9). We suggest modifying the proposed regulation to add the text “unless otherwise provided for in scientific literature or specified by the manufacturer,” applicable to subsections (a), (b), and (c). This would not result in a different standard, but would result in the USP <797> standards applying to all sterile compounding, except when specific information justifies operating outside of the general standard.</p> <p>As such, we recommend the following modification to Section 1751.9: 1751.9 Single-Dose and Multi-Dose Containers; Limitations on Use <u>Unless otherwise provided for in scientific literature or specified by the manufacturer, the following limitations on use shall apply:</u></p> <p>(a) Any single-dose container of sterile drug product or compounded sterile drug product other than an ampule, such as a bag, bottle, syringe or vial, shall be used in its entirety or its remaining contents discarded within the following time limit, depending on the environment: (1) When opened or needle-punctured in an environment with air quality worse than ISO Class 5, within one (1) hour; (2) When opened or needle-punctured in an environment with ISO Class 5 or better air quality, within six (6) hours.</p> <p>(b) Single-dose ampules are for immediate use only, and once opened or needle-punctured shall not be stored for any time period.</p> <p>(c) Unless otherwise specified by the manufacturer, a <u>A</u> multi-dose container shall be used in its entirety or its remaining contents discarded within twenty eight (28) days from initial opening or puncture.</p> |
| 1751.9 | (a)(3) | <p>Comment #22 from Michael Moné, R.Ph., J.D., FAPhA, Cardinal Health Nuclear Pharmacy Services - #8</p> <p>Cardinal Health commented the proposed addition would limit the pharmacist's ability granted</p> |

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| | | <p>under USP 36 <797> to validate alternate technologies. USP 36 <797> provides/or "The use o/technologies, techniques, materials, and procedures other than those described in this chapter are not prohibited so long as they have been proven to be equivalent or superior with statistical significance to those described herein."</p> <p>Cardinal Health proposes the following language change to add to the proposed amendments to 16 CCR §1751.9: 1751.9 Single-Dose and Multi-Dose Containers; Limitations on Use <u>(3) With respect to the preparation of radio pharmaceuticals, an authorized licensed nuclear pharmacist may employ the use of technologies, techniques, materials, and procedures other than those described in USP 36 <797> that are not prohibited so long as they have been proven to be equivalent or superior with statistical significance to those described therein.</u></p> |
| Title 24 | | <p>Comment #16 from BJ Bartleson, RN, MS, NEA-BC, CA Hospital Association (CHA) - #6</p> <p>CHA commented Title 24, Part 2, Chapter 12, 1250.4(5) does not include emergency settings or include settings with an ISO Class 5 hood in a segregated sterile compounding area as environments permissible for compounding sterile drug products. This would prevent pharmacists from preparing lifesaving sterile compounding medications. We understand the proposed mechanical code regulations in Title 24 have not yet been released for public comment because they are under the jurisdiction of the California Building Standards Commission and not the office of Administrative Law.</p> <p>CHA recommends that Title 24, Part 2, Chapter 12, 1250.4(5) be changed to reflect inclusion of the environment that will allow hospitals to perform sterile compounding for emergently needed sterile drug preparations both at the bedside or in settings with an ISO Class 5 hood in a segregated sterile compounding area.</p> <p>CHA recommends that prior to releasing the proposed mechanical code components for public comment, that the Board of Pharmacy meet with the Office of Statewide Health Planning and Development staff to ensure that there is no conflict between existing 2013 mechanical code requirements and those proposed for this regulatory package.</p> |
| Title 24 | | <p>Oral Testimony #1 – Steven Gray, Pharm.D., JD; Doug O’Brien, Pharm.D.; and Donald Kaplan, Pharm.D., Kaiser Permanente (Kaiser) - #6</p> <p>Dr. O’Brien highlighted the regulations are dovetailing with regulations in Title 24 particularly with cytotoxic chemotherapy. The way they dovetail together is that chemotherapy can only be made in a negative pressure room. Current USP 797 standards allow low volume of chemotherapy in regular IV room that positive pressure room using closed system transfer device for safety. All of Kaiser’s hospitals do this. While it may seem like a small thing, the design implies you need to create an IV room that has an ante room, regular IV room that will have to be positive pressure and separate room for chemotherapy that will have to be negative pressure. If you are currently in compliance with USP 797 that allows for an approved low volume in normal positive pressure room, to meet the regulations, you would have to model all cleanroom and would cost about \$1 million per hospital and Kaiser doesn’t see any additional safety added for the public. The current way Kaiser is doing chemotherapy in accordance with USP 797 allows for safety to the public. Kaiser is in favor of 797 but need all parts or most of 797. If only pieces and parts of 797 are taken, it will be difficult to comply. Kaiser believes it will be more difficult in medical office where chemotherapy is made like oncology clinic that</p> |

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| | | has a negative pressure room. This will be more expensive. This part doesn't provide extra safety for public but requires a lot of capital to do changes that we would rather put toward taking care of patients. |
| Title 24 | | <p>Oral Testimony #8 – Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California (CHCC) - #19</p> <p>Dr. Sakai commented on Title 24 to comply would cost \$150,000 and would need room for chemo listed costs \$2 million over 5 year period.</p> |
| Title 24 505.5.1 | | <p>Comment #7 from Doug O’Brien, Pharm.D., and Donald Kaplan, Pharm.D., Kaiser Permanente - #25</p> <p>Kaiser comments on the following: In all pharmacies preparing cytotoxic agents, all compounding shall be conducted within a certified Class II Type A or Class II Type B vertical laminar airflow hood with bag in-bag out design. The pharmacy must ensure that contaminated air plenums that are under positive pressure are leak tight.</p> <p>Kaiser’s Comment: This language is unnecessary. 1751.4(g) already describes the requirements for use of Class II vertical laminar airflow hoods. In addition, 505.5.1 does not mention that a compounding aseptic containment isolator (CACI) can be used for this purpose. The use of a CACI for the preparation of cytotoxic agents is described in 1751.4(g).</p> <p>Kaiser’s Recommendation: Delete 505.5.1.</p> <p>Kaiser’s Identified Impact: operational inefficiency, employee safety.</p> |
| Title 24 1250.4 | (5) | <p>Comment #17 from Tim Lopez, Pharm.D., Community Regional Medical Centers (CRMC) - #2</p> <p>CRMC commented on this section is missing language about principle of displacement airflow. CRMC’s concern is the current regulation and proposed changes do not allow for buffer zones and ante rooms that are separated by a line of demarcation to follow the principle of displacement airflow described in USP <797> (USP-36, NF-31). This section in USP <797> states that buffer areas not physically separated from ante rooms must have 40 feet per minute or more air velocity from the buffer area across the line of demarcation into the ante area.</p> <p>CRMC’s solution: “or displacement airflow of 40 feet per minute from the buffer area to the ante area,”</p> |
| Title 24 505.5.1 | | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #49</p> <p>Dr. Sakai commented on the text, “In all pharmacies preparing cytotoxic agents, all compounding shall be conducted within a certified Class II Type A or Class II Type B vertical laminar airflow hood with bag in-bag out design. The pharmacy must ensure that contaminated air plenums that are under positive pressure are leak tight.” Dr. Sakai commented this language is unnecessary. 1751.4(g) already describes the requirements for use of Class II vertical laminar airflow hoods. In addition, 505.5.1 does not mention that a compounding aseptic containment isolator (CACI) can be used for this purpose. The use of a CACI for the preparation of</p> |

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| | | <p>cytotoxic agents is described in 1751.4(g). The impact is operational inefficiency and employee safety.</p> <p>Dr. Sakai’s Recommendation: Delete 505.5.1.</p> |
| <p>Title 24, Part 2, Chapter 12, Section 1250.6 (6)</p> | | <p>Comment #7 from Doug O’Brien, Pharm.D., and Donald Kaplan, Pharm.D., Kaiser Permanente - #23</p> <p>Kaiser comments on the following: When compounding hazardous drugs, the surrounding environment must provide at least 0.01 water column negative air pressure and 12 air changes per hour.</p> <p>Kaiser’s Comment #1: There needs to be an allowance for a low volume of chemotherapy preparations in biological safety cabinets in clean rooms that also contain other types of laminar air flow hoods. Consider a hospital pharmacy in which a low volume of inpatient chemotherapy is prepared, and where the clean room was remodeled following the original 2004 USP <797> standards. It would likely be a single clean room, with an ante area and a buffer area. That remodel probably cost \$1 to \$2 million, depending on the size of the pharmacy. In order to meet the proposed regulation, this clean room would need to be remodeled again to provide a separate anteroom, positive pressure buffer room, and a negative pressure room for preparing hazardous drugs (chemotherapy). This would cost approx. an additional \$2 million per pharmacy. The cost is excessive when weighed against the incremental safety benefits.</p> <p>Kaiser’s Recommendation #1: Instead, we propose the USP <797> language, with a caveat that “low volume” be defined, since the USP <797> language is subjective and not enforceable. “In facilities that prepare a low volume of hazardous drugs, the use of two tiers of containment (e.g., Closed System Transfer Device within a BSC or CACI that is located in a non-negative pressure room) is acceptable.” We propose this definition:” A low volume is defined as less than or equal to a mean number of twenty doses per week, averaged over a period of one month.”</p> <p>Kaiser’s Comment #2: There needs to be an allowance for ambulatory oncology pharmacies which do not currently meet this requirement, and prepare a high volume of chemotherapy (e.g. greater than twenty doses per week) for administration to patients in medical offices and clinics. These pharmacies are typically equipped with a Class II vertical flow hood in a small ISO Class 7 or ISO Class 8 clean room under positive pressure. It will be very costly and time-consuming to remodel these pharmacies.</p> <p>Kaiser’s Recommendation #2: We propose that ambulatory oncology pharmacies be given a five-year period to come into compliance.</p> <p>Kaiser’s Identified Impact: Remodeling & construction costs: \$115 million for our organization.</p> |
| <p>Title 24, Part 2, Chapter 12, section 1250,</p> | | <p>Comment #2 from Martin Hesky, Pharm.D. – #1</p> <p>Dr. Hesky commented requesting clarification if the board’s language was handling Compounding Aseptic Isolators (CAI) any differently than USP 797 does in certain areas. For example, there is an exception for CAI having to be located in an ISO 7 environment if certain requirements are met; there is an exception for standard garbing requirements if certain</p> |

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| | | <p>requirements are met; and also sterile gloves are not necessarily a requirement although the use of sterile isopropyl alcohol on the gloves is. Dr. Hesky requests the board direct him to the language that disuccess any differences in how CAI's will be regulated.</p> <p>Board Comment Note: Board Inspector Smith responded to Dr. Hesky's question specifying that the proposed regulations reflects changes to Title 24, Part 2, Chapter 12 , section 1250, subdivision 5.3.</p> <p>5.3 A barrier isolator that provides an ISO Class 5 environment for compounding within an ISO Class 7 cleanroom unless documentation from the manufacturer of the barrier isolator permits operation of the barrier isolator in an environment that exceeds ISO Class 7.</p> <p>This language is similar to USP 797 in the section titled Placement of Primary Engineering Controls. The current proposed regulations do not currently exempt from gloving and garb as described in section 1751.5. USP 797 states in the Personnel Cleansing and Garbing section:</p> <p><i>When CAIs and CACIs are the source of the ISO Class 5 (see Table 1) environment, the garbing and gloving requirements for compounding personnel should be as described above, unless the isolator manufacturer can provide written documentation based on validated environmental testing that any component(s) of PPE or personnel cleansing are not required.</i></p> <p>Inspector Smith indicated the attire and gloving in CAI's may be an area for further discussion but wondered how many hood manufacturers have validated studies and are willing to state gloves and attire is not required.</p> |
| <p>Title 24, Part 2, Chapter 12, 1250.4 (6)</p> | | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children's Hospital Central California - #48</p> <p>Dr. Sakai commented on when compounding hazardous drugs, the surrounding environment must provide at least 0.01 water column negative air pressure and 12 air changes per hour. Dr. Sakai commented there needs to be an allowance for a low volume of chemotherapy preparations in biological safety cabinets in clean rooms that also contain other types of laminar air flow hoods. The impact is remodeling and construction costs exceeding \$40 million for our organization.</p> <p>Dr. Sakai's Recommendation: Consider a hospital pharmacy in which a low volume of inpatient chemotherapy is prepared, and where the clean room was remodeled following the original 2004 USP <797> standards. It would likely be a single clean room, with an ante area and a buffer area. That remodel probably cost \$1 to \$2 million, depending on the size of the pharmacy. In order to meet the proposed regulation, this clean room would need to be remodeled again to provide a separate anteroom, positive pressure buffer room, and a negative pressure room for preparing hazardous drugs (chemotherapy). This would cost another \$1 to \$2 million. The cost is excessive when weighed against the incremental safety benefits.</p> <p>Instead, we propose the USP <797> language, with a caveat that "low volume" be defined,</p> |

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| | | <p>since that terminology is subjective and not enforceable. “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.”</p> <p>We propose this definition: A low volume is defined as less than or equal to a mean number of twenty doses per week, averaged over a period of one month.”</p> |
| <p>Title 24, Part 2, Chapter 12, 1250.4 (5)</p> | | <p>Comment #24 from Candace Fong, Pharm.D., and Rachele Reyes Wenger, Dignity Health - #5</p> <p>Dignity Health seeks and supports amendments to the Title 24 section that will be handled through the Building Standards Commission which are in alignment with our recommendations above. We will recommend that Title 24, Part 2, Chapter 12, 1250.4(5) be changed to reflect inclusion of the environment that will allow hospitals to perform sterile compounding for emergently needed sterile drug preparations both at the bedside or in settings with an ISO Class 5 hood in a segregated sterile compounding area.</p> |
| <p>Title 24, Part 2, Chapter 12, 1250.4 (5)</p> | | <p>Comment #20 from Dawn Benton, MBA, California Society of Health-Systems Pharmacists (CSHP) - #9</p> <p>CSHP commented Title 24, Part 2, Chapter 12, 1250.4 (5) does not include emergency settings or include settings with an ISO Class 5 hood in a segregated sterile compounding area as environments permissible for compounding sterile drug products. This would prevent pharmacists from preparing lifesaving sterile compounding medications. CSHP understands that Title 24 section will be handled through the Building Standards Commission. CSHP is adding comments here to reinforce the need to amend these regulations.</p> <p>CSHP recommends Title 24, Part 2, Chapter 12, 1250.4 (5) be changed to reflect inclusion of the environment that will allow hospitals to perform sterile compounding for emergently needed sterile drug preparations both at bedside or in settings with an ISO Class 5 hood in a specified sterile compounding area.</p> |
| <p>Title 24, Part 2, Chapter 12, 1250.4 (5.1)</p> | | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #46</p> <p>Dr. Sakai commented on the storage of items not related to the compounding of parenteral solutions. Dr. Sakai’s comment is the term “solution” may be too narrow of a term. The term “sterile products” will encompass a broader variety of dosage forms that may be compounded such as ophthalmics, bronchial and nasal inhalation solutions.</p> <p>Dr. Sakai’s Recommendation: change from “solutions” to “sterile products.”</p> |
| <p>Title 24, Part 2, Chapter 12, 1250.4 (5.1)</p> | | <p>Comment #15 from Richard Sakai, Pharm.D., FASHP, FCSHP, Children’s Hospital Central California - #47</p> <p>Dr. Sakai commented on any pharmacy that compounds sterile drug products must compound the medication in one of the following environments: 5.1 An ISO Class laminar airflow hood within an ISO Class 7 cleanroom. The cleanroom must have positive air pressure differential relative to adjacent areas. Dr. Sakai’s comment is this language is incomplete. USP <797> articulates a well thought-out description of the sterile compounding environment and engineering controls, based on the input and experience of nationally respected clean room</p> |

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| | | <p>engineers. It is inappropriate to extract a piece of this language and place it in regulations. The impact may be remodeling & construction costs exceeding \$25 million for our organization.</p> <p>Dr. Sakai’s Recommendation Use of displacement airflow described in USP Chapter 797: “For rooms providing a physical separation through the use of walls, doors, and pass-thrus, a minimum differential positive pressure of 0.02- to 0.05-inch water column is required. For buffer areas not physically separated from the ante-areas, the principle of displacement airflow shall be employed. This concept utilizes a low pressure differential, high airflow principle. Using displacement airflow typically requires an air velocity of 40 ft per minute or more from the buffer area across the line of demarcation into the ante-area.”</p> |
| <p>Title 42, Part 2, Chapter 12, Section 1250.4 (5.1)</p> | | <p>Comment #7 from Doug O’Brien, Pharm.D., and Donald Kaplan, Pharm.D., Kaiser Permanente - #22</p> <p>Kaiser comments on the following: Any pharmacy that compounds sterile drug products must compound the medication in one of the following environments: 5.1 An ISO Class laminar airflow hood within an ISO Class 7 cleanroom. The cleanroom must have positive air pressure differential relative to adjacent areas.</p> <p>Kaiser’s Comment: We are assuming this language would apply to a pharmacy that prepares non-hazardous products only. Even then, this language is incomplete. USP <797> articulates a well thought-out description of the sterile compounding environment and engineering controls, based on the input and experience of nationally respected clean room engineers. It is inappropriate to extract a piece of this language and place it in regulations.</p> <p>Kaiser’s Recommendation: Instead, we propose the use of displacement airflow described in USP Chapter 797: “For rooms providing a physical separation through the use of walls, doors, and pass-throughs, a minimum differential positive pressure of 0.02- to 0.05-inch water column is required. For buffer areas not physically separated from the ante-areas, the principle of displacement airflow shall be employed. This concept utilizes a low pressure differential, high airflow principle. Using displacement airflow typically requires an air velocity of 40 ft per minute or more from the buffer area across the line of demarcation into the ante-area.”</p> <p>Kaiser’s Identified Impact: Remodeling & construction costs: exceeding \$60 million for our organization.</p> |

Attachments:

Attachment A – scan pages 53 & 54 of Comment #11 from Rita Shane at Cedar-Sinai

Attachment B – scan pages 154-159 of Comment #22 from Cardinal Health

**METOPROLOL TARTRATE
INJECTION, USP**

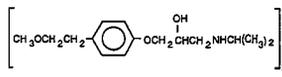
Rx Only

**METOPROLOL TARTRATE
INJECTION, USP**

Rx Only

**DESCRIPTION**

Metoprolol tartrate injection, USP is a sterile solution containing metoprolol tartrate, a selective beta₁-adrenoreceptor blocking agent, available in 5 mL vials for intravenous administration. Each vial contains a sterile solution of metoprolol tartrate USP, 5 mg and sodium chloride USP, 45 mg. Metoprolol tartrate is (+)-1-(isopropylamino)-3-[p-(2-methoxyethyl)phenoxy]-2-propanol L-(-)-tartrate (2:1) salt, and its structural formula is:



Metoprolol tartrate is a white, practically odorless, crystalline powder with a molecular weight of 684.81. Its molecular formula is (C₁₃H₂₃N₂O₃)₂·C₄H₆O₆. It is very soluble in water; freely soluble in methylene chloride, in chloroform, and in alcohol; slightly soluble in acetone; and insoluble in ether.

CLINICAL PHARMACOLOGY

Metoprolol tartrate is a beta-adrenergic receptor blocking agent. *In vitro* and *in vivo* animal studies have shown that it has a preferential effect on beta₁ adrenoreceptors, chiefly located in cardiac muscle. This preferential effect is not absolute, however, and at higher doses, metoprolol tartrate also inhibits beta₂ adrenoreceptors, chiefly located in the bronchial and vascular musculature.

Clinical pharmacology studies have confirmed the beta-blocking activity of metoprolol in man, as shown by (1) reduction in heart rate and cardiac output at rest and upon exercise, (2) reduction of systolic blood pressure upon exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

Relative beta₁ selectivity has been confirmed by the following: (1) In normal subjects, metoprolol tartrate is unable to reverse the beta₂-mediated vasodilating effects of epinephrine. This contrasts with the effect of nonselective (beta₁ plus beta₂) beta-blockers, which completely reverse the vasodilating effects of epinephrine. (2) In asthmatic patients, metoprolol tartrate reduces FEV₁ and FVC significantly less than a nonselective beta-blocker, propranolol, at equivalent beta₁-receptor blocking doses.

Metoprolol tartrate has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at doses much greater than required for beta-blockade. Metoprolol tartrate crosses the blood-brain barrier and has been reported in the CSF in a concentration 78% of the simultaneous plasma concentration. Animal and human experiments indicate that metoprolol tartrate slows the sinus rate and decreases AV nodal conduction.

In controlled clinical studies, metoprolol tartrate has been shown to be an effective antihypertensive agent when used alone or as concomitant therapy with thiazide-type diuretics, at dosages of 100 to 450 mg daily. In controlled, comparative, clinical studies, metoprolol tartrate has been shown to be as effective an antihypertensive agent as propranolol, methyldopa, and thiazide-type diuretics, and to be equally effective in supine and standing positions.

The mechanism of the antihypertensive effects of beta-blocking agents has not been elucidated. However, several possible mechanisms have been proposed: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output; (2) a central effect leading to reduced sympathetic outflow to the periphery; and (3) suppression of renin activity.

By blocking catecholamine-induced increases in heart rate, in velocity and extent of myocardial contraction, and in blood pressure, metoprolol tartrate reduces the oxygen requirements of the heart at any given level of effort, thus making it useful in the long-term management of angina pectoris. However, in patients with heart failure, beta-adrenergic blockade may increase oxygen requirements by increasing left ventricular fiber length and end-diastolic pressure.

Although beta-adrenergic receptor blockade is useful in the treatment of angina and hypertension, there are situations in which sympathetic stimulation is vital. In patients with severely damaged hearts, adequate ventricular function may depend on sympathetic drive. In the presence of AV block, beta-blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta₂-adrenergic blockade results in passive bronchial constriction by interfering with endogenous adrenergic bronchodilator activity in patients subject to bronchospasm and may also interfere with exogenous bronchodilators in such patients.

In controlled clinical trials, metoprolol tartrate, administered two or four times daily, has been shown to be an effective antianginal agent, reducing the number of angina attacks and increasing exercise tolerance. The dosage used in these studies ranged from 100 to 400 mg daily. A controlled, comparative, clinical trial showed that metoprolol tartrate was indistinguishable from propranolol in the treatment of angina pectoris.

In a large (1,395 patients randomized), double-blind, placebo-controlled clinical study, metoprolol tartrate was shown to reduce 3-month mortality by 36% in patients with suspected or definite myocardial infarction.

Patients were randomized and treated as soon as possible after their arrival in the hospital, once their clinical condition had stabilized and their hemodynamic status had been carefully evaluated. Subjects were ineligible if they had hypotension, bradycardia, peripheral signs of shock, and/or more than minimal basal rates as signs of congestive heart failure. Initial treatment consisted of intravenous followed by oral administration of metoprolol tartrate or placebo, given in a coronary care or comparable unit. Oral maintenance therapy with metoprolol tartrate or placebo was then continued for 3 months. After this double-blind period, all patients were given metoprolol tartrate and followed up to 1 year.

The median delay from the onset of symptoms to the initiation of therapy was 8 hours in both the metoprolol tartrate and placebo treatment groups. Among patients treated with metoprolol tartrate, there were comparable reductions in 3-month mortality for those treated early (≤ 8 hours) and those in whom treatment was started later. Significant reductions in the incidence of ventricular fibrillation and in chest pain following initial intravenous therapy were also observed with metoprolol tartrate and were independent of the interval between onset of symptoms and initiation of therapy.

The precise mechanism of action of metoprolol tartrate in patients with suspected or definite myocardial infarction is not known.

In this study, patients treated with metoprolol received the drug both very early (intravenously) and during a subsequent 3-month period, while placebo patients received no beta-blocker treatment for this period. The study thus was able to show a benefit from the overall metoprolol regimen but cannot separate the benefit of very early intravenous treatment from the benefit of later beta-blocker therapy. Nonetheless, because the overall regimen showed a clear beneficial effect on survival without evidence of an early adverse effect on survival, one acceptable dosage regimen is the precise regimen used in the trial. Because the specific benefit of very early treatment remains to be defined however, it is also reasonable to administer the drug orally to patients at a later time as is recommended for certain other beta-blockers.

Pharmacokinetics

In man, absorption of metoprolol tartrate is rapid and complete. Plasma levels following oral administration, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism.

Plasma levels achieved are highly variable after oral administration. Only a small fraction of the drug (about 12%) is bound to human serum albumin. Metoprolol is a racemic mixture of R- and S-enantiomers. Less than 5% of an oral dose of metoprolol tartrate is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no clinical significance. The systemic availability and half-life of metoprolol tartrate in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. Consequently, no reduction in dosage is usually needed in patients with chronic renal failure.

Metoprolol tartrate is extensively metabolized by the cytochrome P450 enzyme system in the liver. The oxidative metabolism of metoprolol tartrate is under genetic control with a major contribution of the polymorphic cytochrome P450 isozyme 2D6 (CYP2D6). There are marked ethnic differences in the prevalence of the poor metabolizers (PM) phenotype. Approximately 7% of Caucasians and less than 1% Asian are poor metabolizers.

Poor CYP2D6 metabolizers exhibit several-fold higher plasma concentrations of metoprolol tartrate than extensive metabolizers with normal CYP2D6 activity. The elimination half-life of metoprolol is about 7.5 hours in poor metabolizers and 2.8 hours in extensive metabolizers. However, the CYP2D6 dependent metabolism of metoprolol tartrate seems to have little or no effect on safety or tolerability of the drug. None of the metabolites of metoprolol tartrate contribute significantly to its beta-blocking effect.

Significant beta-blocking effect (as measured by reduction of exercise heart rate) occurs within 1 hour after oral administration, and its duration is dose-related. For example, a 50% reduction of the maximum registered effect after single oral doses of 20, 50, and 100 mg occurred at 3.3, 5.0, and 6.4 hours, respectively, in normal subjects. After repeated oral dosages of 100 mg twice daily, a significant reduction in exercise systolic blood pressure was evident at 12 hours.

Following intravenous administration of metoprolol tartrate, the urinary recovery of unchanged drug is approximately 10%. When the drug was infused over a 10-minute period, in normal volunteers, maximum beta-blockade was achieved at approximately 20 minutes. Doses of 5 mg and 15 mg yielded a maximal reduction in exercise-induced heart rate of approximately 10% and 15%, respectively. The effect on exercise heart rate decreased linearly with time at the same rate for both doses, and disappeared at approximately 5 hours and 8 hours for the 5 mg and 15 mg doses, respectively.

Equivalent maximal beta-blocking effect is achieved with oral and intravenous doses in the ratio of approximately 2.5:1.

There is a linear relationship between the log of plasma levels and reduction of exercise heart rate. However, antihypertensive activity does not appear to be related to plasma levels. Because of variable plasma levels attained with a given dose and lack of a consistent relationship of antihypertensive activity to dose, selection of proper dosage requires individual titration.

In several studies of patients with acute myocardial infarction, intravenous followed by oral administration of metoprolol tartrate caused a reduction in heart rate, systolic blood pressure, and cardiac output. Stroke volume, diastolic blood pressure, and pulmonary artery and diastolic pressure remained unchanged.

In patients with angina pectoris, plasma concentration measured at 1 hour is linearly related to the oral dose within the range of 50 to 400 mg. Exercise heart rate and systolic blood pressure are reduced in relation to the logarithm of the oral dose of metoprolol. The increase in exercise capacity and the reduction in left ventricular ischemia are also significantly related to the logarithm of the oral dose.

In elderly subjects with clinically normal renal and hepatic function, there are no significant differences in metoprolol tartrate pharmacokinetics compared to young subjects.

INDICATIONS AND USAGE**Myocardial Infarction**

Metoprolol tartrate injection is indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment with intravenous metoprolol tartrate can be initiated as soon as the patient's clinical condition allows (see **DOSE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS**). Alternatively, treatment can begin within 3 to 10 days of the acute event (see **DOSE AND ADMINISTRATION**).

CONTRAINDICATIONS**Hypertension and Angina**

Metoprolol tartrate is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**).

Hypersensitivity to metoprolol tartrate and related derivatives, or to any of the excipients; hypersensitivity to other beta-blockers (cross sensitivity between beta-blockers can occur).

Sick-sinus syndrome.**Severe peripheral arterial circulatory disorders.****Myocardial Infarction**

Metoprolol tartrate is contraindicated in patients with a heart rate < 45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg; or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS**Hypertension and Angina**

Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta-blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, metoprolol tartrate should be administered cautiously.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, metoprolol tartrate should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered metoprolol tartrate, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1 to 2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, metoprolol tartrate administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue metoprolol tartrate therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS, including metoprolol tartrate. Because of its relative beta₁ selectivity, however, metoprolol tartrate may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta₁ selectivity is not absolute, a beta₂-stimulating agent should be administered concomitantly, and the lowest possible dose of metoprolol tartrate should be used. In these circumstances it would be prudent initially to administer metoprolol tartrate in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval (see **DOSE AND ADMINISTRATION**).

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy, including metoprolol tartrate, prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol tartrate, like other beta-blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta-blockers.

Diabetes and Hypoglycemia: Metoprolol tartrate should be used with caution in diabetic patients if a beta-blocking agent is required. Beta-blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Pheochromocytoma: If metoprolol tartrate is used in the setting of pheochromocytoma, it should be given in combination with an alpha blocker, and only after the alpha blocker has been initiated. Administration of beta-blockers alone in the setting of pheochromocytoma has been associated with a paradoxical increase in blood pressure due to the attenuation of beta-mediated vasodilatation in skeletal muscle.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade, which might precipitate a thyroid storm.

Myocardial Infarction

Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta-blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with metoprolol tartrate, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, metoprolol tartrate should be discontinued.

Bradycardia: Metoprolol tartrate produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25 to 0.5 mg) should be administered intravenously. If treatment with atropine is not successful, metoprolol tartrate should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

AV Block: Metoprolol tartrate slows AV conduction and may produce significant first- (P-R interval ≥ 0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, metoprolol tartrate should be discontinued and atropine (0.25 to 0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, metoprolol tartrate should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

**METOPROLOL TARTRATE
INJECTION, USP**

Rx Only

**METOPROLOL TARTRATE
INJECTION, USP**

Rx Only



Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS INCLUDING METOPROLOL TARTRATE. Because of its relative beta₁ selectivity, metoprolol tartrate may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta₂-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should not be used prophylactically. If bronchospasm not related to congestive heart failure occurs, metoprolol tartrate should be discontinued. A theophylline derivative or a beta₂ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta₂ agonists may produce serious cardiac arrhythmias.

PRECAUTIONS

General

Metoprolol tartrate should be used with caution in patients with impaired hepatic function.

Drug Interactions

Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with metoprolol tartrate plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Both digitalis glycosides and beta-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.

Risk of Anaphylactic Reaction

While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

General Anesthetics

Some inhalation anesthetics may enhance the cardiodepressant effect of beta-blockers (see WARNINGS, Major Surgery).

CYP2D6 Inhibitors

Potent inhibitors of the CYP2D6 enzyme may increase the plasma concentration of metoprolol tartrate. Strong inhibition of CYP2D6 would mimic the pharmacokinetics of CYP2D6 poor metabolizer (see CLINICAL PHARMACOLOGY, Pharmacokinetics section). Caution should therefore be exercised when coadministering potent CYP2D6 inhibitors with metoprolol tartrate. Known clinically significant potent inhibitors of CYP2D6 are antidepressants such as fluoxetine, paroxetine or bupropion, antipsychotics such as thioridazine, antirhythmic such as quinidine or propafenone, antiretrovirals such as ritonavir, antihistamines such as diphenhydramine, antimalarials such as hydroxychloroquine or quinidine, antifungals such as terbinafine and medications for stomach ulcers such as cimetidine.

Clonidine

If a patient is treated with clonidine and metoprolol tartrate concurrently, and clonidine treatment is to be discontinued, metoprolol tartrate should be stopped several days before clonidine is withdrawn. Rebound hypertension that can follow withdrawal of clonidine may be increased in patients receiving concurrent beta-blocker treatment.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have been conducted to evaluate carcinogenic potential. In a 2-year study in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.

No evidence of impaired fertility due to metoprolol tartrate was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.

Pregnancy Category C

Metoprolol tartrate has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when metoprolol tartrate is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Metoprolol tartrate is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when metoprolol tartrate is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical trials of metoprolol tartrate in hypertension did not include sufficient numbers of elderly patients to determine whether patients over 65 years of age differ from younger subjects in their response to metoprolol tartrate. Other reported clinical experience in elderly hypertensive patients has not identified any difference in response from the younger patients.

In worldwide clinical trials of metoprolol tartrate in myocardial infarction, where approximately 478 patients were over 65 years of age (0 over 75 years of age), no age-related differences in safety and effectiveness were found. Other reported clinical experience in myocardial infarction has not identified differences in response between the elderly and younger patients. However, greater sensitivity of some elderly individuals taking metoprolol tartrate cannot be categorically ruled out. Therefore, in general, it is recommended that dosing proceed with caution in this population.

ADVERSE REACTIONS

Hypertension and Angina

Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; and hypotension have been reported in about 1 of 100 patients. Gangrene in patients with pre-existing severe peripheral circulatory disorders has also been reported very rarely. (See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS.)

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see WARNINGS). Rhinitis has also been reported.

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients. Vomiting was a common occurrence. Postmarketing experience reveals very rare reports of hepatitis, jaundice and non-specific hepatic dysfunction. Isolated cases of transaminase, alkaline phosphatase, and lactic dehydrogenase elevations have also been reported.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Very rarely, photosensitivity and worsening of psoriasis has been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, and linnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. There have been very rare reports of weight gain, arthritis, and retroperitoneal fibrosis (relationship to metoprolol tartrate has not been definitely established).

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with metoprolol tartrate.

Myocardial Infarction

Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of metoprolol tartrate and placebo described in the CLINICAL PHARMACOLOGY section, the following adverse reactions were reported:

| | Metoprolol Tartrate | Placebo |
|---|---------------------|---------|
| Hypotension (systolic BP < 90 mmHg) | 27.4% | 23.2% |
| Bradycardia (heart rate < 40 beats/min) | 15.9% | 6.7% |
| Second- or third-degree heart block | 4.7% | 4.7% |
| First-degree heart block (P-R ≥ 0.26 sec) | 5.3% | 1.9% |
| Heart failure | 27.5% | 29.6% |

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.

Potential Adverse Reactions

A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to metoprolol tartrate.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometric tests.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

Postmarketing Experience

The following adverse reactions have been reported during postapproval use of metoprolol tartrate: confusional state, an increase in blood triglycerides and a decrease in High Density Lipoprotein (HDL). Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency.

OVERDOSAGE

Acute Toxicity

Several cases of overdosage have been reported, some leading to death.

Oral LD₅₀'s (mg/kg): mice, 1158 to 2460; rats, 3090 to 4670.

Signs and Symptoms

Potential signs and symptoms associated with overdosage with metoprolol tartrate are bradycardia, hypotension, bronchospasm, and cardiac failure.

Treatment

There is no specific antidote.

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see WARNINGS, Myocardial Infarction).

On the basis of the pharmacologic actions of metoprolol tartrate, the following general measures should be employed:

Elimination of the Drug: Gastric lavage should be performed.

Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

Hypotension: A vasopressor should be administered, e.g., norepinephrine or dopamine.

Bronchospasm: A beta₂-stimulating agent and/or a theophylline derivative should be administered.

Cardiac Failure: A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

DOSAGE AND ADMINISTRATION

Myocardial Infarction

Early Treatment: During the early phase of definite or suspected acute myocardial infarction, treatment with metoprolol tartrate can be initiated as soon as possible after the patient's arrival in the hospital. Such treatment should be initiated in a coronary care or similar unit immediately after the patient's hemodynamic condition has stabilized.

Treatment in this early phase should begin with the intravenous administration of three bolus injections of 5 mg of metoprolol tartrate each; the injections should be given at approximately 2-minute intervals. During the intravenous administration of metoprolol tartrate, blood pressure, heart rate, and electrocardiogram should be carefully monitored.

In patients who tolerate the full intravenous dose (15 mg), metoprolol tartrate tablets, 50 mg every 6 hours, should be initiated 15 minutes after the last intravenous dose and continued for 48 hours. Thereafter, patients should receive a maintenance dosage of 100 mg twice daily (see Late Treatment below).

Patients who appear not to tolerate the full intravenous dose should be started on metoprolol tartrate tablets either 25 mg or 50 mg every 6 hours (depending on the degree of intolerance) 15 minutes after the last intravenous dose or as soon as their clinical condition allows. In patients with severe intolerance, treatment with metoprolol tartrate should be discontinued (see WARNINGS).

Late Treatment: Patients with contraindications to treatment during the early phase of suspected or definite myocardial infarction, patients who appear not to tolerate the full early treatment, and patients in whom the physician wishes to delay therapy for any other reason should be started on metoprolol tartrate tablets, 100 mg twice daily, as soon as their clinical condition allows. Therapy should be continued for at least 3 months. Although the efficacy of metoprolol tartrate beyond 3 months has not been conclusively established, data from studies with other beta-blockers suggest that treatment should be continued for 1 to 3 years.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Metoprolol Tartrate Injection, USP is available as:

| | | |
|------------------|----------------------------|----------------|
| NDC 0517-1355-10 | 5 mg/5 mL Single Dose Vial | Packages of 10 |
| NDC 0517-1355-25 | 5 mg/5 mL Single Dose Vial | Packages of 25 |

Storage

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Do not freeze.

PROTECT FROM LIGHT. Retain in carton until time of use.

Discard unused portion.

Vial stoppers do not contain natural rubber latex.

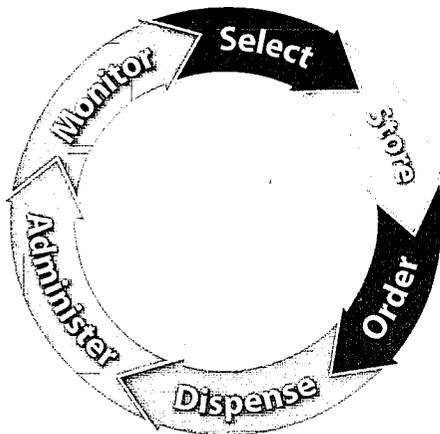
To report SUSPECTED ADVERSE REACTIONS, contact American Regent, Inc. at 1-800-734-9236 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

IN1455
Rev. 3/10
MG# 26651

**AMERICAN
REGENT, INC.
SHIRLEY, NY 11967**

FDA-approved radiopharmaceuticals

Medication Management



This is a current list of all FDA-approved radiopharmaceuticals. Nuclear medicine practitioners that receive radiopharmaceuticals that originate from sources other than the manufacturers listed in these tables may be using unapproved copies.

| | Radiopharmaceutical | Manufacturer | Trade Names | Approved Indications in Adults (Pediatric use as noted) |
|---|--|----------------|-------------|--|
| 1 | Carbon-11 choline | Mayo Clinic | - | Indicated for PET imaging of patients with suspected prostate cancer recurrence based upon elevated blood prostate specific antigen (PSA) levels following initial therapy and non-informative bone scintigraphy, computerized tomography (CT) or magnetic resonance imaging (MRI) to help identify potential sites of prostate cancer recurrence for subsequent histologic confirmation |
| 2 | Carbon-14 urea | Kimberly-Clark | PYtest | Detection of gastric urease as an aid in the diagnosis of H.pylori infection in the stomach |
| 3 | Fluorine-18 florbetapir | Eli Lilly | Amyvid™ | |
| 4 | Fluorine-18 sodium fluoride ¹ | Various | - | PET bone imaging agent to delineate areas of altered osteogenesis |
| 5 | Fluorine-18 fludeoxyglucose ¹ | Various | - | As a PET imaging agent to: <ul style="list-style-type: none"> • Assess abnormal glucose metabolism in oncology • Assess myocardial hibernation • Identify regions of abnormal glucose metabolism associated with foci of epileptic seizures |

Package Inserts may be viewed at <http://nps.cardinal.com/MSDSPI/Main.aspx>

Note: See page six for footnotes

Radiopharmaceuticals that may potentially have unapproved copies of FDA-approved commercially available radiopharmaceuticals in the marketplace.

| | Radiopharmaceutical | Manufacturer | Trade Names | Approved Indications in Adults (Pediatric use as noted) |
|----|-------------------------------------|--------------------------------------|--------------------|---|
| 6 | Gallium-67 citrate | Covidien Lantheus Medical Imaging | - - | Useful to demonstrate the presence/extent of: <ul style="list-style-type: none"> • Hodgkin's disease • Lymphoma • Bronchogenic carcinoma Aid in detecting some acute inflammatory lesions |
| 7 | Indium-111 capromab pentetide | Jazz Pharmaceuticals | ProstaScint® | <ul style="list-style-type: none"> • A diagnostic imaging agent in newly-diagnosed patients with biopsy-proven prostate cancer, thought to be clinically-localized after standard diagnostic evaluation (e.g. chest x-ray, bone scan, CT scan, or MRI), who are at high-risk for pelvic lymph node metastases • A diagnostic imaging agent in post-prostatectomy patients with a rising PSA and a negative or equivocal standard metastatic evaluation in whom there is a high clinical suspicion of occult metastatic disease |
| 8 | Indium-111 chloride | Covidien GE Healthcare | - Indiclor™ | Indicated for radiolabeling: <ul style="list-style-type: none"> • ProstaScint® used for in vivo diagnostic imaging procedures |
| 9 | Indium-111 pentetate | GE Healthcare | - | For use in radionuclide cisternography |
| 10 | Indium-111 oxyquinoline | GE Healthcare | - | Indicated for radiolabeling autologous leukocytes which may be used as an adjunct in the detection of inflammatory processes to which leukocytes migrate, such as those associated with abscesses or other infection |
| 11 | Indium-111 pentetreotide | Covidien | Octreoscan™ | An agent for the scintigraphic localization of primary and metastatic neuroendocrine tumors bearing somatostatin receptors |
| 12 | Iodine I-123 iobenguane | GE Healthcare | AdreView™ | Indicated for use in the detection of primary or metastatic pheochromocytoma or neuroblastoma as an adjunct to other diagnostic tests. Indicated for scintigraphic assessment of sympathetic innervation of the myocardium by measurement of the heart to mediastinum (H/M) ratio of radioactivity uptake in patients with New York Heart Association (NYHA) class II or class III heart failure and left ventricular ejection fraction (LVEF) ≤ 35%. Among these patients, it may be used to help identify patients with lower one and two year mortality risks, as indicated by an H/M ratio ≥ 1.6. Limitations of Use: In patients with congestive heart failure, its utility has not been established for: selecting a therapeutic intervention or for monitoring the response to therapy; using the H/M ratio to identify a patient with a high risk for death. |
| 13 | Iodine I-123 ioflupane ² | GE Healthcare | DaTscan™ | Indicated for striatal dopamine transporter visualization using SPECT brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian syndromes (PS) in whom it may help differentiate essential tremor due to PS (idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy) |
| 14 | Iodine I-123 sodium iodide capsules | Cardinal Health Covidien | - - | Indicated for use in the evaluation of thyroid: <ul style="list-style-type: none"> • Function • Morphology |
| 15 | Iodine I-125 human serum albumin | IsoTex Diagnostics | Jeanatope | Indicated for use in the determination of: <ul style="list-style-type: none"> • Total blood • Plasma volume |
| 16 | Iodine I-125 iothalamate | IsoTex Diagnostics | Glofil-125 | Indicated for evaluation of glomerular filtration |

| | Radiopharmaceutical | Manufacturer | Trade Names | Approved Indications in Adults (Pediatric use as noted) |
|----|----------------------------------|---------------------------------------|-------------------------|---|
| 17 | Iodine I-131 human serum albumin | IsoTex Diagnostics | Megatope | Indicated for use in determinations of: <ul style="list-style-type: none"> • Total blood and plasma volumes • Cardiac output • Cardiac and pulmonary blood volumes and circulation times • Protein turnover studies • Heart and great vessel delineation • Localization of the placenta • Localization of cerebral neoplasms |
| 18 | Iodine I-131 sodium iodide | Covidien | – | Diagnostic: <ul style="list-style-type: none"> • Performance of the radioactive iodide (RAI) uptake test to evaluate thyroid function • Localizing metastases associated with thyroid malignancies Therapeutic: <ul style="list-style-type: none"> • Treatment of hyperthyroidism • Treatment of carcinoma of the thyroid |
| | | DRAXIMAGE | HICON™ | |
| 19 | Iodine I-131 tositumomab | GlaxoSmithKline | BEXXAR® | Indicated for: Treatment of patients with CD20 antigen-expressing relapsed or refractory, low grade, follicular, or transformed non-Hodgkin's lymphoma, including patients with Rituximab-refractory non-Hodgkin's lymphoma |
| 20 | Molybdenum Mo-99 generator | Covidien | Ultra-TechneKow® DTE | Generation of Tc-99m sodium pertechnetate for administration or radiopharmaceutical preparation |
| | | Lantheus Medical Imaging | Technelite® | |
| 21 | Nitrogen-13 ammonia ¹ | Various | – | Indicated for diagnostic Positron Emission Tomography (PET) imaging of the myocardium under rest or pharmacologic stress conditions to evaluate myocardial perfusion in patients with suspected or existing coronary artery disease |
| 22 | Radium-223 dichloride | Bayer HealthCare Pharmaceuticals Inc. | Xofigo® | Indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease |
| 23 | Rubidium-82 chloride | Bracco Diagnostics | Cardiogen-82® | PET myocardial perfusion agent that is useful in distinguishing normal from abnormal myocardium in patients with suspected myocardial infarction |
| 24 | Samarium-153 lexidronam | Jazz Pharmaceuticals | Quadramet® | Indicated for relief of pain in patients with confirmed osteoblastic metastatic bone lesions that enhance on radionuclide bone scan |
| 25 | Strontium-89 chloride | Bio-Nucleonics | – | Indicated for the relief of bone pain in patients with painful skeletal metastases that have been confirmed prior to therapy |
| | | GE Healthcare | Metastron™ | |
| 26 | Technetium-99m bicisate | Lantheus Medical Imaging | Neurolite® | SPECT imaging as an adjunct to conventional CT or MRI imaging in the localization of stroke in patients in whom stroke has already been diagnosed |

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Radiopharmaceuticals that may potentially have unapproved copies of FDA-approved commercially available radiopharmaceuticals in the marketplace.

| | Radiopharmaceutical | Manufacturer | Trade Names | Approved Indications in Adults (Pediatric use as noted) |
|----|--|---------------------|--------------------|--|
| 27 | Technetium-99m disofenin | Pharmalucence | Hepatology® | Diagnosis of acute cholecystitis as well as to rule out the occurrence of acute cholecystitis in suspected patients with right upper quadrant pain, fever, jaundice, right upper quadrant tenderness and mass or rebound tenderness, but not limited to these signs and symptoms. |
| 28 | Technetium-99m exametazine | GE Healthcare | Ceretec™ | <ul style="list-style-type: none"> • As an adjunct in the detection of altered regional cerebral perfusion in stroke • Leukocyte labeled scintigraphy as an adjunct in the localization of intra abdominal infection and inflammatory bowel disease |
| 29 | Technetium-99m macroaggregated albumin | DRAXIMAGE | – | <ul style="list-style-type: none"> • An adjunct in the evaluation of pulmonary perfusion (adult and pediatric) • Evaluation of peritoneo-venous (LaVeen) shunt patency |
| 30 | Technetium-99m mebrofenin | Bracco Diagnostics | Choletec® | As a hepatobiliary imaging agent |
| | | Pharmalucence | – | |
| 31 | Technetium-99m medronate | Bracco Diagnostics | MDP-Bracco™ | As a bone imaging agent to delineate areas of altered osteogenesis |
| | | DRAXIMAGE | – | |
| | | DRAXIMAGE | MDP-25 | |
| | | GE Healthcare | MDP Multidose | |
| | | Pharmalucence | – | |
| 32 | Technetium-99m mertiatide | Covidien | Technescan MAG3™ | <p>In patients > 30 days of age as a renal imaging agent for use in the diagnosis of:</p> <ul style="list-style-type: none"> • Congenital and acquired abnormalities • Renal failure • Urinary tract obstruction and calculi <p>Diagnostic aid in providing:</p> <ul style="list-style-type: none"> • Renal function • Split function • Renal angiograms • Renogram curves for whole kidney and renal cortex |
| 33 | Technetium-99m oxidronate | Covidien | Technescan™ HDP | As a bone imaging agent to delineate areas of altered osteogenesis (adult and pediatric use) |
| 34 | Technetium-99m pentetate | DRAXIMAGE | – | <ul style="list-style-type: none"> • Brain imaging • Kidney imaging: <ul style="list-style-type: none"> - To assess renal perfusion - To estimate glomerular filtration rate |
| 35 | Technetium-99m pyrophosphate | Covidien | Technescan™ PYP™ | <ul style="list-style-type: none"> • As a bone imaging agent to delineate areas of altered osteogenesis • As a cardiac imaging agent used as an adjunct in the diagnosis of acute myocardial infarction • As a blood pool imaging agent useful for: <ul style="list-style-type: none"> - Gated blood pool imaging - Detection of sites of gastrointestinal bleeding |
| | | Pharmalucence | – | |
| 36 | Technetium-99m red blood cells | Covidien | UltraTag™ | <p>Tc99m-labeled red blood cells are used for:</p> <ul style="list-style-type: none"> • Blood pool imaging including cardiac first pass and gated equilibrium imaging • Detection of sites of gastrointestinal bleeding |

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Radiopharmaceuticals that may potentially have unapproved copies of FDA-approved commercially available radiopharmaceuticals in the marketplace.

| | Radiopharmaceutical | Manufacturer | Trade Names | Approved Indications in Adults (Pediatric use as noted) |
|----|-------------------------------------|----------------------------------|--------------------|--|
| 37 | Technetium-99m sestamibi | Cardinal Health | - | <p>Myocardial perfusion agent that is indicated for:</p> <ul style="list-style-type: none"> • Detecting coronary artery disease by localizing myocardial ischemia (reversible defects) and infarction (non-reversible defects) • Evaluating myocardial function • Developing information for use in patient management decisions <p>Planar breast imaging as a second line diagnostic drug after mammography to assist in the evaluation of breast lesions in patients with an abnormal mammogram or a palpable breast mass</p> |
| | | Covidien | - | |
| | | DRAXIMAGE | - | |
| | | Lantheus Medical Imaging | Cardiolite® | |
| | | Pharmalucence | - | |
| 38 | Technetium-99m sodium pertechnetate | Covidien | - | <ul style="list-style-type: none"> • Brain Imaging (including cerebral radionuclide angiography)* • Thyroid Imaging* • Salivary Gland Imaging • Placenta Localization • Blood Pool Imaging (including radionuclide angiography)* • Urinary Bladder Imaging (direct isotopic cystography) for the detection of vesico-ureteral reflux* • Nasolacrimal Drainage System Imaging <p>(*adult and pediatric use)</p> |
| | | Lantheus Medical Imaging | - | |
| 39 | Technetium-99m succimer | GE Healthcare | - | An aid in the scintigraphic evaluation of renal parenchymal disorders |
| 40 | Technetium-99m sulfur colloid | Pharmalucence | - | <ul style="list-style-type: none"> • Imaging areas of functioning reticuloendothelial cells in the liver, spleen and bone marrow* • It is used orally for: <ul style="list-style-type: none"> - Esophageal transit studies* - Gastroesophageal reflux scintigraphy* - Detection of pulmonary aspiration of gastric contents* • Aid in the evaluation of peritoneo-venous (LeVeen) shunt patency • To assist in the localization of lymph nodes draining a primary tumor in patients with breast cancer or malignant melanoma when used with a hand-held gamma counter. <p>(*adult and pediatric use)</p> |
| 41 | Technetium-99m tetrofosmin | GE Healthcare | Myoview™ | <p>Myocardial perfusion agent that is indicated for:</p> <ul style="list-style-type: none"> • Detecting coronary artery disease by localizing myocardial ischemia (reversible defects) and infarction (non-reversible defects) • The assessment of left ventricular function (left ventricular ejection fraction and wall motion) |
| 42 | Technetium-99m tilmanocept | Navidea Biopharmaceuticals, Inc. | Lymphoseek® | Indicated for lymphatic mapping with a hand-held gamma counter to assist in the localization of lymph nodes draining a primary tumor site in patients with breast cancer or melanoma |
| 43 | Thallium-201 chloride | Covidien | - | <ul style="list-style-type: none"> • Useful in myocardial perfusion imaging for the diagnosis and localization of myocardial infarction • As an adjunct in the diagnosis of ischemic heart disease (atherosclerotic coronary artery disease) • Localization of sites of parathyroid hyperactivity in patients with elevated serum calcium and parathyroid hormone levels |
| | | GE Healthcare | - | |
| | | Lantheus Medical Imaging | - | |

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| | Radiopharmaceutical | Manufacturer | Trade Names | Approved Indications in Adults (Pediatric use as noted) |
|----|---------------------------------|---------------------------|-------------|---|
| 44 | Xenon-133 gas | Lantheus Medical Imaging | - | <ul style="list-style-type: none"> The evaluation of pulmonary function and for imaging the lungs Assessment of cerebral flow |
| 45 | Yttrium-90 chloride | MDS Nordion | - | Indicated for radiolabeling: <ul style="list-style-type: none"> Zevalin® used for radioimmunotherapy procedures |
| | | Eckert & Ziegler Nuclitec | - | |
| 46 | Yttrium-90 ibritumomab tiuxetan | Spectrum Pharmaceuticals | Zevalin® | Indicated for the: <ul style="list-style-type: none"> Treatment of relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma (NHL) Treatment of previously untreated follicular NHL in patients who achieve a partial or complete response to first-line chemotherapy |

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¹Subsequent to promulgation of 21 C.F.R. Part 212, Current Good Manufacturing Practices (cGMP) for PET Radiopharmaceuticals, firms manufacturing and distributing this drug are required to submit either a NDA or an ANDA by June 12, 2012 and manufacture following cGMP Part 212 regulations as of December 11, 2011 for its continued distribution and sale.

²This is a Schedule II controlled substance under the Controlled Substances Act. A DEA license is required for handling or administering this controlled substance.

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cardinalhealth.com

Cardinal Health
7000 Cardinal Place
Dublin, Ohio 43017