Comments on Proposed Revision to USP <797>
Jim Ponto, June 2006

I remain concerned that USP <797> has moved in status from an information chapter (ie, number >1000) to an enforceable chapter (ie, number <1000). It appears to me that <797> (formerly <1206>) is closer to an ideal standard, that is, a high goal that is continuously strived for. Although it is possible to attain such a goal, it may be approached incrementally based on limited resources (financial, personnel, etc). This is in contrast to the current enforceable <797> which is a de facto minimum standard for all to meet.

I have yet to be convinced of the necessity for <797> to be a minimum standard. I view it as overly prescriptive, overly stringent, and lacking flexibility for special situations. Compliance with all requirements will be very costly. To what benefit is this cost compared? Reports of patient harm relating to contaminated CSPs have generally involved grossly bad professional practice. I am not aware of significant problems associated with CSPs prepared with good-faith efforts. Moreover, recently published data by Thomas et al. (see below) do not support the assumption that compliance with <797> reduces contamination rates compared to traditional practice. Hence it appears to me that compliance with <797> will incur high costs for marginal benefit.

Limiting my comments to the specific category of short-lived radiopharmaceutical CSPs (which are administered on the same day of preparation, generally within a few hours after preparation), I believe that compliance with <797> will incur high costs for little, if any, additional benefit. I am not aware of patient injury related to contaminated short-lived radiopharmaceutical CSPs. Furthermore, compounding of short-lived radiopharmaceuticals presents special challenges relating to radiation protection practices.

Moreover, these short-lived radiopharmaceuticals CSPs are administered in a relatively short time after preparation: administration takes place the same day of preparation, generally within a few hours after preparation, with an absolute beyond-use time of 12-18 hours. In a substantial fraction of uses, the short-lived radiopharmaceutical CSP is administered just beyond 1 hour, narrowly missing the "immediate use" exemption. Nonetheless, <797> classifies these short-lived radiopharmaceutical CSPs as "low-risk level CSPs" which requires compliance with the full gamut of environmental and procedural controls prescribed for other "low-risk level CSPs" that may be delayed in administration for up to 48 hours, 14 days, or 45 days if stored at controlled room temperature, cold temperature, or in solid frozen state, respectively.

Therefore, I propose the creation of a new category of CSPs, which essentially bridges the sharp divide between "immediate use" and "low-risk level" CSPs. For lack of a better term, I will simply call this "same-day CSPs." For these "same-day CSPs", I would endorse the following requirements:

- personnel training and media fill challenge testing

- handling in a properly functioning ISO 5 hood (in a limited access room but not necessarily in a clean room)
- good aseptic technique, especially no contact contamination on the critical surfaces (but not necessarily donning cleanroom garments and following other cleanroom procedures)

Administration of these "same-day CSPs" should be administered within hours of preparation, with a maximum beyond-use time of 18 hours (or 24 hours? or 12 hours?)

I believe that this proposal is reasonable, in terms of both cost and safety. These CSPs will maintain a high likelihood of sterility and apyrogenicity at a minimal increase in cost. My belief is supported by data recently published by Thomas et al. [Thomas M, Sanborn MD, Couldry R. I.V. admixture contamination rates: traditional practice site versus a class 1000 cleanroom. Am J Healthsyst Pharm. 2005; 62:2386-2392]. These authors used simulated product media fill testing to compare contamination rates in a traditional practice site and in a cleanroom site. The traditional practice site employed an ISO 5 hood in a limited access room (but without a buffer room, anteroom, or filtered air supply), whereas the cleanroom site employed an ISO 5 hood inside an ISO 6 cleanroom with positive pressure filtered air, accessed via an ISO 7 buffer room from an ISO 8 anteroom. Procedures in the traditional practice site included handwashing and good aseptic technique (but not wearing cleanroom garb and not spraying material with 70% alcohol), whereas procedures in the cleanroom included surgical scrub washing, donning cleanroom garments, and spraying equipment with 70% alcohol. Rates of contamination for the media fills were not significantly different: 0.296% (6/2027) for the traditional practice site and 0.344% (7/2030) for the cleanroom site. Air sampling revealed no viable organisms in either ISO 5 hood although the surrounding environment had an average of 100 CFUs/m^2 in traditional practice site vs. an average of 13 CFUs/m^2 in the cleanroom. The authors conclude that when CSPs are prepared within an ISO 5 hood, the operator becomes the most important variable affecting microbial contamination. The authors state: "It is dangerous to assume that the use of a cleanroom will independently improve the quality of patient care by eliminating contamination. Once a baseline environmental quality (class 100 LAF hood) is established, admixture quality assurance efforts should focus on other critical factors. Continuous quality assurance of personnel's aseptic technique, including effective monitoring and training for the personnel preparing admixtures is paramount. The use of media-fill runs to validate personnel, processes, and equipment also ensures the quality of sterile products. Finally, the proper functioning of LAF hoods should be established."

In summary, I propose the creation of a reasonable, practical, and cost-effective category of "same-day CSPs" for inclusion of short-lived radiopharmaceutical CSPs. Requirements would be intermediate between those for "immediate use" and "low-risk level" CSPs, limited to personnel training and testing, use of a properly functioning ISO 5 hood, and good aseptic technique.