TO: US Pharmacoepial Convention – USP <797> Comment Period
FROM: American Society of Anesthesiologists (ASA), American Association of Nurse Anesthetists (AANA), American Academy of Anesthesiologist Assistants (AAAA), Anesthesia Patient Safety Foundation (APSF)
RE: ASA, AANA, AAAA and APSF Joint Letter response on revisions to USP 797
Date: November 30, 2018

Line Number (s)	Existing Text	Proposed Comments	Proposed Rationale/Scientific Evidence
GENERAL COMMENTS	N/A	The American Society of Anesthesiologists (ASA), American Association of Nurse Anesthetists (AANA), the American Academy of Anesthesiologist Assistants (AAAA) and the Anesthesia Patient Safety Foundation (APSF) jointly submit our comments and concerns regarding the proposed revisions to the U.S. Pharmacopeial Convention (USP) Chapter <797>. USP <797> revisions include updated requirements for sterile compounding activities and exclude administration of medication. We appreciate USP's desire to improve <797> but believe the revisions, if approved without edit, could cause confusion and misinterpretation among multiple stakeholders leading to an increased chance of inhibiting anesthesia workflow and negatively impacting patient care. The revisions to USP 797 include definitions of administration and compounding that will have the unintended consequence of ensnaring qualified anesthesia providers in unnecessary and arbitrary processes. To alleviate many of these concerns, USP <797> should explicitly state that "the one-hour rule for compounding medications does not apply in an operating or procedure room setting. Local policy should determine the proper time period, based on scientific evidence, when a compounded medication should be discarded from use in such settings."	The language as proposed will result in substantial burdens (both in time and costs) to qualified anesthesia providers and other healthcare providers. Clear language is necessary for regulatory agencies and accreditation bodies who interpret the implementation of USP <797> in a variety of locations in hospitals, Ambulatory Surgery Centers (ASCs) and other locations where patient surgical, procedural and diagnostic care is delivered. We are unaware of any studies demonstrating that administering any drug that was compounded or prepared at a time exceeding one hour compromises sterility, increases risk of contamination of the syringe or negatively affects patient outcomes in the operating room or perioperative environment. Recent articles, including Stedman, et al, "How Long Is Too Long? The Prespiked Intravenous Debate", have indicated that studies on pre-spiking intravenous (IV) bags "revealed no microbial growth within 24 hours of an IV spike." Although pre-spiking an IV bag does not fall within the definition of "compounding," the language in the chapter should state that compounded medications may be administered until the end of the case. Conflict between USP <797> language and regulatory guidance from the FDA will only serve to confuse healthcare providers, facility administrators and regulatory and accreditation surveyors in determining proper procedures. To prevent confusion, USP should align their definitions with regulatory bodies before finalizing this chapter.

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		Such language simplification would clarify that the aseptic and sterile procedures for preparing and administering medications in the operating room and other procedure rooms are not subject to the rules set forth for sterile compounding. This language change would acknowledge the unique way qualified anesthesia providers prepare drugs and administer drugs to patients as part of their everyday workflow in the operating and procedure rooms. In addition, these proposed changes to USP <797> will affect the patient's perioperative team in ambulatory settings or other locations that do not have a pharmacy where the lack of an ISO 5 location will unnecessarily delay care or affect the care provided for patients. Many of our concerns could be addressed by carving out the operating and procedure room settings from USP <797> requirements. We are also concerned with recent language from the US Food and Drug Administration (FDA) on its "Guidance on the Selection of the Appropriate Package Type." Although the document is currently listed as "non-binding recommendations," we believe that FDA language on the document may change in the future. We are concerned that some trade magazines have already omitted the non-binding language. Regardless, the FDA document changes the manufacturer's labeling for sterile medication in regard to administration. FDA guidance now uses the "single patient use" term (which is more consistent with medication administration in the perioperative environment) but provides more regulatory burden for the manufacturer's labeling that requires a prior approval supplement. The other change in term from "single-use" to "single-dose" does not impose such burden.	USP must consider the current drug shortages crisis and discourage policies that exacerbate the issue and compromise patient care.

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		The FDA changes would affect how stakeholders interpret the revised USP <797> since USP <797> refers to manufacturers' labeling with regard to administration. Although we recognize that USP <797> states "Administration of medication, including withdrawal of doses, is out of the scope of this chapter", we are nonetheless concerned that new FDA guidance may affect the following USP <797> sentence that states "Administration of medication should follow the manufacturer's or compounder's labeling of the sterile medication" (Lines 18-21). Such confusion in terms between the FDA and USP will cause unnecessary confusion for qualified anesthesia providers and other providers, accrediting organizations, manufacturers and other stakeholders. In general, the inaccurate interpretation of USP <797> by facility administrators, accrediting agencies or other stakeholders will increase costs significantly without any benefit to patient safety. We ask that USP be precise in its definitions to avoid confusion and unintended burdens that delay or harm patient care. USP must consider the impact of the proposed USP 797 policies on drug shortages. The American Society of Health-System Pharmacists notes that there are currently 199 drugs in short supply. This year, there have been severe shortages of injectable anesthetic drugs, which have prevented optimal patient care. These shortages have been a consistent problem for anesthesia providers and lead to suboptimal pain control or sedation for patients. Linda J. Mason, M.D., FASA, President, American Society of Anesthesiologists	

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		Garry Brydges, DNP, MBA, ACNP-BC, CRNA, FAAN, President, American Association of Nurse Anesthetists (AANA) Nick Davies, CAA, President/Executive Committee Chair, American Academy of Anesthesiologist Assistants (AAAA) Mark A. Warner, M.D. and President, Anesthesia Patient Safety Foundation (APSF)	
Lines 5-8	Sterile compounding is defined as combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug or bulk drug substance to create a sterile medication.	We question whether the definition of sterile compounding is appropriate for the general application of USP <797> to a wide range of persons and situations. The definition of sterile compounding by USP is taken from the FDA regulation on Facility Definition Under Section 503(b) of the Federal Food, Drug, and Cosmetic Act. USP <797> offers several definitions of compounding but does not define the individual elements of sterile compounding or its relationship to a specific location where compounding is expected to take place. The conflation of a facility-based regulation to any action within a healthcare setting is problematic not just for qualified anesthesia providers and other providers but for facility administrators and accrediting organizations. USP <797> compounding language is similar to several actions a qualified anesthesia provider may complete when preparing and *administering* a drug in the operating or procedure room. Qualified anesthesia providers combine, dilute, reconstitute and otherwise alter a drug with the intent of administering that sterile medication. Without specific context, regulatory authorities will in the future, as they have in the past, misinterpret this definition as applying to the actions of qualified anesthesia providers and other providers in the operating and procedure room.	Examples of what constitutes and does not constitute compounding would potentially alleviate misinterpretation of USP recommendations and assist the health care community in understanding where the compounding definitions apply.

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		We encourage USP to provide specific and workable examples of circumstances where healthcare providers' actions would be considered as compounding. Combined with lines 71-77, we fear that such a broad definition of compounding can lead to non-operating room experts and accrediting agencies misinterpreting administration as compounding. For example, USP is silent on when a qualified anesthesia provider would be "compounding" as opposed to "administering" a sterile medication. To assuage any confusion, USP should clearly define specific instances when a member of the perioperative team is compounding and when they are administering. We prefer an explicit carve out for the operating room and procedure room setting from the USP 797 requirements. In lieu of that straightforward approach, we suggest USP provide some additional examples of what is *not* compounding. For example, we would argue that preparation for a pending operation when the patient is not yet in the room would not be considered compounding. The nuances of administering medications safely and in an efficient manner that saves time and cost while enhancing patient outcomes should not be prevented by a technical interpretation of administration versus compounding.	
Lines 13-16	For the purposes of this chapter, administration means the *direct* and *immediate* application of a conventionally manufactured product or a CSP to a patient by injecting, infusing or otherwise providing a sterile medication in its final form.	USP provides no concrete definition or context concerning "direct and immediate application." We request deletion of this language in the perioperative environment. Alternatively, USP should clarify this language with specific examples or interpretations of what constitutes "direct and immediate application." USP should provide clear examples of how they intend this language to be interpreted by local administrators, healthcare providers and regulatory authorities.	The direct and immediate language is vague and has the potential for misinterpretation by providers, hospital administrations, accrediting organizations and other stakeholders. We note the Association for Professionals in Infection Control and Epidemiology (APIC) Position Paper: Safe Injection, Infusion, and Medication Vial Practices in Health Care (2016) includes reasonable recommendations for providers on this issue and appreciates the workflow of anesthesia professionals. We also point to a 2017 study published in *Anesthesia and Analgesia*: "How Long Is Too Long? The Prespiked Intravenous Debate" for

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		We note the use of "immediate" in lines 24-32, where USP describes preparation of non-hazardous CSPs, suggests "immediate" is one-hour – at least as used in the context of that provision. We are unclear if this means that, essentially, the proposed revisions still intend to require anesthesia providers to follow the one-hour rule. The language muddles any revisions as it may be interpreted that "direct and immediate" administration means that you must administer within one hour of preparation or else you must follow all USP 797 requirements. If that is the intent, we oppose that language and interpretation and request language that indicates administration in the perioperative environment means the application of a conventionally manufactured product or a CSP to a patient by injecting, infusing or otherwise providing a sterile medication in its final form.	further consideration by USP. This study analyzed whether there was increased infection risk within four hours of spiking an IV fluid bag. The results indicated that there was "no bacterial growth in prespiked normal saline IV bags in a perioperative environment" and that "prespiking of normal saline IV bags in advance should pose no risk of infection to a patient if prepared within 4 hours." Please note, the 4-hour timeline chosen for this study was chosen to "stimulate typical real-world OR settings."
Lines 16-18	For guidance on administration of CSPs, see the Centers for Disease Control and Prevention's (CDC) *Safe Injection Practices to Prevent Transmission of Infections to Patients.*	The CDC's *Safe Injection Practice to Prevent Transmission of Infections to Patients* provides easy-to-understand and straight-forward recommendations. USP's recommendations go far beyond the CDC recommendations and are confusing to reconcile. Again, USP explains that administration is out of the scope of the chapter but provides confusing context adding to the definition of administration.	Simplification of the definition of administration would remove confusing context that requires additional interpretation.
Lines 24-32	Preparation of non-hazardous CSPs for a single patient using only sterile starting ingredients when administration will begin within 1 hour of beginning the preparation (e.g., within 1 hour of initial entry into or puncture of a single-dose container) is not required to meet the standards in this chapter. Any unused starting ingredient that is not labeled as a multiple dose container must be discarded after preparation is complete. Additionally, preparation of sterile medications for immediate	We also note the use of "immediate" in lines 24-32, where USP describes preparation of non-hazardous CSPs, suggests "immediate" is one-hour – at least as used in the context of that provision. We are unclear if this means that, essentially, the proposed revisions still intend to require anesthesia providers to follow the one-hour rule whether preparing a nonhazardous CSP using sterile ingredients or administering a manufactured or compounded product The language seems to muddle any revisions as it may be interpreted that "direct and immediate" administration means that you must administer within one hour of preparation or else you must follow all USP 797 requirements.	Using clear and consistent terms throughout the document will decrease the likelihood of misinterpretation during implementation.

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	administration should be performed in accordance with evidence-based information for physical and chemical compatibility of the drugs administered.		
Lines 29-32	Additionally, preparation of sterile medications for immediate administration should be performed in accordance with evidence-based information for physical and chemical compatibility of the drugs administered.	Consistent with our comments on Lines 13-16, we request the removal of "immediate" as it is vague and open to misinterpretation. "Immediate" follows the explanation that "[p]reparation of non-hazardous CSPs for a single patient using only sterile starting ingredients when administration will begin within 1 hour of beginning the preparation … is not required to meet the standards of this chapter." This language contained in the same paragraph implies the undefined "immediate" means within one hour of preparation. Administration of medications in the perioperative environment may not always be within one hour due to the necessity of preparing emergency medications in advance of emergencies and other workflow issues. We oppose the use of "direct and immediate" and the one-hour rule in the context of anesthesia administration.	"Immediate administration" is vague and has the potential to be misinterpreted by providers, facility administrators, accrediting organizations and other stakeholders. We point USP to the Association for Professionals in Infection Control and Epidemiology (APIC) Position Paper: Safe Injection, Infusion, and Medication Vial Practices in Health Care (2016) that includes reasonable recommendations for providers on this issue and appreciates the workflow of anesthesia professionals.
Lines 71-77 GENERAL COMMENTS	This chapter describes the minimum requirements that apply to all persons who prepare CSPs in all places where CSPs are prepared. This includes, but is not limited to, pharmacists, technicians, physicians, veterinarians, dentists, naturopaths, chiropractors, and nurses in all places including, but not limited to, hospitals and other healthcare institutions, patient treatment sites, infusion facilities, pharmacies, and physicians' or veterinarians' practice sites.	USP should clearly define who is a compounder and identify the most frequent and common situations that USP is addressing within a facility. USP should provide insight into special circumstances when non-pharmacy healthcare professionals are compounding. USP should also consider the unique circumstances of different practice locations. For example, we ask that USP consider ambulatory surgery centers and outpatient facilities that do not have on-site compounding pharmacists. USP <797> for them would create a significant burden when delivering care to patients, especially related to the potential lack of ISO Class 5 air requirements at those facilities.	N/A

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Lines 158-162	All personnel involved in the compounding of CSPs must be initially trained and qualified by demonstrating proficiency in compounding CSPs. Personnel must complete requalification every 12 months in appropriate sterile compounding principles and practices.	We are concerned that USP is unintentionally broadening the scope of USP <797> which could result in substantial training requirements that will prove burdensome both in time and costs. Most qualified anesthesia providers are NOT subject to compound training currently. The lack of clarity in who is a compounder could have multiple cost ramifications for departments and facilities. For instance, if USP, a regulator, or accrediting agency deems that a healthcare provider in an operating or procedure room setting is compounding when the intention is administration, the facility and department would not only be cited but would have to create a training program for the provider and similar providers in that scenario. Such a requirement would pose a significant cost burden on the facility and individual provider.	A misinterpretation of USP <797> may unintentionally cause facilities and regulatory agencies to require costly and burdensome annual compounding training for providers outside of the scope of USP <797>.
Lines 1515-1548	CSPs must be labeled with legible identifying information to prevent errors during storage, dispensing, and use. The term labeling designates all labels and other written, printed, or graphic matter on an article's immediate container or on, or in, any package or wrapper in which it is enclosed, except any outer shipping container. The term label designates that part of the labeling that is on the immediate container. The label on the immediate container of the CSP must, at a minimum, display prominently and legibly the following information: • Assigned internal identification number (e.g., prescription, order, or lot number)	We are concerned that another possible negative effect of the proposed language is to increase the labeling requirements for qualified anesthesia providers. We believe if this language is interpreted incorrectly and inappropriately applied to qualified anesthesia providers, there will be serious safety concerns including reduced legibility due to the amount of information required to be on the label. Such a scenario could also increase the burden on qualified anesthesia providers to complete a compounding record. Additionally, we believe this language will be further complicated by the FDA's recently released "Guidance on the Selection of the Appropriate Package Type."	Conflict between USP <797> language and regulatory guidance from the FDA will confuse healthcare providers, facility administrators and regulatory and accreditation surveyors in trying to determine proper anesthesia labeling procedures. To prevent confusion, USP should align their definitions with regulatory bodies before finalizing this chapter.

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	• Active ingredient(s) and their amounts, activities, or concentrations • Storage conditions if other than controlled room temperature • Date prepared • BUD • Indication that the preparation is compounded The label on the immediate container of the CSP must additionally display prominently the following information: • Route of administration if it is not obvious from the container, or when necessary for the safe use of the CSP • Total amount or volume if it is not obvious from the container • If it is a multiple-dose container, a statement stating such • Contact information of the compounding facility if the CSP is to be sent outside of the facility in which it was compounded Additionally, the labeling of the CSP must provide any applicable special handling instructions or warning statements. Labeling procedures must be followed as described in the facility's SOPs to prevent labeling errors and CSP mix-ups. The label of the CSP must be verified to ensure that it conforms with the:		

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	1. Prescription or medication order; 2. Master Formulation Record, if required (see *9.2 Creating Master Formulation Records*); and 3. Compounding Record (see *9.3 Creating Compounding Records*) All labels must also comply with applicable jurisdictional laws and regulations.		
Lines 1710-1719	A conventionally manufactured single-dose container is a container–closure system that holds a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements. If a single-dose vial is entered or punctured in worse than an ISO Class 5 air, it must be used within 1 hour or by the end of the case in which it will be used, and any remaining contents must be discarded. If a single-dose vial is entered or punctured only in an ISO Class 5 or cleaner air, it may be used up to 6 hours after initial entry or puncture. Opened single-dose ampules must not be stored for any time period.	We request additional clarity and examples on when these provisions would and wouldn't apply. We recommend stating that the second sentence applies to a "to follow" case, when the drugs are prepared in the pharmacy or prepared for the next patient. We request that USP revise the language "it must be used within 1 hour or by the end of the case" to "it must be used by the end of the case" for clarity and because the one-hour rule should not apply to cases in the operating or procedure room. Alternatively, if USP includes the one-hour rule for other locations, the sentence could be edited as follows: "… it must be used within 1 hour or by the end of the case, whichever time is longer" as there are several possible interpretations of this language.	Our proposed clarifications would alleviate confusion about the circumstances in which the one-hour rule still applies.
Lines 2140-2143	**Compounded sterile preparation (CSP):** A preparation intended to be sterile that is created by combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug product or bulk drug substance.	We request clarification on the reason compounding is defined three ways throughout the proposed chapter. We request explanation of how each of these definitions would be applied in certain settings and context. Furthermore, we request clarification of the term "intended to be sterile" on page 160, line 2140.	One consistent definition of compounding would create less confusion.

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Lines 2144-2150	**Compounding:** The process of combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug or bulk drug substance to create a sterile medication. Preparing a conventionally manufactured sterile product in accordance with the directions contained in approved labeling provided by the product's manufacturer is not compounding as long as the product is prepared for an individual patient and follows the provisions for administration.	We request clarification on the reason compounding is defined three ways throughout the proposed chapter. We request how each of these definitions would be applied in certain settings and context. In addition, typically the manufacturer's directions are not easily accessible in the perioperative environment. These instructions do not fit in the dispensing cabinets. Moreover, cases in the operating or procedure rooms may take place when the pharmacy is closed (e.g., labor epidurals).	One consistent definition of compounding would create less confusion.