

Questions from BUD Webinar Asked by Attendees

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Q: A single dose vial can be used for 14 days if prepared at low risk level and refrigerated?

A: A single-dose vial can be used to prepare a CSP that can be stored for up to 14 days refrigerated. A single-dose vial may be used as a multiple-dose vial for up to 6 hours if left within an ISO Class 5 environment.

Q: If drawing up syringes from an MDV can we use the syringes for the 28 day period the vial would be assigned? Would micro testing for this batch be required?

A: I would consider any syringes drawn up from a MDV to be a low-risk level CSP and subject to the respective BUD (e.g., 14 day refrigerated BUD). My opinion is based on the fact that you are putting the drug into a different container that may not have been tested as rigorously as the drug in a vial. Consideration must be given to the chemical stability of the drug in syringe over any period of time. BUD may be extended beyond 14 days refrigerated if sterility testing is performed in keeping with USP Chapter <71> and the chemical stability of the drug over the chosen time period is assured.

Q: If we use 250mg from a premix metronidazole bag to make a 750mg dose with another premix bag how long is the remaining 250mg stable? The 750mg stability? What is the difference between the new 750mg bag and left over 250mg bag, aren't both considered single dose units that should only be stable for 6 hours?

A: If a premix bag is not punctured, then the BUD of the bag is according to the manufacturer's dating. If you use one 500mg bag as a single dose vial, then you can give the new 750mg bag a beyond-use date as a low-risk level CSP. The remaining 250mg bag can be used for additional doses or discarded after 6 hours.

Q: Address BUD with the use of port savers

A: This is a great question but to my knowledge, there is no evidence in the literature yet demonstrating that these port savers improve the microbial sterility of vials.

Q: What about eyeglasses?

A: This webinar was about BUD. I don't consider them jewelry and they are essential to safe compounding practices. Consider reviewing previous webinar Q&A's in addition to the FAQs posted on the USP website <http://www.usp.org/audiences/pharmacist/797FAQs>

Q: At what risk level is it necessary to test for endotoxin?

A: This answer comes directly from the chapter: "All high-risk level CSPs, except those for inhalation and ophthalmic administration, that are prepared in groups of more than 25 identical individual single-dose packages (e.g., ampuls, bags, syringes, vials) or in MDVs for administration to multiple patients or that are exposed longer than 12 hours at 2 degrees to 8 degrees and longer than 6 hours at warmer than 8 degrees before they are sterilized shall be tested to ensure that they do not contain excessive bacterial endotoxins (see Bacterial Endotoxins Test <85> and Pyrogen Test <51>). In the absence of a bacterial endotoxins limit in the official monograph or other CSP formula source, the

CSP shall not exceed the amount of USP Endotoxin Units (per hour per kilogram of body weight or square meters of body surface area) specified in Bacterial Endotoxins Test <85> referenced above for the appropriate route of administration.”

Q: Beyond use date for complex mixtures?

A: Without any additional information about your definition of a “complex mixture,” I would consider the mixture to be either medium or high-risk level.

Q: Can BUD time limits be applied to single-dose vial use after initial entry, if not what makes the technique different that would limit a SDV sterility to only 6 hours after initial puncture?

A: No, BUD limits cannot be applied to a single-dose vial use after initial entry because the vial does not contain any antimicrobial preservatives and is being used as a multiple-dose vial. Refer to USP Chapter <1> Injections for more information on the definition of single-dose and multiple-dose vials.

Single-Dose Container (see General Notices and Requirements and Containers for Injections under Injections <1>)—A single-dose container is a single-unit container for articles (see General Notices and Requirements) or preparations intended for parenteral administration only. **It is intended for a single use.** A single-dose container is labeled as such. Examples of single-dose containers include prefilled syringes, cartridges, fusion sealed containers, and closure-sealed containers when so labeled.

Q: Can the name of the ASHP article referenced please be repeated?

A: Stucki C, Sautter A, et al. Microbial contamination of syringes during preparation: The direct influence of environmental cleanliness and risk manipulations on end-product quality. *AJHP* 2009; 66:2032-6.

Q: Can we please get the reference to the ASHP article on contamination rates?

1. Trissel LA, Ogundele AB, Ingram DS et al. Using medium-fill simulation to establish a benchmark microbiological contamination rate for low-risk-level compounding. *Am J Health-Syst Pharm.* 2003; 60:1853-1855.
2. Trissel LA, Gentempo JA, Anderson RW et al. Using medium-fill simulation to evaluate the microbiological contamination rate for USP medium-risk-level compounding. *Am J Health-Syst Pharm.* 2005; 62:285-288.
3. Trissel LA, Gentempo JA, Saenz LM et al. Effect of two work practice changes on the microbiological contamination rates of pharmacy-compounded sterile preparations. *Am J Health-Syst Pharm.* 2007; 64:837-841.

Q: Can you expand how you can do sterility testing?

A: Sterility testing needs to be performed according to USP Chapter <71>: Sterility Test. Please find attached an article from IJPC on Sterility Testing.

Q: Can you explain BUD that should be applied to multi-dose vials?

A: USP Chapter <797> is very clear on the BUD of a multi-dose vials. It is:

“Multiple-dose containers (e.g., vials) are formulated for removal of portions on multiple occasions because they usually contain antimicrobial preservatives. The BUD after initially entering or opening (e.g., needle punctured) multiple-dose containers is 28 days (see Antimicrobial Effectiveness Testing <51>) unless otherwise specified by the manufacturer.”

Q: Can you provide information on using mini bag plus and/or vial mates for compounding in sterile hood vs on nursing floors? My IV Room is using the information provided by the manufacturer which is shorter than expected given that the vials are not even being punctured.

A: Each vial-bag system is different and you should refer to the package insert for specific guidance on how and where to assemble these systems as well as how long they can be stored. BUDs range from 15 days to 10 weeks.

Q: Can you share documentation from 797 that sterility for BUD testing must be performed on every batch?

A: If the BUD limits that correspond to the Risk Levels in USP 797 are exceeded, the chapter specifies that sterility testing is required. Please refer to your copy of the USP chapter, USP Chapter <71> Sterility Tests and the FAQs on the USP website for more specifics.

Q: Clindamycin vials and RTU bags are to be stored at room temperature. When a bag or syringe is compounded, should it be stored in the fridge (because it has been manipulated) or at room temp?

A: RTU bags should be stored according to manufacturer’s directions and USP Chapter <797>. Any compounded doses prepared should be stored according to package insert, references books (e.g., Trissel’s Handbook of Injectable Drugs) or other resources relative to ideal storage conditions.

Q: I am confused about BUDs of vials vs. IV bags. For example, once reconstituted, a vanco vial is stable x 8 hours (based on 797), however, once the bag is compounded, it is stable for longer. Why is that a bag has a longer BUD compared to the vial?

A: The bag is a final dosage form and based on the risk level associated with its preparation, its BUD will be dictated by risk level. A Vancomycin vial is typically a single-dose or pharmacy bulk package that needs to be handled according to its definition as a single-dose or pharmacy bulk package.

Q: Could you explain why sterile IPA is necessary over non-sterile IPA.

A: This question has been answered multiple times in previous webinar Q&As and on the FAQs on the USP website. Please refer to those resources.

Q: Did I hear you say that all MDVs should be stored in the refrigerator?

A: Ideally, any vial, unless prohibited (e.g., crystallization) should be stored in the refrigerator between uses to slow any potential microbially growth. It is not required and you should refer to the product’s package insert.

Q: Does process validation play a role in not having to evaluate BUD especially between batches?

A: No. Please consult the FAQs on the USP website for more information about this topic.

Q: What about dealing with investigational drugs for clinical research. We have a retest date. Can we follow the USP 797 guidelines for BUD upon completing a compound using this particular investigational product?

A: I don't understand this question. Please email me directly for more follow-up.

Q: Doesn't USP <795> limit packaged or compounded preparations to a BUD of 90 days?

A: USP <795> refers to nonsterile compounding. There is a BUD algorithm within USP <795> that provides guidance for the BUD for aqueous solutions that do not have a known BUD which is 14 days, refrigerated.

Q: How does the application of robotics affect this decision?

A: Excellent question. Based on my professional experience with robotics, I believe a robotic compounding system that has been aseptically validated (with achievement of statistical significance), would allow the BUD of CSPs to be extended to the same as the compound's chemical stability.

Q: I believe that we fully comply with the new 797 standards - but I am confused by our "finger dab" testing. After 24 hours of incubation, how many CFU's = Action point?

A: Since initial gloved fingertip testing is used to evaluate the competency of personnel in performing hand hygiene and garbing procedures, that requirement is zero (0) colonies (both hands combined) for 3 consecutive tests before the employee is allowed to compound CSPs for human use. The rationale for zero CFUs here is that in this case, the gloved fingertip sampling is performed to verify that the compounding staff can perform hand hygiene and garbing without contaminating themselves. Thereafter, on subsequent gloved fingertip sampling occurrences the recommended Action Level for annual gloved fingertip verification is up to 3 colonies per test per plate. In these cases the staff are generally performing the gloved fingertip sampling during media fill verification or other compounding and are inside of ISO Class 5 conditions.

Q: How about a home care setting in which a morphine drip might need to hang on a patient for a week (at room temperature)?

A: USP Chapter <797> only applies to pre-administration manipulation, storage, handling, and transportation. Once the CSP is hanging on the patient, USP Chapter 797 is not applicable. Taken directly from the Chapter: "The standards in this chapter do not pertain to the clinical administration of CSPs to patients via application, implantation, infusion, inhalation, injection, insertion, instillation, and irrigation, which are the routes of administration."

Q: If making a batch of a CSP what quantity makes it a medium risk vs. low risk?

A: Low-risk according to my interpretation of the chapter is one CSP prepared from one source vial. If you are preparing multiple doses from a bulk vial (e.g., Cefazolin 10gm vial) then you have a medium-risk level CSP. Please review the ASHP USP <797> Discussion Guides that were published in 2004 and 2008.

Q: How can a nationwide compounder of high risk intrathecal solutions, receive the order on day 1 prepare, the solution, ship it to you overnight to arrive on day 2., and still assign it a 90 BUD?

A: I don't know. I would contact the compounder and ask them to provide you with documentation and substantiation for their BUDs.

Q: How can you tell if you have too many products in your hood for preparation & you are not interrupting sterile air flow? (chemo hood)

A: This in-service was about BUDs. The most important determinant for not interrupting airflow in a BSC is assuring that the front and back grills are not blocked. Refer to the owner's manual for the specific BSC you use or ask your hood certifier to perform a smoke test, which would be the best test.

Q: How do extrapolate Extended Stability data from Bing's book to the updated guidelines?

A: I don't understand this question. Please email me directly for more follow-up.

Q: How does 797 BUD apply to alternate packaging systems such as Add-Vantage or Minibag-Plus? Would manufacturer expiration recommendations apply?

A: See my response to an earlier question.

Q: How does mixing drugs in bacteriostatic saline/water affect stability and BUD?

A: In my opinion, if bacteriostatic saline or water is used to reconstitute a drug for direct administration (IV push or IM) and the drug is NOT diluted further (e.g., 50 mL bag), then I would consider it a low-risk level CSP.

Q: How often should temperatures be checked in all storage areas in the hospital environment to ensure stability?

A: It depends on hospital policy and other regulations (Department of Health, The Joint Commission, etc), but the following is taken directly from the Chapter: "A controlled temperature area shall be monitored at least once daily and the results documented on a temperature log."

Q: I keep hearing people say that BUD doesn't apply once the dose is hanging on the patient. That doesn't make sense to me.

A: USP Chapter <797> only applies to pre-administration manipulation, storage, handling, and transportation. Once the CSP is hanging on the patient, USP Chapter 797 is not applicable. As taken directly from the Chapter: "The standards in this chapter do not pertain to the clinical administration of CSPs to patients via application, implantation, infusion, inhalation, injection, insertion, instillation, and irrigation, which are the routes of administration."

Q: There is some infection control data out there regarding hang times for continuous infusions and that letting things hang on a patient for 72 hours allows less manipulation and potential for contaminating the line. How do you pair that with USP 797 BUD?

A: It is similar to the sell by and use by dating of milk. You can use the milk after its sell date but the store cannot sell it after its date. USP Chapter <797> applies to pre-administration activities and not to the clinical administration of CSPs.

Q: If an anesthesiologist prepares an emergency med in the OR "just in case they need it", what kind of BUD can this syringe get?

A: Under the circumstances you described, it would be considered an immediate-use CSP and limited to one-hour BUD.

Q: If an organization decides to use sterility testing can you please review the requirements of Chapter 71.

A: You should refer directly to USP Chapter <71>: Sterility Tests and the attached IJPC article. http://www.pharmacyonesource.com/images/simplifi797/Sterility_and_BUD.pdf

Q: If SDV vials and IV bags are hanging in the cleanroom hood attached to the TPN compounder, can they be used throughout the day (over 24 hours), or must they be discarded every 6 hours? They are only punctured once by the tubing.

A: Each SDV and IV bag has a specific use by date in its package insert that should be followed.

Q: BUD as I understand it refers to storage time not administration time. Is it acceptable to allow a LVP prepared in an immediate use risk level to hang over a 24 hr period?

A: USP Chapter <797> does not apply to hang time. I would need to know more information about this immediate-use CSP to comment.

Q: If there is documented extended stability in the literature, can you use that date or do you still have to do your own end product testing?

A: BUD involves both chemical stability and microbial sterility. Extended chemical stability data can be used if sterility testing is done if BUD extends those in USP Chapter <797>.

Q: When you put an expiration date on a compounded product, does that date include the infusion time? If the product reaches the date before the infusion is complete should the infusion be stopped?

A: No. The BUD only applies for all activities prior to administration.

Q: In High Risk compounding such as Alum for irrigation, is it acceptable to use 0.22micron filtration in the Bladder irrigation circuit (for sterilization) w/ a BUD of 24 hours? Please comment. Thank you.

A: Yes, this would fall within the parameters of USP Chapter <797>.

Q: Is there a quantity limit to the batch size that determines if you need to conduct sterility testing if exceeding the BUD when the manufacturer has stability data beyond the BUD?

A: No, there is not quantity limit to the batch size. BUD in USP Chapter <797> is based on both microbial sterility and chemical stability.

Q: Did you say that all opened MDV should be stored at a refrigerated temperature?

A: No that is not an absolute and must be based on the manufacturer's product literature and instructions. When permissible based on the product package insert, an MDV should be refrigerated to slow the growth of any potential microbial contamination.

Q: Low risk compound refrigerated for 2-3 days and then frozen; how does this affect BUD and Expiration?

A: It depends on several factors that need to be considered on a drug by drug basis. Without more information, I cannot answer the question.

Q: Our nurses mix IVs at night while the pharmacy is closed (septic pt etc). How long are those bags good for once they are mixed?

A: Without additional information about where these IVs are made, they would fall within the immediate-use provision of USP Chapter <797>, ergo use within 1 hour unless they are compounded under the conditions described for Low Risk Level CSPs with 12 hour or less BUD.

Q: The milk I buy at Costco always has longer BUD than my grocery store - Why? Similarly, commercial sterile compounders (CAPS, Pharmedium, Ameridose) have sometimes widely divergent BUD for different products. Why not more similar?

A: Re: milk, I don't know. It may have to do local health laws or their process of pasteurization or storage. Re: commercial sterile compounders, I don't know why they are not more similar but it might have to do with data they obtained by performing their own stability studies. A company might choose to publish that information in the public domain or they may choose not to publish and consider that proprietary information. Either way, you may want to ask them that question. It is my opinion that all commercial sterile compounders should share data substantiating assigned BUDs with their customers in keeping with the requirements of the Chapter.

Q: USP 71 requires bacteriostatic and fungastatic test to verify your sterility test if valid. Are you able to use only direct inoculation to comply with USP 71? Some people do not do the sterility test via filtration but only use direct inoculation.

A: Membrane filtration is the preferred method of doing sterility testing vs. direct inoculation. Direct inoculation is limited to final volumes of 40 mL or less according to USP Chapter <71>-Sterility Tests.

Q: We are a home infusion pharmacy, making TPN per specific patient orders. In this case is each order (7 bags) a batch? Would we need to test each patients bags every week to obtain extended dating?

A: Currently, TPN can be given 9 days refrigerated BUD. If you want to extend the BUD, then you would need to do sterility testing each time the bags are made. Keep in mind however, that regardless of the outcome of batch specific sterility testing, BUD is a function of both sterility and stability so you would need to reference published chemical stability for TPN. To the best of my knowledge, evidence of extended chemical stability (beyond 9 days) has not been published.

Q: We have discussed making individual syringes out of a multi-dose vial of a med that is in short supply (such as Celestone or hydromorphone). What should the beyond use dating be? In the original vial it is 28 days after first entering the vial.

A: I would consider these low-risk level CSPs and subject to 14 day refrigerated BUD.

Q: What about drawing up Drug X into individual dose syringes? Trissel's gives this drug a 30 day STABILITY at room temperature.

A: I don't understand this question. Please email me directly for more follow-up.

Q: What is the beyond use date when multiple syringes for multiple patients are drawn from the same multi-dose vial (14 days vs 9 days)?

A: If the drug is not diluted further, I would consider it a low-risk level CSP and subject to the 14 day refrigerated dating.

Q: What is the typical BUD for assembled mini-bag plus systems?

A: You need to refer to the specific information contained in the manufacturer's package insert. The date ranges span 15 days to 10 weeks depending on the manufacturer's system.

Q: When the BUD is reached, is the expectation that the actual infusion of the IV admixture be halted (BUD is 11/18 1300 yet the product is being infused and the volume in the bag would provide therapy until 11/19 1400)?

A: BUD applies to be pre-administration activities. Think about the sell by and use by dating of milk. I would not halt the infusion.

Q: Why is it acceptable to use a single dose vial for only 6 hours if maintained in the IV hood, but the contents of the vial may be added to an IV bag without preservatives and gain a beyond use date of 14 days (provided stability is not less).

A: The IV bag is a final dosage form and will not be manipulated further. A single dose vial by definition is a single-dose container but is going to be manipulated and subject to potential contamination.