

General

1. Are hospital pharmacies subject to the rules of <797>, 503A, and 503B?

Yes, according to the FDA "Pharmacies located within a hospital or standalone pharmacies that are part of a health system frequently provide compounded drug products for administration within the hospital or health system. Some of these compounders have registered with FDA as outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act) and others are state-licensed pharmacies subject to section 503A of the FD&C Act."

2. In a 503B when working with shortage list items (i.e. lidocaine), there are no sterile products available, so would you not have to use bulk ingredients? Shortage medication production is one purpose of the 503B isn't it?

The FDA's Draft Guidance on using bulk drug substances states "One of the conditions that must be met for a drug product compounded by an outsourcing facility to qualify for exemptions under section 503B is that the outsourcing facility may not compound a drug using a bulk drug substance unless (a) the bulk drug substance appears on a list established by the Secretary identifying bulk drug substances for which there is a clinical need, or (b) the drug compounded from such bulk drug substances appears on the drug shortage list in effect under section 506E of the FD&C Act at the time of compounding, distribution, and dispensing."

3. Any opinions on the new Bulks List Guidance from last week? Seems that as it currently state 503Bs should be staying away from Bulk ingredients. Agree/Disagree?

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Beyond Use Dating

1. Can a 503B (since they are held to cGMP) ever claim "expiration date" rather than "BUD"?

The FDA's 503B Draft Guidance states "Under section 503B (a) (10) (A) (iii) (VI) of the FD&C Act, the compounded drug product must be labeled with an expiration date."

2. For a 503A, if stability study is performed on a specific batch size, for example (500) for a formula, can that BUD be assigned for a smaller batch size with the same ratio of ingredients (250)? Or should stability study be repeated for each batch size the pharmacy might want to make?

Stability studies are specific to the formulation, container/closure, storage condition, etc. With proper process validation each batch of drug product should produce the same product therefore stability should not be batch size dependent.

3. For 503A pharmacies, is using published scientific literature a valid method to extend BUD?

Yes literature can be used to determine a BUD. USP <797> says that using literature to extend a BUD is considered a theoretical BUD. When using a theoretical BUD there is a likelihood of error or inaccuracy in BUD assignment. There are many things to take into consideration such as formulation differences, storage condition differences, container/closure differences, etc. The more exact the literature match, the likelihood of error reduces. The more differences, the higher likelihood of error. USP <797> states direct testing is the only way to get a truly valid BUD. Whether literature or direct testing is used to assign a BUD, the justification needs to be documented.

Beyond Use Dating (continued)

4. If using published scientific literature as a 503A pharmacy; does that contradict the statement from the FDA about only using PI information?

<797> allows 503As to use literature for BUD assignment but the 503B draft guidance requires the use of reliable, meaningful, and specific stability indicating methods to determine the stability of compounded preparations.

5. How would you determine temperature excursion limits from a forced degradation test?

Generally speaking you would not. Once the method was established as stability indicating, using forced degradation studies, further evaluation of the product could be done at higher or lower temperatures on stability to provide data on storage excursions.

6. Can excursion data be determined from product monographs or literature?

USP monographs do not address temperature excursions for each product. Literature may be used to investigate temperature excursion impact on stability. 503A's may be able to use the literature to support stability but again this would be theoretical data with a likelihood of error.

7. Is a 28 day 'in-use' time the limit for MDV's? Can 503A pharmacies conduct testing to increase the 'in-use' time?

According to USP <797> BUD's can be extended by 4 methods (product label, consultation with product manufacturer, literature research, and direct testing). Extending use period beyond that assigned by a product manufacturer is not recommended.

8. The most current revised USP 797 doesn't expressly say extended BUD's are allowed. Any information if that was just inadvertently left out?

The proposed version of USP <797> does not allow for BUD extension.

9. So if I do force degradation study and use PCCA chemicals and they are not available next time, can I use Medisca products? Does it have to be same manufacturer?

As long as the formulation is exactly the same stability should not have to be repeated.

10. 503A ... if we use bracketed BUD study, do we have to use exact same chemicals from the same distributor? If they used 10ml vial can we use 1 ml?

As long as the formulation is exactly the same stability should not have to be repeated. Be sure to look into the formulations of the commercial products. If those formulations are different, the stability may also be different.

11. Can you clarify the difference between BUD and expiration date?

USP refers to a BUD as any date assigned to a compounded beyond <797>'s use periods. FDA defines their allowable use periods as BUDs and says that the BUD needs to be used as the expiration date. If you would like to label your products with a use period longer than FDA's use periods, you must conduct stability testing to determine the expiration date.

Beyond Use Dating (continued)

12. If a product has a stability of 7 days, how can we go around having it tested before release under 503B guidelines, given that shipping and testing from the laboratory would take at least 4-7 days?

The 503B draft guidance states “If each batch of the finished drug product has a completed sterility test before release, the finished drug product is labeled with a BUD of not more than 14 days (at USP controlled room temperature or refrigerated) or not more than 45 days (in a solid frozen state between -68.5 °C and -10 °C) beyond completion of the sterility test (e.g., for a sterility test that takes 14 days to complete, the BUD would not exceed 28 days at USP controlled room temperature). Notwithstanding the conditions outlined above, for sterile preserved drugs, the finished drug product is labeled with a BUD of not more than 30 days beyond completion of the sterility test. The other option is to fully validate your sterilization method using bioindicators. This validation would remove the sterility testing requirement but would not remove the endotoxin and potency testing requirements.

13. What documentation do you need to change the BUD date on products for 503B; to extend the date where do you document the new date? Do you need an SOP or protocol?

As a 503B facility, the most important documentation to have for extending BUD’s is stability test results using test methods that are reliable, meaningful and specific. Yes, as a 503B facility FDA’s expectation is cGMP level documentation meaning everything should be governed by SOPs. SOPs and stability test data needs to be stored in a traceable and quickly accessible location such as with the rest of your SOP’s.

Release Testing

1. Can you clarify the volume of solution per container that must be tested in <71>? Table 2 in <71> provides volumes to be tested which are based on the total volume contained in each container.

See Table 2 in USP <71>. It is important to notice that the title of Table 2 says “for Each Medium”. There are 2 media types used in USP <71> testing. The speaker’s example was a 10 mL vial. Table 2 says that for containers with 1-40 mL half of the contents of each vial (5 mL) must be used per medium (2). That is a total of 10 mL per vial must be used in the sterility test.

2. Please clarify that USP requires endotoxins testing for USP <797> low and medium risk compounds. Or is it best practice recommendation? Where is the risk of endotoxin introduction?

USP <797> states “All high-risk level CSP’s, 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° to 8° and longer than 6 hours warmer than 8° before they are sterilized shall be tested to ensure that they do not contain excessive bacterial endotoxins. However, since bacterial endotoxins are released when gram negative bacteria die, endotoxin testing is recommended each time sterility testing is required to make sure there wasn’t bacterial growth and death before the sterility test was initiated. Common sources of endotoxin include water, API’s, compounding equipment (glassware, plastic ware), gloves, reagents, and buffers.

3. Are 503As required to perform endotoxin testing for low/medium risk products labeled sterile (but not necessary non-pyrogenic)?

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Release Testing (continued)

- 4. If container closure integrity testing is done at the end of a stability program and it passes, is a sterility test still required?**

<https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM146076.pdf>

- 5. If we are a 503A pharmacy and are using syringe filters with FTM and TSB to test each sterile compound we make in house when USP <71> doesn't apply, do we have to do method suitability for each compound we use these for even if USP <71> doesn't apply? We aren't required to run these tests. We are just doing it as a best practice for our pharmacy.**

Method suitability should be established for all sterility test methods. Without method suitability, there isn't proof that the test method is capable of detecting contaminating microorganisms.

- 6. For Sterility testing by <71>, there is an extensive volume requirement (endotoxins, etc..) that may exceed the standard 10% or no more than 10 items for submission. How is that handled?**

The requirements for sterility test volumes are stated in Tables 2 and 3 in USP <71>. Any additional tests may require additional articles if all of the volume in the sterility test articles are used in the sterility test.

- 7. For 503A, what <71> testing is required/recommended?**

USP <71> testing is required if exceeding USP's storage periods, for High Risk products prepared in groups >25, MDV's for admin to multiple patients, or if the preparations are exposed to longer than 12 hours at 2°C to 8°C before sterilization or longer than 6 hours at > 8°C before sterilization.

- 8. What if you are making a batch for a single patient and it is a month supply (30 doses)? Do you need to do a method suitability test and submit 4 vials for testing?**

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- 9. Are the sterility tests that are being done by labs that test like USP<71>, but the sample size is not the same as USP<71>? Are we wasting our money and time?**

USP <71> is the preferred sterility test method, but USP <71> does allow for alternative test methods as long as they have been demonstrated to be at least as effective and reliable as USP <71>. If the alternative test method is being utilized because batch sizes are too small then some testing is better than no testing but making larger batch sizes so USP <71> requirements can be met should be considered.

- 10. I would like to find out what we would need to make a change in our container/closure for a preparation. (i.e. switching from one syringe manufacturer to another).**

The answer depends on what your concerns are related to making the change. There is potential that stability may have to be repeated if you cannot justify that the materials of construction are similar enough between the 2 container/closure systems that stability would not be impacted by the change. Repeating stability would not require any justification. If you are concerned about sterility, method suitability would not have to be repeated unless the fill volume changed.

Release Testing (continued)

11. California considers anything over 1 DOSE is a batch.

Correct. Thank you, our slides have been updated to match the current definition of a batch which reads "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."

12. So every time you make a batch over 10, you have to do potency testing?

That is FDA's expectation if you are a 503B facility.

13. Why would sterility be done at 60 and 90 days but endotoxin only at 90 days?

In the example, endotoxin testing was performed at Day 0 and Day 90. Endotoxins are released when gram negative bacteria die. Sterility tests capture current growth. At the very least, endotoxin tests should be performed at the beginning and end to confirm no temporary growth occurred in the product that was not detected by intermediate sterility tests.

14. Are there any rapid sterility methods that are approved for use by FDA?

Yes, however there was a very large amount of validation to support the use of the rapid method. On a recent webinar presented by a pharmaceutical company that received FDA approval for the use of a rapid sterility test method, the pharma company stated in order to achieve the approval there was around 9 months of planning the appropriate validation and 12 months of hands-on laboratory execution of the method validation protocol. That was the amount of work necessary for 1 product.

To view webinar recording, visit: <https://attendee.gotowebinar.com/recording/3709859274463882507>.