

Stability Studies

1. If potency over time studies are not acceptable to extend BUD, then why is it offered?

Potency point-in-time studies only indicate the potency of a compounded preparation at that specific point. To extend a compounded preparation's BUD would require a validated stability-indicating method and subsequent stability testing. 483's issued by the FDA indicate that this practice may not be allowed in the future but could be helpful for screening and initial formulation development. If potency testing over time indicates the product is not stable, additional formulation work, change of packaging or storage condition is needed. If potency over time shows the product is stable, initiating a full stability study is recommended.

2. Usually the Assay is Potency over time test by just testing time points of the active ingredients.

Yes, assays are designed to test the potency of active ingredients.

3. Is assay USP <621> different from a standard potency test performed?

USP <621> Chromatography chapter contains general procedures, definitions, and calculations of common parameters and describes general requirements for system suitability. This is not an assay in itself but provides guidelines for setting up potency assays.

4. If we test potency does that fulfill the USP 621 requirements?

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5. Is there an acceptable degradation limit? Would you consider that preparation as stable?

At minimum the Assay of the product concentration should remain within the established specification, generally 90% to 110% of the label claim. Testing multiple lots (generally 3) at several time points allows for trending of the results (if trends are observed) and evaluation of lot to lot variability on the stability of the product. If a decrease in potency is observed over the course of the study and the results are within specification there should also be an assessment of the impact of the potential degradation products on the patient.

6. Many bases are marketed with formulas where they studied compounds to give it extended BUD like testosterone 2% cream can get 90 days with base A. If I use a different ingredient would you need to do a new micro test?

The stability of any product may be formulation specific. Any ingredient change warrants a new stability study. A microbiology test is recommended for all new lots.

7. What would need to be tested if the base can be provided with the necessary testing for the life of the expiration of the base used in the preparation of a compounded medication?

The beyond use date is for the base only and typically does not include ingredients compounders may add. The BUD can change if interactions occur between ingredients. The chemical, physical, and microbiological properties of the compound should be considered when designing the stability study.

Stability Studies (continued)

- 8. Are compounders actually performing the stability indicating tests? When I had inquired before these tests can run up to \$10,000. If this test should be performed for each formulation, how is this financially feasible for compounders?**

Yes, many compounders are performing stability studies with validated stability indicating methods. The cost of the study must be weighed against the benefits gained from the study. The potential benefits of performing a stability study are increased compounding efficiency and reduced drug waste.

- 9. Can you provide information on the difference between a Stability Indicating Method vs Stability Indicating Assay? Can the later be used for extension of a BUD of a non-sterile preparation?**

According to FDA guidelines (Guidance for Industry, Analytical Procedures and Methods Validation, FDA, 2015), a Stability Indicating Method (SIM) is defined as a validated analytical procedure that accurately and precisely measure active ingredients (drug substance or drug product) free from process impurities, excipients and degradation products. The stability indicating method must be validated for the specific formulation being tested. The stability indicating method is used to perform the assay (test) and ultimately extend the BUD.

- 10. Given the cost-intensive nature of stability studies, do you foresee some sort of middle ground for compounders (i.e. varying column characteristics to evaluate robustness/etc.) that might better indicate stability beyond a simple potency test without requiring a full-blown stability study?**

No, the observations in 483's issued to compounding pharmacies have stated the methods used to determine stability (BUD) were not reliable, meaningful, and specific. By reliable, meaningful, and specific, the FDA means fully validated and stability indicating. Several state boards of Pharmacy and the proposed USP <797> state that stability indicating methods must be used to extend BUD's.

- 11. If an excipient has a shorter BUD than an active ingredient, what is the BUD? The lesser or the active?**

In any compounded preparation, the BUD should not exceed that of any ingredient.

- 12. Prior to the FDA regulations concerning BUD, many topical compounds had a BUD of 6 months. What was the prevalence of contamination on those compounds?**

Unknown. The prevalence of microbial growth in compounds is due to several factors including the process used to make the compound, the presence of antimicrobial preservatives, and the potential of the compound to support microbial growth.

- 13. So a time point study is just one piece of the stability study?**

Yes, testing the concentration of the drug is just one component of a stability study. Testing should include evaluation of the physical, chemical, and microbiological properties of the product.

- 14. So to confirm, if there is a validated method used from USP 621, there is no need to further validate that method for stability indicating studies? Or a USP monograph?**

USP <621> Chromatography chapter contains general procedures, definitions, and calculations of common parameters and describes general requirements for system suitability. It does not provide validated methods for testing. USP monograph methods are typically not stability indicating.

Stability Studies (continued)

- 15. If a USP monograph exists that assigns a range outside of the usual 90-110% (i.e. vitamin E solutions), are compounders allowed to follow the specific monograph limits without also performing the additional USP monograph tests?**

All USP monograph tests are recommended.

- 16. Don't you need to have 3rd party verification for these tests in order to extend BUD? I didn't think you could do it in house?**

Stability studies can be performed in-house and do not require a 3rd party.

Non-sterile products

- 1. Question about new CA regulations. They state: (3) Extension of a beyond use date is only allowable when supported by the following: (A) Method Suitability Test, (B) Container Closure Integrity Test, and (C) Stability Studies. Aren't the first 2 specific to sterile only? You don't do method suitability or CCIT on non-sterile do you?**

Method suitability and container closure integrity tests can be performed on nonsterile products. Think of method suitability as a validation of a test procedure. While the California regulations are likely referring to sterility testing when they state a Method Suitability Test is required, there are also method suitabilities related to USP <61> & USP <62>, which are tests for nonsterile products. Nonsterile products still propose risk to patients if they are contaminated with sufficient amounts of objectionable microorganisms (e.g. oral products should be free of *E. coli*). CCIT should still be included in a stability profile for nonsterile products.

- 2. Is it possible for a non-sterile product to be tested for potency and bacterial content at the 6 month mark and that would suffice as enough documentation to increase BUD to 180 days?**

Testing one time point does not provide a reliable stability profile and is not advisable. The stability profile of a formulation requires more than two tests at the target date. As discussed in the presentation, there are a series of tests that should be performed at intervals during the course of the study to properly demonstrate stability. An initial time point (T=0) should be tested to demonstrate the starting point of the stability samples. Testing throughout the study is important for trending and for elimination of questions related to potential microbial growth and death during the storage period.

- 3. When trying to extend topical creams beyond 30days, why would you need microbiological data since it's non-sterile in the first place and not taken orally?**

Nonsterile products can contain objectionable organisms that could potentially harm patients. For example, *Staphylococcus aureus* should not be present in any topical cream. In addition to specific objectionable organisms, the total bioburden of the preparation should be demonstrated to be at acceptable levels based on the route of administration. USP <1111> is the informational chapter providing guidance on this. Both the absence of specific organisms and the total count of microbes over time in the study demonstrates the overall microbiological quality of the formulation. USP <61> and <62> are integral components of a non-sterile stability study.

Non-sterile products (continued)

- 4. In a non-sterile preparation how does one consider the need to perform a microbial study of a preprepared base that has studies performed on it already and the base has been marketed for specific use? Is there something we can check via a CofA or information we can ask for from the base manufacturer?**

Any alteration to a prepared base can potentially disrupt the quality of the product, which necessitates performing a stability study. An alteration could potentially introduce microorganisms, change physical/chemical properties of the ingredients, or affect ingredient activity. Proper testing is the only way to ensure quality is maintained.

- 5. Can a USP <62> test be performed as a process validation so this test wouldn't need to be performed each time a solid dosage form was prepared or done in triplicate?**

USP <62> is an important part of process validation, but that should not be the only time a product is tested for USP <62>. The test itself should be performed on every batch/lot to prove microbial quality was maintained throughout the compounding process. A regular quality control testing plan should be put in place; especially in the case of USP <62>, since it looks for objectionable organisms based on route of administration. Please refer to informational chapter USP <1111> for information on specified microorganisms based on route of administration. Also, it is recommended to test finished products for specific organisms recovered during environmental monitoring.

- 6. Would it be possible to provide a chart similar to the one provided for the sterile product for a non-sterile preparation, showing the different tests that would be required and suggested in extending the BUD?**

There is a chart on slide 24 that compares stability testing for sterile and nonsterile products. Table 2 – Selected Compendial Testing Methods for Bulk Substances and Various Dosage Forms (slides 65-67) includes tests for both sterile and nonsterile products.

BUD Webinar Q&A

Compare and Contrast Stability

Sterile Preparations	NonSterile Preparations
USP 51 – Preservative Effectiveness	USP 51 – Preservative Effectiveness
USP 71 – Sterility	USP 61 – Microbial Limits
USP 85 – Endotoxin	USP 62 – Absence of Specified Organisms
USP 341 - Preservative Quantification	USP 341 – Preservative Quantification
USP 621 - Assay	USP 621 - Assay
USP 788/789 – Particulate Matter	
USP 791 - pH	USP 791 - pH



Non-sterile products (continued)

USP <1163> Table 2 - Selected Compendial Methods for Bulk Substances and Various Dosage Forms:

Table 2. Selected Compendial Testing Methods for Bulk Substances and Various Dosage Forms

Bulk Substances and Dosage Forms	Testing Method ^a													
	Wt	Vol	pH	Osm	RI	Sp Gr	MP	UV/Vis	HPLC	GC	IR	Sterile	Endotoxin	PM
Bulk substances	-	-	+	-	+	-	+	+	+	+	+	-	+ ^b	-
Capsules	+	-	-	-	-	-	-	-	+	+	-	-	-	-
Emulsions	+	+	+	-	-	+	-	-	+	+	-	-	-	-
Gels	+	+	+	-	+	+	-	-	+	+	-	-	-	-
Inhalations	+	+	+	+	+	+	-	+	+	+	-	+	+	-
Injections	+	+	+	+	+	+	-	+	+	+	-	+	+	+
Inserts	+	-	-	-	-	+	+	-	+	+	-	-	-	-
Irrigations	+	+	+	+	+	+	-	+	+	+	-	+	+	-
Lozenges	+	-	-	-	-	-	-	-	+	+	-	-	-	-
Nasals	+	+	+	+	+	+	-	+	+	+	-	* ^c	-	-
Ophthalmics	+	+	+	+	+	+	-	+	+	+	-	+	-	+ ^d
Otics	+	+	+	+	+	+	-	+	+	+	-	-	-	-
Powders	+	-	-	-	-	-	-	-	+	+	-	-	-	-
Semisolids	+	-	+	-	-	+	+	-	+	+	-	-	-	-
Solutions, nonsterile	+	+	+	+	+	+	-	+	+	+	-	-	-	-
Sterile implant gels	+	+	+	+	+	+	-	+	+	+	-	+	+	-
Sterile implant solids	+	+	-	-	-	-	+	+	+	+	-	+	+	-
Sticks	+	-	-	-	-	+	+	-	+	+	-	-	-	-
Suppositories	+	-	-	-	-	+	+	-	+	+	-	-	-	-
Suspensions, nonsterile	+	+	+	-	-	+	-	-	+	+	-	-	-	-
Tablets	+	-	-	-	-	-	-	-	+	+	-	-	-	-

^a Wt, weight; Vol, volume; Osm, osmolality/osmolarity; RI, refractive index; Sp Gr, specific gravity; MP, melting point; UV/Vis, ultraviolet/visible spectroscopy; HPLC, high-performance liquid chromatography; GC, gas chromatography; IR, infrared spectroscopy; PM, particulate matter; +, test applicable; -, test not applicable.

^b Endotoxin testing may be needed for bulk substances used in compounding some sterile preparations.

^c *, microbial limits (see *Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use* <1111> and *Pharmaceutical Compounding—Sterile Preparations* <797>).

^d Solutions only, not suspensions or ointments.

7. Are the objectionable organisms in USP valid for non-human (veterinary) preparations or are there other organisms that should be considered?

Compounders for veterinary medicine must abide by USP regulations per USP chapters <795> & <797>. It can be assumed the objectionable organisms recommended testing would be similar. Also be sure to reference USP since there are several veterinary monographs.

Sterile products

1. Is there a window of time, from when a container is depyrogenated/sterilized, that you have to use the container without needing to depyrogenate/sterilizing it again?

There is not a specific amount of time that is applicable to all container types. The most effective way to establish use dates for containers is to perform a time point study that establishes pre-sterilization/ depyrogenation microbial/ endotoxin load; then test sterility and endotoxin at timepoints with storage conditions and packaging exactly the same way as at your facility.

2. How do you prevent introducing contaminants with the tools you are using the conduct the tests?Stringent standard operating procedures should be set in place to prevent any contamination of samples. Proper training and qualification of laboratory personnel are essential to reduce risk of introducing microbes into test samples. In addition, a robust environmental monitoring program should be established for quality assurance.

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