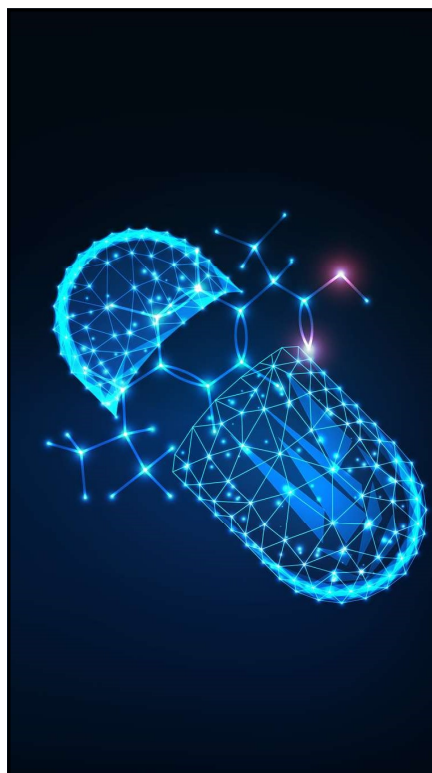




What to Expect When You're Expecting ... To Run a Stability Study

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PLANNING YOUR STUDY

LET'S GET TO WORK!



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PLANNING YOUR STUDY



**UNDERSTAND
USP CHAPTER
REQUIREMENTS**



TARGET BUD



TIMEPOINTS



TESTS



**OBTAIN A
QUOTE**

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TARGET BUD

- Based on USP <795> Requirements for Non-Sterile
- Based on USP <797> Requirements for Sterile
Category 1, 2, or 3



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USP <795>**BUD Limit by Type of Preparation in the Absence of a USP-NF Compounded Preparation Monograph or CNSP-Specific Stability Information**

Type of Preparation	BUD (days)	Storage Temperature ^b
Aqueous Dosage Forms ($a_w \geq 0.60$)		
Nonpreserved aqueous dosage forms ^c	14	Refrigerator
Preserved aqueous dosage forms ^c	35	Controlled room temperature or refrigerator
Nonaqueous Dosage Forms ($a_w < 0.60$)		
Oral liquids (nonaqueous) ^d	90	Controlled room temperature or refrigerator
Other nonaqueous dosage forms ^e	180	Controlled room temperature or refrigerator

^a A shorter BUD must be assigned when the physical and chemical stability of the CNSP is less than the BUD limit stated in the table (see 10.4 CNSPs Requiring Shorter BUDs).

^b See *Packaging and Storage Requirements* (659).

^c An aqueous preparation is one that has an a_w of ≥ 0.6 (e.g., emulsions, gels, creams, solutions, sprays, or suspensions).

^d A nonaqueous oral liquid is one that has an a_w of < 0.6 .

^e Other nonaqueous dosage forms that have an a_w of < 0.6 (e.g., capsules, tablets, granules, powders, nonaqueous topicals, suppositories, and troches or lozenges).

<https://www.usp.org/sites/default/files/usp/document/events-and-training/2022-11-08-gc-795-open-forum-website-posting.pdf>

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USP <795>

▶ In the **Presence** of CNSP-Specific Stability Information

- BUD may be extended up to a maximum of 180 days
 - Stability-indicating analytical method for the API(s), CNSP formulation, and material of composition of the container closure that will be used
 - An aqueous CNSP must be tested for (51) antimicrobial effectiveness at the end of the BUD
 - Bracketing can be utilized to provide flexibility
 - If compounding from a *USP-NF* compounded preparation monograph, the BUD must not exceed the BUD specified in the monograph
- ▶ Shorter BUDs may be required
- If components have an earlier expiration date or BUD
 - If ingredients are known to be susceptible to decomposition

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USP <797>

BUD Limits by Category

Compounding Category	Environment (minimum requirements)	BUD Limit
Immediate Use	Uncontrolled environment with no primary engineering control (PEC)	4 hours at any storage condition
Category 1	ISO Class 5 PEC placed in unclassified environment	12 hours at controlled room temperature 24 hours refrigerated
Category 2	ISO Class 5 PEC placed in an ISO Class 7 buffer room	1 - 45 days at controlled room temperature 4 - 60 days refrigerated 45-90 days frozen
Category 3	ISO Class 5 PEC placed in an ISO Class 7 buffer room Note: There are additional facility and personnel requirements	60-90 days at controlled room temperature 90-120 days refrigerated 120-180 days frozen

Storage times for BUDs at each temperature are not additive and the CSP may not be used past the original assigned BUD. Controlled room temperature is 20° to 25°C, refrigerated 2° to 8°C, frozen -25° to -10°C.

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USP <797>

BUD for Category 2

Compounding Method	Sterility Testing Performed and Passed	Controlled Room Temperature (20° to 25°C)	Refrigerator (2° to 8°C)	Freezer (-25° to -10°C)
Aseptically Processed CSPs	No	Prepared from one or more nonsterile starting component(s): 1 day	Prepared from one or more nonsterile starting component(s): 4 days	Prepared from one or more nonsterile starting component(s): 45 days
Aseptically Processed CSPs	No	Prepared from only sterile starting components: 4 days	Prepared from only sterile starting components: 10 days	Prepared from only sterile starting components: 45 days
Aseptically Processed CSPs	Yes	30 days	45 days	60 days
Terminally Sterilized CSPs	No	14 days	28 days	45 days
Terminally Sterilized CSPs	Yes	45 days	60 days	90 days

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USP <797>**BUD for Category 3**

Compounding Method	Sterility Testing Performed and Passed	Controlled Room Temperature (20° to 25°C)	Refrigerator (2° to 8°C)	Freezer (-25° to -10°C)
Aseptically Processed CSPs	Yes	60 days	90 days	120 days
Terminally Sterilized CSPs	Yes	90 days	120 days	180 days

Additional requirements: personnel, environmental, Stability indicating method study supporting BUD, particulate matter for injections, and ophthalmic solutions, container closure integrity test, sterility, and endotoxin

Maximum Batch Size: 250 Units



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TIMEPOINTS

- **Chapter Minimums - Depends on the Test**
 - Particulate Matter Requirement once per formulation with acceptable results (Injection or Ophthalmic Solution)
 - Container Closure Integrity Testing once per formulation and for each container closure system
- **Beginning / End - Snapshots at T=0 and T=Final**
- **Beginning / Intermediates / End**
 - Rolling Data about the Product
 - Timepoints to fall back on if there is an issue
- **From USP 2023 Formulation and Stability Reference Doc**
 - "The test Intervals must include at least the initial and final timepoints. It is strongly recommended to also have at least one interim timepoint. More timepoints provide better identification or trends of the formulation behavior. Where feasible, study results will benefit from having at least five time points in total (including initial and final)."



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TESTS

- A validated, stability-indicating API potency assay method is required
- Chapter Minimums
 - USP <795> Potency, CCIT, Antimicrobial Effectiveness (if multi-dose)
 - USP <797> - Potency, Particulate Matter, CCIT, Antimicrobial Effectiveness (if multi-dose)



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TESTS			
USP 2023 Formulation and Stability Reference Doc, “Musts” vs “Shoulds”			
USP <797> Stability MUSTS	USP <797> Stability SHOULD S	USP <795> Stability MUSTS	USP <795> Stability SHOULD S
Appearance	pH	Appearance	pH
Particulate Matter		Potency	USP <60> Tests for Burkholderia
Potency		Impurities/Degradants	USP <61> Bioburden
Impurities / Degradants		Antimicrobial Effectiveness	USP <62> Test for Specific Organisms
Sterility			
Endotoxin			
Antimicrobial Effectiveness			
CCIT			

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OBTAIN A QUOTE

- Collaborate with a Contract Lab that has experience with stability work for compounding pharmacies
- Communicate goals, product information, and desired BUD / timepoints / tests chosen
- Contract labs have a vast knowledge base and can help you leverage your plan for success with industry experience

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EXECUTE YOUR STABILITY STUDY

I SIGNED MY QUOTE, NOW WHAT?




COMPOUNDING PHARMACY
OWNER SUMMIT

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EXECUTE YOUR STABILITY STUDY



**POINT OF
CONTACT WITH
LAB**



**SAMPLE
REQUESTS**

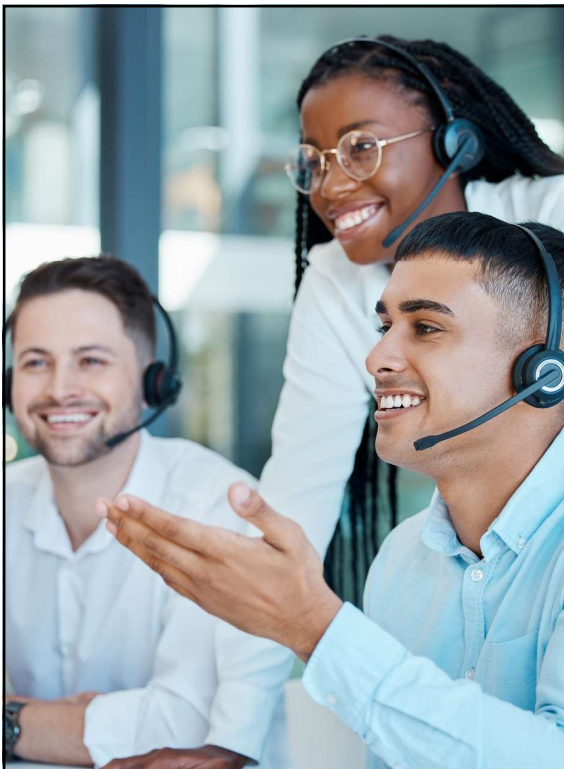


METHOD WORK



**SAMPLE
REQUIREMENTS**

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EXECUTION STEPS

Get a solid point of contact with your lab

- Project Manager or Sales Representative: someone you know will get back to you if you have questions
- There may be a wait, depending on lab capacity, from when a quote is signed to when the project starts
- Customer service is key for a smooth stability study
- Information flowing freely between compounder and contract lab is critical



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TWO REQUESTS FOR SAMPLES

1. Samples for Method Work

- Stability-Indicating Potency Bench Work (Validation / Verification)
- Sterility Method Suitability
- Antimicrobial Effectiveness Method Suitability
- Other tests that may require upfront method work
- May or may not have to be sterilized or in the final finished product container, check with the lab

2. Samples for the Stability Study

- This will need to be enough product sample to cover all the tests at all the timepoints, plus extras just in case
- Stability Study quotes usually have an estimate

Sample Requests May Be Several Weeks Apart



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METHOD WORK

- **Sample needs will depend on whether there is an existing method to verify at the lab or if a new method is being developed and validated.**
- **Expect a request for a finished product and a placebo, e.g., your formulation without the API**
- **Important questions to ask about your stability study potency method**
 - Confirm the **method is stability-indicating**, USP <1225> Compliant, and utilizes forced degradation to develop
 - Confirm the **method is formulation-specific**
 - Both criteria **MUST BE MET** to satisfy USP/ FDA requirements!
- **Additional product samples will be needed for test methods other than potency**
 - Example: USP <71> Sterility will require some multiple of the normal test amount for method suitability



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METHOD WORK - PEPTIDES

Some method work is more difficult than others – Peptides

- High-performance liquid chromatography (HPLC) has proven extremely versatile for the separation and quantification of peptides in the last 25 years.
- Common peptides used in compounding are Semaglutide, Liraglutide and Tirzepatide
- Stability-indicating HPLC methods for ~20 therapeutic peptides with molecular size range from 6 to 51 amino acids are currently available
- HPLC method development for peptides can be challenging and difficult due to the distinct characteristics of peptides.



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METHOD WORK - PEPTIDES

What makes peptides distinct and potentially difficult?

- **Peptide Stability:** Peptides are susceptible to oxidation, hydrolysis and photolysis.
 - For example, when Semaglutide preparations are stressed, many different degradant peaks appear.
 - The formulation has a big effect on peptide stability and new peaks seem to show up in every new formulation tested
- **Separating Degradants & Impurities:** Peptide impurities and degradants have similar structures and properties to the actual peptide
 - Method development can be very complex to separate everything from the peptide you want to assess
 - It takes a skilled chemist to achieve a stability assay method that is reliable and specific for the target when so many unknown compounds can appear
- **Peptide Solubility:** Even the sample prep can be difficult and figuring out what diluent is best for the peptide and the formulation as a whole takes time



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SAMPLE REQUIREMENTS

EXAMPLE OF A STABILITY STUDY SAMPLE REQUIREMENT TABLE, 2 ML VIAL W/ 2 ML FILL

Test	# per Timepoint				Total Tested	Extra	# of Lots	Total
	0	30	60	90				
Appearance	**	**	**	**	**	**	1	**
pH	3	3	3	3	12	3	1	15
Particulate Matter	10	10	10	10	40	10	1	50
API Assays	3	3	3	3	12	3	1	15
Container Closure	11	/	11	11	33	11	1	44
Sterility	20	/	20	20	60	20	1	80
Endotoxin	1	/	1	1	3	1	1	4
Antimicrobial Effectiveness	30	/	30	30	90	30	1	120
Totals					250	78	1	328

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SAMPLE REQUIREMENTS

WHAT FACTORS CONTRIBUTE TO CALCULATING THE NUMBER OF SAMPLES NEEDED?

- **USP Volume/ Article Requirements**
 - Example: USP <788> Particulate Matter requires 10 articles if < 25 mL, or 1 if > 25 mL
- **Container Size/ Fill**
- **Client Decisions**
- **Lab Recommendations**
- **Method or Technology Requirements**
 - Example: Potency method may have a volume requirement, or the pH test may need a certain amount to immerse the pH probe

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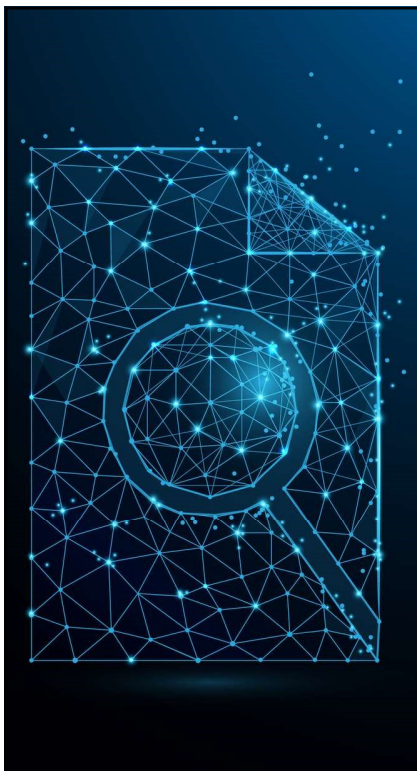


COA, REPORTS, AND MILESTONES

IT IS ALL COMING TOGETHER!



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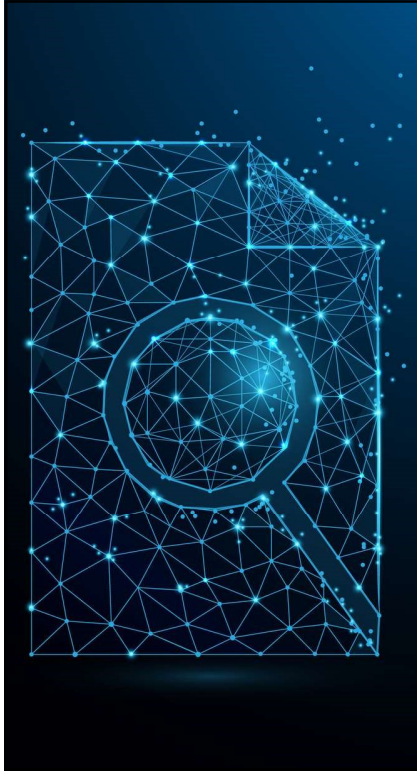
COA AND REPORTS

Certificates of Analysis (CoAs)

- **Find out if the lab will be releasing these as timepoints are completed**
 - This provides an up-to-date assessment of your product's stability profile
 - Can be used to revise the BUD as you reach and pass each timepoint
- **In addition to digital copies, print and compile with all documentation to create a product file/binder.**



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COA AND REPORTS

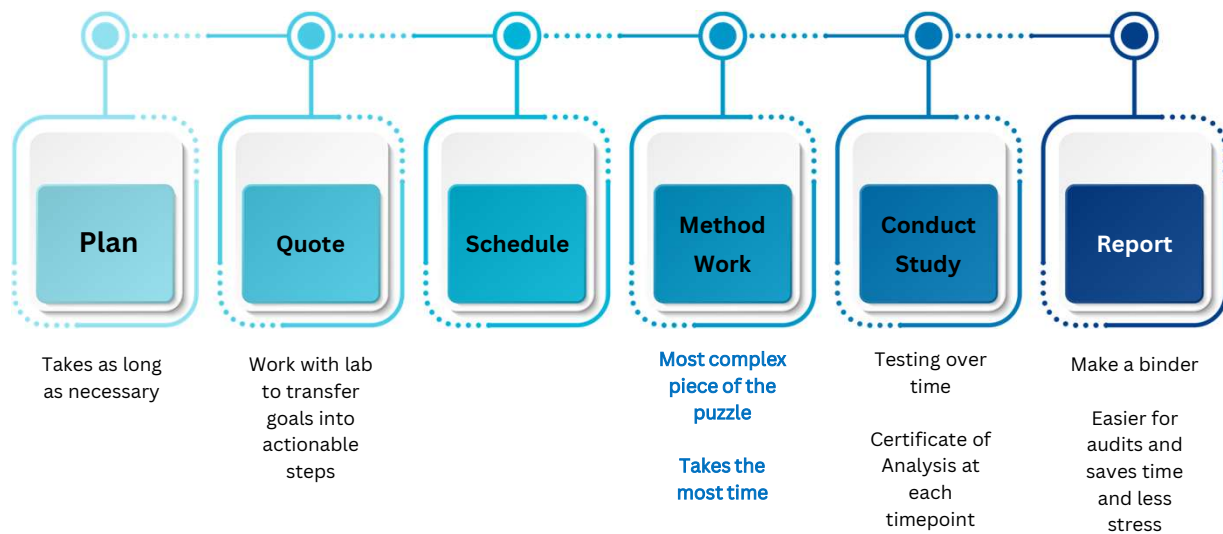
Reports

- **At the conclusion of the study, USP expects a report based on the 2023 Formulation and Stability Reference Document:**
 - “A study summary should be written and maintained for reference by internal staff and auditors. The summary outlines the objective of the study and includes specifics about the preparation, container closure, and storage conditions. The summary must reference the stability study protocol that contains specific test methods and specifications”
- **This could be written by the compounder or the contract lab**




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STABILITY STUDY STEPS AND MILESTONES




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PITFALLS, DELAYS, AND FRICTION POINTS



What is the Hold Up?



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PITFALLS, DELAYS, AND FRICTION POINTS

- **Stability Studies take planning, equipment, product, bench work, documentation work, and significant collaboration from all parties**
 - Don't wait until the last minute and expect to accomplish everything
 - The whole process, from planning to quoting to method work to stability study to final report, can take 6+ months
- **A firm plan that is clearly communicated between compounder and contract lab is a big help!**
 - Changes to the plan or product could have a significant effect on the work to do or work already done

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PITFALLS, DELAYS, AND FRICTION POINTS

- **If a stability study is in the works, be prepared to devote some compounding time and space to the method work and stability study samples**
 - The sooner the contract lab gets your samples when requested, the sooner the method work or stability study can begin!
- **Allow time for emails and phone calls between lab and compounder and internal discussions to work out the details**
- **Contract labs may have a wait time based on industry factors, demand for studies, regulatory changes, internal capacity, and complexity of the product to test.**



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THANK YOU



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