Compounder's International
Analytical Laboratory
Better Quality Through Quality Testing
800.788.9922
compounderslab.com

Please note: Our email address is lab@compounderslab.com

Extending a BUD: Potency Over Time (POT) vs. Stability Indicating Assay (SIA)

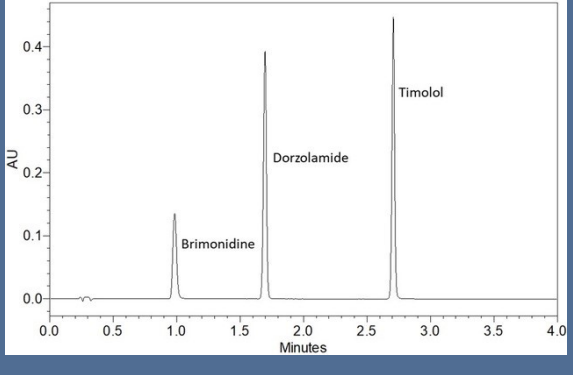
In our lab, some of the most common questions we receive from 503A pharmacies and 503B outsourcing facilities involve the means of extending the beyond use dating of their preparations and products. According to the USP General Chapters <795> and <797> there are default beyond use dates (BUD) that are allowed for sterile and non-sterile preparations and products made by compounders. However, if there is a desire to extend beyond those default dates, the primary option available is to demonstrate, by laboratory-generated data, that the product still meets quality requirements after a longer period of time. To accomplish this, stability testing is required. There are two approaches to this testing which will demonstrate stability of the active ingredient potency. They are: 1) Potency Over Time (POT) stability studies, and 2) Stability Indicating Assay (SIA) stability studies. Both of these focus on the active ingredient(s) and determine the time frame during which they maintain their potency.

The Bigger Picture

We will get into a discussion on these two approaches in a moment, but first, it should be pointed out that potency alone is not the only criterion for stability. There are other factors involved which could affect the stability of a preparation as well. Among these would be a change in color, fragrance, or texture. Also, a change in pH, or the development of crystals or particulates. Furthermore, microbial growth or a defect that develops in the container or packaging such that leakage or contamination could occur. In addition, there could be leaching of a harmful substance from the container into the product, or some part of the container, such as the rubber septum or syringe plunger tip, could absorb a portion of the active ingredient(s) leaving the preparation sub-potent. These changes, and others, which might occur over time should be considered and perhaps included as a part of a stability study. In fact, here at CIAL, much of our daily lab work is devoted to addressing these sorts of questions, along with testing the stability of the active ingredient(s), and sometimes, the antimicrobial agents as well.

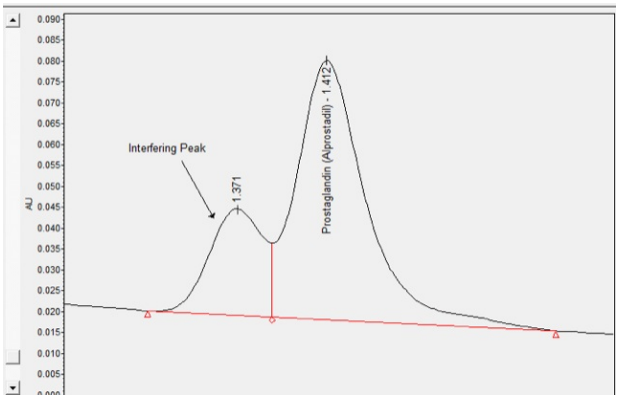
Instruments Used to Test Potency

As we consider the means of testing ingredients in a preparation or product, some of the most powerful tools available for this purpose are High Performance Liquid Chromatography (HPLC) or Ultra High Performance Liquid Chromatography (UHPLC) instruments. These instruments are ideal for this purpose because they are capable of quantifying the ingredients of interest by separating them from other substances in the formulation. Thus, they can be *specific* for quantifying the compounds being tested for their stability. Between these two types of instruments, UHPLC is newer and much more powerful. It is faster and produces very sharp peaks in the chromatogram, thus it is able to separate complex mixtures more easily. It is also more sensitive, able to detect lower potency levels. For these reasons, we only use UHPLC in our lab.



Potency Over Time

As stated earlier, there are two approaches to using these powerful instruments for the determination of an appropriate BUD. Potency Over Time (POT) stability studies involve developing a method of preparing a sample for analysis, and a UHPLC method that can isolate the ingredient(s) of interest from other active or inactive ingredients. This method combination is then used at periodic time points, perhaps monthly, to determine potency of the active(s). Initially, a sample of the product is tested as close as possible to the date it was made so as to determine the starting potency. This is often called the “Baseline Potency”. The preparation is then stored under the appropriate conditions, (room temperature, refrigeration, or freezer) then removed from storage periodically to again be tested. This is repeated until the potency has declined to near the limit of the allowed range (usually a 10% decline in potency from the starting potency). If it takes 180 days to reach this point, the product can be given a 180 day BUD.



There are drawbacks to this approach, however. Significantly, a validation of the testing method for the specific formulation has not been performed. This means that the method combination being used might not be completely reliable over the ensuing months of the study. Also, it is possible that during the study, breakdown of the active(s) or even an interaction among or degradation of excipient ingredients, could occur. These newly formed substances could make it challenging to accurately quantify the potency of an active. If this occurs, the chromatographic method may need to be adjusted or redeveloped to remove the interference(s).

Stability Indicating Assay

The other technique, a Stability Indicating Assay (SIA) stability study, which is becoming the preferred method, includes all the above steps. However, it seeks to solve the interference problem of the POT technique before the stability study begins. So, SIA starts differently from a POT study and is accomplished in two phases. The initial phase (Phase 1) seeks to solve the interference problem by creating all potential breakdown products in a preparation before the analytical method is developed. This is achieved by forcibly degrading the entire product, actives and inactives alike, under five conditions of: heat, light, acid, base, and an oxidizer, in an attempt to quickly generate all possible breakdown products which might occur during the period of the upcoming study. The purpose of this is to allow development and validation of the analytical method in the presence of all potential compounds, active(s), inactive(s), and breakdown substances, and make sure there are no interferences. This interference-free method will now be used in Phase 2, the actual stability study. The proper BUD can now be determined by periodic testing.

A Bit More Involved

The SIA technique involves a great deal more work, however, and thus takes more time before the actual stability study can begin. Here is an outline that includes many of the steps.

- **Step 1.** Develop an initial test method before the forced degradation steps.
- **Step 2**. Treat the sample using the five conditions described above.
- **Step 3.** Using the initial method, constantly check the amount of degradation under each set of conditions until there is at least a 10% degradation, if possible. This can take several days to accomplish.
- **Step 4.** Check for interferences for each of the five degradant conditions. If any are found, modify the method to solve the interference problem. Now check all five again for any interferences with the new method.
- **Step 5.** Repeat Step 4 as many times as required until there are no interferences from any of the five conditions.
- **Step 6**. Now that the method is free from interference, it must be validated.
- **Step 7**. Validation includes testing the method for:
    - Specificity: It must be proven that the method is testing for the correct ingredient and only that ingredient.
    - Accuracy: It must be proven to provide the correct answer as to the amount of each ingredient in the sample.
    - Sensitivity: It must be proven that the method is sufficiently sensitive to quantify even the lowest possible amount.
    - Linearity: It must identify the range of potencies that can be tested and provide accurate results.
    - Precision: It must prove the results are repeatable.
    - Ruggedness: It must demonstrate that multiple people using multiple instruments, or a single instrument on multiple days, will obtain the same results.
    - Robustness: It must demonstrate that the method will provide correct results even if there are some minor variations in the process.
    - System Suitability: The method must include a number of instrument-related criteria that will provide assurance the instrumental method can be depended upon to work properly and provide correct potency values.
- **Step 8.** A 16-18 page report is generated, and sent to the pharmacy, documenting the Phase 1 method.

All of this work can take many days, or even several weeks to complete.

- **Step 9.** Embark on Phase 2 of the Stability Study using the Validated SIA method and determine the BUD.

Making the Choice

Determining the approach to take when ordering a stability study often comes down to cost or agency requirement. A 6-month Potency Over Time stability study with one or two active ingredients will often range $1,000 - $2,000. Whereas, the same product stability-tested under SIA methodology will likely range $12,000 or more. This cost can be prohibitive for many compounders when sales do not support this expense. The 503A compounding pharmacies must meet the requirements of the states where they reside or where they ship medications. Many states (but not all) will accept POT stability data so it is wise to check with all state boards where you ship, to know their requirements. All 503B Outsourcing Facilities are regulated by the FDA. These pharmacies must establish their BUDs by the SIA method. It is useful to recognize that regulatory requirements are subject to change and using the SIA method is the most widely accepted. States which allow POT data currently might require SIA data in the future. Certainly, the FDA would like all BUDs to be based upon SIA method studies and it is likely that the USP will require it as well in upcoming revisions. As you consider all these factors, whichever way you decide, we will do our best to provide accurate data for your BUD labeling.

Bracketing

Whether establishing BUDs by the POT or by the SIA methods, it is often wise to keep an eye on future potency requirements for similar formulations. Establishing the BUD of a formulation at a

particular potency will not establish the BUD of the same formulation at a different potency, unless that other potency is also tested. It is therefore wise to perform the stability study at both the highest as well as at the lowest potency likely to be encountered. This is known as “potency bracketing”. With bracketing data in hand, it can safely be assumed that the same BUD can be used at these high and low potencies, as well as for all potencies in-between. This common practice saves time and cost, and is encouraged by the FDA.

Bottom Line

We hope this discussion has brought some clarity to the process of extending beyond use dating for compounded preparations. Since every pharmacy and formulation is unique, we usually find it helpful to dialogue with our customers about their goals for BUD testing prior to submitting samples. We welcome your questions and are happy to put together a quote for you which will cover the tests, time points, amounts of sample needed, and costs. This way you will have all the information you need, with no surprises. Please call 1(800)788-9922 or email lab@compounderslab.com. We look forward to hearing from you!

Give Us A Try

We think you will find working with us a refreshing experience! We are centrally located in the US (Colorado) so samples can easily be shipped to us overnight from whereever you are located.

We look forward to working with you!

Ronald Sutton, President

VIEW OUR PRICE LIST **SAMPLE SUBMISSION FORMS**

Phone (CO) | 303.471.8015
Phone (US) | 800.788.9922
Fax | 303.569.6101

lab@compounderslab.com
www.compounderslab.com