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Current & Practical Compounding Information for the Pharmacist.

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Beyond-Use Dates and Stability Indicating Assay Methods in Pharmaceutical Compounding

GOALS AND OBJECTIVES

Goal: To provide information on how beyond-use dates can be determined based on stability-indicating assay methods in pharmaceutical compounding.

Objectives: After reading and studying the article, the reader will be able to:

1. Discuss the differences between potency testing and stability testing.
2. List the five types of stability of concern to pharmacists.
3. Describe the steps involved in conducting a stability study.
4. Evaluate stability study data and assign a beyond-use date.
5. Assign a default beyond-use date if no data is available, based on USP Chapters <795> and <797>.

INTRODUCTION

One of the most important activities of a compounding pharmacist is the assignment of a beyond-use date for a compounded preparation. It is essential that the date be reasonably determined from either laboratory testing or using official default standards.

It should be noted that there is a difference in the purposes of potency tests and stability tests. Potency testing, quantitative testing, is designed to determine how much of an active drug is present in a sample. Stability tests are used to determine an expiration date or a beyond-use date for a preparation. Methods of determining potency may or may not be stability-indicating, as will be discussed later. Stability can be determined only by a stability-indicating method, which can determine both potency and stability. However, a potency test may or may not be able to determine stability.

Stability is the extent to which a product retains within specified limits and throughout its period of storage and use (i.e., its shelf life) the same properties and characteristics that it possessed at the time of its manufacture.

There are five types of stability of concern to pharmacists.

1. **Chemical stability** where each active ingredient retains its chemical integrity and labeled potency within the specified limits.
2. **Physical stability** where the original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability are retained.
3. **Microbiologic stability** includes sterility or resistance as well as the situation where resistance to microbial growth is retained according to the specified requirements. Antimicrobial agents retain effectiveness within specified limits.
4. **Therapeutic stability** where the therapeutic effect remains unchanged.
5. **Toxicologic stability** where there is no significant increase in toxicity.

Chemical stability is important for selecting storage conditions (temperature, light, humidity), selecting the proper container for packaging and dispensing (glass vs plastic, clear vs amber or opaque, cap liners) and anticipating interactions when mixing drugs and dosage forms.

Stability and expiration dating are based on reaction kinetics, the study of the rate of chemical change and the way this rate is influenced by concentration of reactants, products, and other chemical species and by factors such as solvent, pressure and temperature.

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DRUG STABILITY, EXPIRATION DATES AND BEYOND-USE DATES

The required demonstration by the FDA of drug stability for commercially manufactured dosage forms is different for each step of drug product development, such as for a 2-week preclinical study, an early Phase I study, a limited Phase II trial, a pivotal Phase III clinical study, or for a New Drug Application. Before approval for marketing and generally a long shelf life of 2-3 years, a product's stability must be assessed with regard to its formulation; the influence of its pharmaceutical ingredients, the influence of the container and closure, the manufacturing and processing conditions, packaging components, conditions of storage; anticipated conditions of shipping, temperature, light and humidity; and anticipated duration and conditions of pharmacy shelf life and patient use, among others.

For pharmaceutical compounding, the General Notices of the USP state: "The label on the container or package of an official compounded preparation shall bear a beyond-use date. The beyond-use date is the date after which a compounded preparation is not to be used. Because compounded preparations are intended for administration immediately or following short-term storage, their beyond-use dates may be assigned based on criteria different from those applied to assigning expiration dates to manufactured drug products."

EXPIRATION DATES

To ensure that a drug product meets applicable standards of identity, strength, quality and purity at the time of use, it must bear an expiration date determined by appropriate stability testing. Stability studies conducted in the preformulation phase of commercial product development include solid-state stability of the drug alone, solution phase stability, and stability in the presence of expected excipients.

BEYOND-USE DATES

The beyond-use date is the date after which a compounded preparation is not to be used and is determined from the date the preparation is compounded. Compounders are to consult and apply drug-specific and general stability documentation and literature when available, and to consider the nature of the drug and its degradation mechanism, the container in which it is packaged, the expected storage conditions, and the intended duration of therapy when assigning a beyond-use date. Beyond-use dates are to be assigned conservatively.

When using manufactured solid dosage forms to prepare a solution or aqueous suspension, the compounder is also to consider factors such as hydrolysis and the freeze-thaw properties of the final preparation before assigning a beyond-use date. In assigning a beyond-use date for a compounded drug preparation, the compounder is to use all available stability information as well as his or her pharmaceutical education and experience. All stability data must be carefully interpreted in relation to the actual compounded formulation.

FIVE COMMON FLAWS IN STABILITY STUDIES

Five common flaws reported in 1983 in pharmaceutical stability studies of extemporaneously prepared formulations include the following:[1]

1. Lack of complete description of the materials, test conditions and methods;
2. Failure to use a stability-indicating analytical technique;
3. Failure to perform an analytical determination at the outset;
4. Use of inadequate numbers of test samples and replicate assays; and
5. Conclusions that overreach or otherwise fail to fit the results.

By 1987, articles published were generally doing a better job but there still remained room for improvement. The most common recurring problem was the use of analytical methods for which validation of the stability-indicating capability was either inadequate or nonexistent.

STABILITY-INDICATING METHODS

The purpose of a stability-indicating assay method is to accurately quantitate the intact drug or drugs in the presence of decomposition products and other components/excipients. It is best that all components in the formulation be present to confirm there is not any peak overlap between the excipients, degradants and the active drug. This is essential to provide accurate and reliable results.

Generally, the development of a stability-indicating assay method involves subjecting the samples containing the drug (and preferably the complete formulation) to the following conditions:

1. Extremes of pH (generally using strong acids and bases).
2. Extremes of temperature, especially high temperature (boiling).
3. Addition of an oxidation agent (hydrogen peroxide).
4. Exposure to light.

The complete drug formulation should be exposed to these conditions, in addition to just the drug in aqueous solution. The purpose of this activity is to ensure that the peak representing the drug in a chromatogram is only due to the drug itself and not due to a degradation product or an excipient(s). Some HPLCs have "peak purity" software that can be of great value in this procedure.

The use of exaggerated conditions of temperature, humidity, light and others to test the stability of drug formulations is termed accelerated stability testing. An example would be a study conducted for 6 months at 40° C with 75% relative humidity. In stress testing, temperature elevations, in 10° C increments higher than used in accelerated studies, are employed until chemical or physical degradation. Once the most stable formulation is ascertained, its long-term stability is predicted from the data generated from continuing stability studies.

HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

High Performance Liquid Chromatography (HPLC) is the most common method used in pharmaceutical analysis today. It is based on differential solubility between the components in the sample for the solvent system (mobile phase) and the stationary phase.

The most common HPLC method today involves hydrophilic mobile phases and hydrophobic stationary phases. The hydrophobic stationary phase is selected in conjunction with the hydrophilic mobile phase. The purpose is to adjust the "hydrophilicity" and "hydrophobicity" of the two phases to the point that the "active" drug is separated from the degradation products and the excipients based upon their partitioning between the two phases. If the drug has a greater affinity for the mobile phase, it will elute faster. If the drug has an affinity for the stationary phase, it will be held back some and elute slower. For example, a C8 column is an 8-carbon coating on a beaded support packed into a stainless steel or other column containing

fittings on each end. A mobile phase consisting of varying proportions of water, methanol, acetonitrile, buffers, etc. is selected and modified to obtain the desired separation.

A pump is required to push the mobile phase through, usually at pressures of 1,000 to 2,000 psi or higher. The effluent coming from the column passes through a detector (generally ultraviolet) connected to a computer where the response of the detector is monitored. As each individual "component" or group of "components" comes out the end of the column and passes through the detector, it shows up as a peak on the chromatogram.

The peak height or peak area is proportional to the concentration of the entities being detected. A test for linearity is also required to confirm that the increase in drug concentration is linear with the peak height/area. It is a matter of experimentation to obtain the proper conditions (mobile phase, stationary phase, flow rate, temperature, detection method and/or wavelength) for the analysis. The process, once completed, then requires standards for the development of a standard curve which is used for quantitation purposes.

THE STABILITY STUDY

For a study to be conducted, the sample must be properly prepared. The formulation should be one that is widely used or can be widely compounded by pharmacists. The ingredients should be commonplace and the formulation relatively simple. Sufficient sample should be prepared to allow for multiple containers for different storage conditions and sampling times.

Storage conditions should include at least room temperature and refrigerated temperature. Frozen temperature is a good addition, and other temperatures as required.

Sampling times should include an initial sample right after preparation (time-zero), and then at representative time intervals based upon the desired potential storage times. This can include 1, 3, 7, 14, 30, 60, 90, 120, 180 days if that is reasonable.

Sufficient material should be prepared for at least triplicate containers at each storage condition. From each of these triplicate containers, at least one or two samples can be obtained at the specific sampling interval. Each obtained sample is analyzed individually. It is apparent that if only triplicate containers are involved, and only one sample is obtained, then 3 data points is all that is obtained at each sample interval. If one is spoiled, then that is a problem. However, if two or three samples are obtained from each container and there are triplicate containers, then 6 or 9 data points would be possible and if one or more is spoiled, there is still sufficient numbers for interpretation. Sample-handling must be considered to ensure the sample is not decomposed or altered between the time of sampling and analysis.

Once the study experimentation is complete, the next step is data analysis and interpretation. Generally, descriptive statistics are obtained and placed into a table format such as Tables 1 and 2 below.

DATA PRESENTATION

Generally, the data that is presented in studies will be in tabular form and sometimes, in graphic form. The time-zero sample is customarily set to 100% and each subsequent data value compared to the time-zero value. Generally, the subsequent data is either around 100% or below. Occasionally, a data value greater than 100% is obtained after time-zero. This can be related to improper container mixing when sampling, improper sample mixing prior to analysis, evaporation of solvent, analytical variability, and others.

In looking at the data, one looks at the standard deviations to make sure the data is reasonably "tight". Then, looking at the means, one observes whether there is a tendency for drug degradation or if the drug appears to be relatively stable. If the values stay close to 100%, then the formulation appears stable. If the values decrease over time, then one has to determine what is happening at about the 90% value. The drug preparation must retain at least 90% of the time-zero value to be considered stable at a respective time point; and, this includes the standard deviation value. For example, if a data value is 92.2% +/- 1.3, then the value ranges from 90.9 to 93.5, which is acceptable. However, if the data value is 92.2% +/- 3.1, then the value ranges from 89.1 to 95.3%; since the low value is less than 90%, this cannot be used as the time for which the drug is still stable. Interpretation between sampling times is possible but must be based upon knowledge of whether the degradation occurs as zero order, first order, or other. It is generally best to look at the data and then assign a beyond-use date conservatively as appropriate.

In addition to drug concentration, pH determinations and physical observations should be made at each sampling time. Physical observations can include general appearance, color, ease of resuspending (if a suspension), clarity, uniformity, gas formation, odor, etc.

When compounding on the basis of extrapolated or less than concrete information, the pharmacist is well advised to keep the formulation simple and not to shortcut but use the necessary pharmaceutical adjuvants to prepare the prescription.

ASSIGNING BEYOND-USE DATES ACCORDING TO USP <795> AND <797>

The following information is summarized in Figure 1, a flow chart for assigning beyond-use dates.[2]

In the absence of stability information that is applicable to a specific drug and preparation, the following maximum beyond-use dates are recommended for nonsterile compounded drug preparations that are packaged in tight, light-resistant containers and stored at controlled room temperature unless otherwise indicated.

Non-Sterile Preparations
For Nonaqueous Liquids and Solid Formulations—
Where the Manufactured Drug Product is the Source of Active Ingredient—The beyond-use date is not later than 25% of the time remaining until the product's expiration date or 6 months, whichever is earlier.

Where a USP or NF Substance is the Source of Active Ingredient-The beyond-use date is not later than 6 months.

For Water-Containing Formulations (prepared from ingredients in solid form)-The beyond-use date is not later than 14 days for liquid preparations when stored at cold temperatures between 2° and 8° C (36° and 46° F).

For All Other Formulations-
The beyond-use date is not later than the intended duration of therapy or 30 days, whichever is earlier.

These beyond-use dates may be exceeded when there is supporting valid scientific stability information that is directly applicable to the specific preparation (i.e., the same drug concentration range, pH, excipients, vehicle, water content, etc.).

Sterile Preparations
All the following are in the absence of a program of sterility testing in place. If a sterility testing program is in place, the BUDs listed previously for nonsterile preparations can be used.

For a low-risk level preparation, the storage periods cannot exceed the following time periods: before administration, the compounded

sterile products (CSPs) are properly stored and are exposed for not more than 48 hours at controlled room temperature, for not more than 14 days at a cold temperature, and for 45 days in solid frozen state between -25° and -10° C.

For a medium-risk preparation, the storage periods cannot exceed the following time periods: before administration, the CSPs are properly stored and are exposed for not more than 30 hours at controlled room temperature, for not more than 9 days at a cold temperature, and for 45 days in solid frozen state between -25° and -10° C.

For a sterilized high-risk level preparation, the storage periods cannot exceed the following time periods: before administration, the CSPs are properly stored and are exposed for not more than 24 hours at controlled room temperature, for not more than 3 days at a cold temperature, and for 45 days in solid frozen state between -25° and -10° C.

EXAMPLES

Now, let's look at two examples of stability studies where beyond-use dates have been assigned. These were reported in Volume 15, Number 1 of Secundum Artem. These examples will demonstrate how a reasonable "beyond-use date" can be obtained from the data presented.

Example 1: Valacyclovir hydrochloride[3]

The valacyclovir hydrochloride 50 mg/mL oral liquid was prepared using the caplets and a porcelain mortar; the caplets were first crushed to a fine powder. The suspension vehicle (Ora-Sweet or Ora-Sweet SF with Ora-Plus) was added with mixing between additions. The product was transferred to an amber glass bottle where the final vehicle was added by rinsing the mortar and adding to the final container (5 rinses); the bottles were stored at refrigerated temperature and sampled weekly for four weeks. The data is shown in Table 1.

Table 1. Stability of valacyclovir 50 mg/mL oral liquids at refrigerated temperatures.

	% Initial Concentration Remaining at 4° C	
Day	Ora-Sweet /Ora-Plus	Ora-Sweet SF /Ora-Plus
0 (mg/mL)	51.6 (0.2)*	52.4 (0.2)*
2	97.0 (3.1)	99.5 (4.3)
7	94.5 (2.1)	96.8 (2.4)
14	92.6 (0.5)	94.7 (1.9)
21	91.6 (2.4)	90.1 (3.8)
28	87.7 (1.1)	87.4 (0.6)

*Actual initial values are used for 100%

One can reasonably state that the data shows both preparations are stable in the refrigerator for 14 days. The standard deviations are too great to extend the storage period to 21 days as the actual range may include 89.2 to 94.0 for the Ora-Sweet/Ora-Plus combination and 86.3 and 93.9 for the Ora-Sweet SF/Ora-Plus combination. Since the values drop below 90.0%, that time cannot be used. It may be reasonable to interpolate between 14 days and 21 days if the order of the reaction is known. The pH values remained unchanged as did the physical observations.

Example 2: Terbinafine hydrochloride[4]

Terbinafine hydrochloride 25 mg/mL was prepared using the terbinafine tablets. The tablets were crushed to a fine powder in a mortar and a small quantity of the vehicle (Ora-Plus and Ora-Sweet; 1:1) was used for make a smooth paste. Additional volumes of the vehicle were added and the preparation transferred to a graduate where it was brought to final volume. The suspension was packaged in amber polyethylene prescription bottles and stored at both room and refrigerated temperatures. Samples were withdrawn for up to 91 days. The results are shown in Table 2.

Table 2. Stability of terbinafine hydrochloride 25 mg/mL in amber polyethylene prescription bottles is stable at both room and refrigerated temperatures for up to 42 days.

	% Initial Concentration Remaining	
Day	25° C Ora-Sweet /Ora-Plus	4° C Ora-Sweet /Ora-Plus
0 (mg/mL)	27.7 (1.5)*	26.5 (0.9)*
7	95.2 (0.8)	98.7 (3.3)
14	97.8 (1.4)	95.3 (2.1)
28	95.5 (3.1)	96.4 (2.3)
42	93.7 (1.9)	96.6 (1.3)
56	79.0 (4.0)	87.4 (3.7)
70	71.8 (4.0)	76.3 (1.9)
91	72.6 (2.3)	77.6 (2.1)

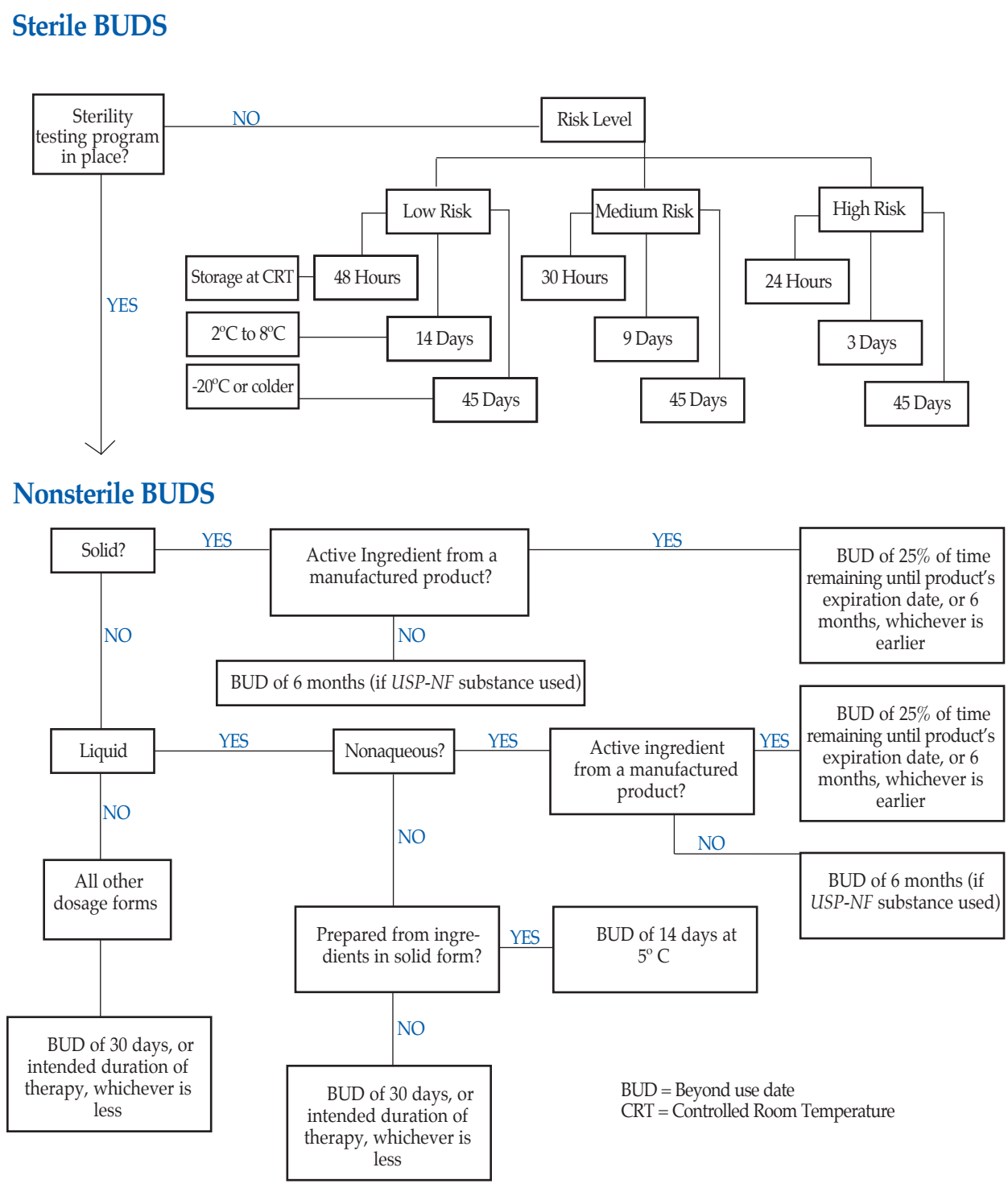
*Actual initial values are used for 100%

The data shows that terbinafine hydrochloride 25 mg/mL is stable for up to 42 days in polyethylene prescription bottles at both room and refrigerated temperatures. The pH of the suspension decreased only very slightly over 91 days, from an initial pH 5.6 to 5.5. It may be reasonable to interpolate between 42 days and 56 days if the order of the reaction is known.

CONCLUSION

Potency assays and stability-indicating assays each play a crucial role in pharmaceutical compounding. Beyond-use dates (BUD) should be established using stability-indicating assays that are capable of differentiating the intact drug from any degradation products. Potency testing is important to confirm that compounding processes are under control and that the final preparation is within the allowable limits of +/- 10%. In the event documented data is not available for a beyond-use date, the USP default dates can be used for assigning the BUD.

Figure 1: Flow chart that can be used for assigning beyond dates of nonsterile and sterile compounded preparations.



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