Chapter 14

Storage and Beyond-Use Dating

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Introduction

Pharmacists should always assign beyond-use dates (BUDs) to compounded sterile preparations (CSPs) that accurately reflect the stability and sterility of the components under the intended preparation, packing, shipping, storage, and administration conditions. To do this, the pharmacist must understand the chemical and physical factors that affect the sterility and stability of all components in a preparation. The pharmacist must also consider the contribution of environmental, operational, and personnel factors to the quality of a compounded preparation.[1] The storage and beyond-use dating issues for radiopharmaceuticals is outside the scope of this chapter (Chapter 13).

Expiration Date

The expiration date is the shelf life assigned to a commercially manufactured drug product. It reflects the longest time period during which the product will meet the requirements of the USP compendial monograph, under the stated storage conditions.[2] Typically, this is when 90% or more of the labeled active ingredient is available, and it may also reflect the time period when drug or container degradation byproducts remain below compendial maximum levels. Expiration dates are applied to intact formulations by the manufacturer and are based on rigorous testing.

Beyond-Use Date

When a product is reconstituted, diluted, and transferred into another container or administration device, the practitioner must establish an appropriate BUD for the preparation. Beyond-use dating is a relatively new term for pharmacy personnel. The BUD is the date or time after which a product (e.g., a compounded preparation) should not be used. The BUD is rarely established based on a specific assay of the preparation.[2] USP Chapter <797> Pharmaceutical Compounding—Sterile Preparations requirements applicable to CSPs clarify that

this is the date or time after which the CSP should not be stored or transported. It is determined from the date or time the preparation is compounded.[3]

The BUD must be based on professional experience and interpretation of reliable sources of information. **Table 14-1** summarizes criteria for acceptable levels of stability in dispensing practice. The BUD assigned to a CSP is based on two factors: *stability* and *sterility*. The first is the active ingredient chemical stability, or maximum time period in which 90% or greater of a labeled active ingredient is measurable in the solution and container specified, under the stated storage and administration conditions.[1,4,5] The second major factor is the sterility limitation for the risk level.[1,5] The BUD reflects the potential for microbial, physical, or chemical contamination during compounding.[3] Each CSP should be labeled with specific storage requirements, the BUD, and latest time of day for use (when appropriate).[3] See Chapter 15 for more information about labeling.

The concentration or bioavailability of the active ingredients in a preparation can be affected by physical, chemical, and delivery system–related incompatibility or instability. *Incompatibility* refers to a physical or chemical phenomenon that reduces the concentration of the active ingredient(s). Examples include concentration-dependent precipitation and acid-base reactions. *Physical* or *visual incompatibilities* are terms that describe visible changes in the appearance of a preparation, such as precipitation, cloudiness or haziness, color change, viscosity change, cracking, and effervescence.

Instability usually refers to the chemical processes that result in a degradation or change in the active ingredients, including hydrolysis, oxidation, reduction, and photodegradation reactions. These changes are generally continuous and irreversible, and can form degradation products, which are therapeutically inactive and may exhibit toxicity. Examples include hydrolysis, oxidative, and other heat-catalyzed reactions.[2,3,6,7]

Common incompatibilities or instabilities often are classified as *physical* or *chemical*, although all incompatibilities are chemical-based phenomena. In some cases, incompatibilities can result from solubility changes or interactions with the container rather than to molecular changes in the active ingredient.

Physical Incompatibilities

Solubility

Drugs can be maintained in aqueous solution as long as their concentrations are below the saturation solubility. Supersaturated solutions are likely to precipitate or form crystals. Drugs with poor water solubility are often formulated with water-miscible cosolvents such as ethanol, propylene glycol, and

Table 14-1.
Criteria for Acceptable Levels of Stability[6]

Type	Conditions Maintained
Chemical	Active ingredient(s) retain chemical integrity, labeled potency within specified limits
Physical	Physical properties are maintained (e.g., appearance, uniformity, dissolution, suspension)
Microbiological	Sterility or resistance to microbial growth is retained Antimicrobial agents (e.g., preservatives) retain effectiveness
Therapeutic	Intended therapeutic effect remains unchanged
Toxicological	No significant increase in toxicity occurs (e.g., leaching of toxic chemicals, development of toxic degradation products)