Stability Testing, Shelf Life and Product Expiration Dating

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Reagents available for laboratory, research, and clinical use are often acquired with a specified expiration date. Yet, many are not, depending on the manufacturer and reagent type. What a manufacturer does is frequently determined by how they label the product.

The U.S. Food and Drug Administration [FDA] has defined categories by which reagents can be labeled based on their "intended use".[1,2] Individual reagents (*e.g.*, antibodies) intended for clinical diagnostic laboratory use will be labeled as an *In Vitro Diagnostic* [IVD] or *Analyte Specific Reagent* [ASR]. Under these categories, specified expiration dates must be supported by stability testing which establishes the product shelf life.[3,5]

Stability, shelf life, and *expiration date* are all clarified in interdependent definitions. Stability can be "constancy of a property over time"[3] or more specifically for reagents, "the extent to which a product retains, within specified limits, and through its period of storage and use...the same properties and characteristics it possessed at the time of manufacture".[4] Although shelf life and expiration dating can be distinctly different in practice, they are frequently considered interchangeably. FDA defines these characteristics separately, shelf life being "the term or period during which a commodity remains suitable for intended use"; expiration dating being "the termination of shelf life, after which a percentage of the commodity, *e.g.*, medical devices, may no longer function as intended". As laboratory reagents are generally tested in the same manner and considerations as pharmaceuticals"[4,6], the current United States Pharmacopoeia [USP] definition of expiration dating is equally applicable, validly taking into account the material's packaging - "the time interval that a [product] is expected to remain with the approved shelf-life specification provided that it is stored under the conditions defined on the label in the proposed containers and closure".[7]

Regardless of the interpretation exercised, the basic considerations are the same, and usually ultimately linked to performance parameters. A multiplicity of factors can affect a product's stability and shelf life. For example, intrinsic factors such as protein concentration, pH and temperature; physical characteristics such as viscosity; storage conditions; and packaging.[3,4,7,8] Testing is done under a formal written protocol[4,7,9], with the actual level of testing dependent on the material, its application, and established knowledge of its inherent properties. For biological reagents, at a minimum, evaluation would perhaps be performed as a protein concentration and a performance test, both to written specifications.

Over the longer time frame, in terms of lot-to-lot variation, it is required that there be process validation for the manufacture of clinical use reagents[10] (*i.e.*, validation that each lot produced is identical to the one before it), and this is usually paralleled with stability testing. With recent expectations of vendors becoming more rigid, many are following these "good manufacturing practices" (GMP) for noncritical reagents as well. Thus, by validating each lot manufacture as identical (*i.e.*, meets identical specifications), stability is essentially validated as well. Companies will generally put at least one lot/year into stability testing, or each lot if made less than once per year, with a minimum of three lots to establish a stability base line.

The actual stability time points are relatively standard across reagent type, whether device or drug. This is commonly every three months over the first year, every six months for the second year, and annually thereafter[4,7,9]. Most reagent claims of stability will not extend beyond three years. These "real-time" stability data are required in all cases, but are frequently prefaced and approximated by 'accelerated' or stress stability testing.[4,6,8] An accelerated testing program involves subjecting the reagent to exaggerated or stressed storage conditions in an effort to simulate the effects of long-term storage.[3,4,6-8] For example, a reagent

with a recommended storage at 4° C might be stored at 37° C and/or -20° C, and subsequently tested after approximately six weeks to extrapolate to a 12-month shelf-life when stored at 4° C. However, the translation of these results to actual product expiration dating frequently is not this simple, but rather based on a mathematical calculation of some complexity, depending on the method of confidence and taking into account the various conditions affected.[4,6,7,9,11] One example of such calculation, in brief, is as follows[4]:

(a) For establishment of a valid accelerated test protocol, raise the temperature a maximum of 20-25° above ambient.

(b) Evaluate a six (6) month old solution of the product in question at a storage temperature of 45° C, assuming normal storage being at an ambient temperature of 25° C.

(c) A storage deterioration factor such as 'Q_{10}' is employed. In this particular method, Q_{10} assumes that the "ratio of times to equivalent damage at two temperatures, usually 10° C apart" is a constant.[8] In this case, $Q_{10} = 1.8$.

(d) The 'acceleration factor' is then equal to $1.8^2 = 3.24$.

(e) As the length of storage time is six months, then the shelf life can be estimated by the accelerated age plus the real age of the reagent. Accelerated age = 6 months x 3.24 = 19.44 months. Accelerated age plus real age = 19.44 months plus 6 months = 25.44 months, or approximately two (2) years, assuming the reagent has passed all the specified testing qualifications following the six-month period.

There are various arguments for and against the accuracy of accelerated testing and which method is most predictive. Regardless of these, in a good, comprehensive stability program, accelerated testing results are subsequently reinforced by real-time stability data. Accelerated methods may often be employed to take a product to market more quickly, and at times confer the added advantage of representing the reagent's integrity when subjected to extreme conditions during shipping.

Given all the factors that can affect reagent stability, product expiration dates should be followed with caution. Such indications of shelf-life should be a general guide, as they are not intended to replace individual laboratory evaluation of the material or the proper use of accurate and reliable performance controls in laboratory analyses. ■

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