Can I Use Those Eyedrops after the Expiration Date?

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I am frequently asked by colleagues and friends whether it is acceptable to use medications after the expiration date. They propose that medications are "good" long after their expiration date. For example, Cantrell et al chemically evaluated a number of long-expired oral medications and found that many medications still had at least the labelled amount of drug. Some even had 20-25% more, and one had 300% more. A few had much less than the labelled amount.[1]

If I am in a flippant mood, I respond to my colleagues and friends by asking: "Would you use milk after its expiration date" (Figure 1)? If I am in a more serious mood, I simply say: "No, it is not acceptable." When the questioner then asks why, this opens the door for me to explain what goes into assigning the expiration date.

The manufacture of ophthalmic drugs was covered in a previous article in this journal.[2] In that article, my co-author and I wrote "…The stability data is evaluated in order to assign an expiration date system for the product." Drugs are evaluated to assure the proper identification, quality, purity, and strength of the drug. The requirements for stability testing are discussed in a series of International Conference on Harmonisation (ICH) guidance on quality (Q1A through Q1F [http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html]). The analytical tests performed on a product include the active ingredient and the potential development of any degradation products. All sterile products undergo a test for sterility. For preserved products, there is both a chemical assay of the preservative and a biological assay for the capability of the product to prevent growth of microorganisms (Antimicrobial Effectiveness Test). There are also tests for physicochemical properties (e.g., volume, pH, particulates).

The expiration date is an extrapolation. That is, pharmaceutical scientists evaluate early stability data on a given lot and extrapolate the duration of time at which it is expected to still be within specification. Shown in Figure 2 is an example of the decreasing amount of active ingredient in a drug product. In this case, the specifications call for a 5% variance on the label claim amount of active ingredient. In this example, the calculated variance suggests that the product would be stable for 24-36 months stored at 25°C and 60% relative humidity. Also evaluated for this product is the development of a degradation product. In the same storage conditions, the concentration of the degradation product was estimated to exceed the specification limit of 1.4% at approximately 27 months (Figure 3). One typically uses a conservative estimate — i.e., the lower 95% confidence interval for concentration of active (i.e., the lowest it might be) and the upper 95% confidence interval for concentration of a degradation product (i.e., the highest it might be). For a liquid ophthalmic product, similar calculations would be performed for pH and volume. Also, sterile products must pass the sterility tests at each time point. These analytical data are all considered in setting an expiration date for a product. Finally, some formulations may fail because the particulate count rises or the formulation becomes unstable (i.e., the active ingredient falls out of solution or suspension).

While such tests are conducted throughout the development of a new product, the final formulation and container/closure system (i.e., bottle and tip, or unit dose container) are not typically finalized until Phase 3. The duration of stability data on this final product can vary depending upon the duration of the Phase 3 clinical studies. However, in general, it is on the order of 12-18 months real-time stability. Stability studies can also be performed in exaggerated conditions (e.g., 40°C/25% Relative Humidity [**RH**] for a product to be stored at room temperature, 25°C/60% RH for a product intended to be refrigerated). These data are used to project (i.e., extrapolate) a shelf life, which is proposed to regulatory authorities in the New Drug Application. As noted above, both the manufacturer and the regulatory authority tend to be conservative in setting a shelf life for the initial application. As more data are obtained for the product, the company may submit them to the regulatory authority, proposing a longer shelf life.

Disclosure: Gary D. Novack, PhD (PharmaLogic Development, Inc., San Rafael CA) consults with numerous pharmaceutical firms.

Figure 1. Expiration dating of milk.

However, as noted in the ICH Q1A(R2) document, "There should be a direct link between the label storage statement and the demonstrated stability of the drug product."

As to the conservative aspect of setting a shelf life, in the early stages of product development with limited data, a manufacturer may choose to create an overage (i.e., a bit "on the high side") in order to meet the minimum requirements at the expiration date. Thus, as liquid may evaporate through plastic bottles, volume in the product at time of manufacture may be higher than the label claim. A manufacturer could also add more active ingredient — but not too much, as the actual amount in the bottle at time of manufacture could not exceed the label claim by more than a small amount (on the order of 5-10%). One of the ICH guidances, Q1A(R2) describes evaluation of potential water loss for drug products packaged in semi-permeable containers. For example, for a product to be stored at room temperature, "…a 5% loss in water from its initial value is considered a significant change for a product packaged in a semi-permeable container after an equivalent of 3 months' storage at 40°C/No More Than (**NMT**) 25% RH. However, for small containers (1 mL or less) or unit-dose products, a water loss of 5% or more after an equivalent of 3 months' storage at 40°C/NMT 25% RH may be appropriate, if justified" (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1A_R2/Step4/Q1A_R2__Guideline.pdf).

Among some of my colleagues and friends, there is a perception that manufacturers would prefer to have a short expiration date, so that patients have to buy more product. This is not the case. The shorter the shelf life, the more challenging the logistics for the manufacturer to produce the product, ship it to wholesalers, who, in turn, ship it to pharmacies, who maintain

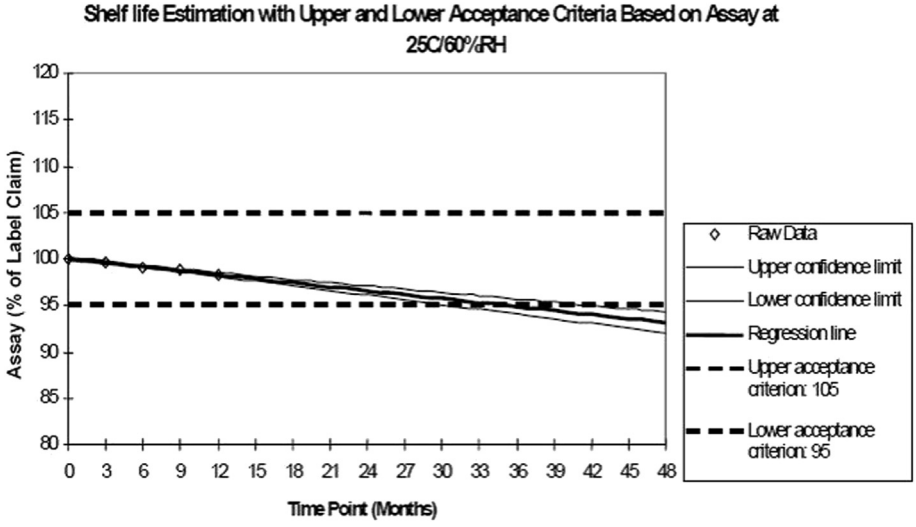

Figure 2. Expiration dating: Stability of active ingredient. (From: ICH Harmonised Tripartite Guideline: Evaluation for Stability Data: Q1E (June 2004). 60% RH ¼ 60% relative humidity. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073380.pdf.)