### 8.3. Process

Filling ampoules under nitrogen for solutions that are susceptible to oxidation is one example of a processing method that can improve stability. Of course, the most common process variable that is adjusted to control stability is selection of the package components and materials, and readers specifically interested in this topic are referred to Dixie Dean's chapter.

### 8.4. Formulation

The literature is replete with accounts of proven and potential methods of improving product stability and hence shelf life. All that is provided in this section are some general concepts that can, if appropriate, be explored in more detail.

In the past, stability overages,* which allowed a relatively easy method to improve shelf life, were quite common. Indeed, there are many drug products on the market in different parts of the world that contain a stability overage of up to 10% of label claim. However, a number of regulatory agencies, including FDA, are now showing much more reluctance than previously to approve such overages for drug products.† This reluctance to approve the use of stability overages probably stems from a number of causes.

First, there is concern about the possible increase in toxicity that might accompany the use of a stability overage. If a product for which compendial potency limits are 90–110% is released onto the market at 100% of label claim, then the maximum amount of any degradation product that could be present in the product up until the expiration date is 10%. However, if the product is released at 110% of label claim, then it is conceivable that in some instances there could be up to 20% of degradation product. If the degradation product, or part thereof, is toxic, use of a stability overage has *doubled* the potential hazard to which a patient is exposed.

Second, if stability overages are allowed, then the range of potencies to which a patient may be subjected is increased. For example, suppose that a patient who has a repeat prescription for drug X (which is known to have a relatively low range of acceptable therapeutic blood levels) finishes tablets of lot A101, which has a potency of 90%, and is then supplied with tablets from B103, which has a potency of 110%. Then (even neglecting degradation of drug while the tablets are under control of the patient and not considering content uniformity) we can see that the patient may experience a 20% variation in blood levels. In contrast, in the absence of a stability overage, the maximum potency variance would only be 10%. This substan-

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* Overages are of three types: container, manufacturing, and stability. A *container* overage is added to allow for the fact that it is not possible in some cases to remove all the contents from a container. Thus ampoules labeled 1.0 mL are normally filled with 1.1 mL. A *manufacturing* overage is added when it is known that relatively small and reproducible amounts of active are always lost during the manufacturing process although we are using modern equipment and facilities and well-trained staff. A manufacturing overage is, of course, dissipated by the time final product testing is completed.

† Vitamin products, which are classified by the FDA as food supplements (unless they are administered by the oral route or supplied under a doctor's prescription), still have substantial overages—sometimes up to 100% of label claim.