multidose pen injector. Example preservatives used in several marketed dual chamber package systems include benzyl alcohol and *m*-cresol. If a multidose product is desired then appropriate compendial antimicrobial effectiveness testing (AET) must be preformed to assure that the correct preservative and concentration are chosen for the product. It should be noted that, depending on where the product is to be marketed, there may be different AET requirements. It is also important that the stability of the preservative is monitored over the product shelf life to assure that sufficient preservative is present to meet compendial AET. Losses of the preservative due to degradation or sorption to the package are two potential routes that should be evaluated during development studies and formal International Conference on Harmonization (ICH) stability studies to support product registration.

FILL VOLUME DETERMINATION FOR EACH CHAMBER

The goal for any freeze-dried product is that it can be reconstituted to produce a specific drug concentration on addition of the reconstitution vehicle and that the desired dose can be properly delivered to the patient. Therefore, it is important for the formulator to understand all of the parameters that must be determined to enable the label dose in these dual chamber packages to be properly administered. The equations below summarize the relationships for those parameters that need to be experimentally measured to determine the appropriate fill for each chamber to manufacture a product that can administer the labeled dose.

Equation 1: Label dose = (deliverable volume) × (reconstituted drug concentration)

Equation 2: Deliverable volume = (total reconstituted volume) − (hold-up volume for reconstituted package)

Equation 3: Total reconstituted volume = (volume transferred from diluent chamber) + (volume displacement factor created by the reconstituted freeze-dried cake)

Equation 4: Volume transferred from diluent chamber = (volume in diluent chamber) − (hold-up volume from the diluent chamber)

Equation 5: Reconstituted drug concentration = (amount of active ingredient)/(total reconstituted volume)

Therefore, the key parameters that need to be experimentally determined include the following:

a. The volume displacement factor created by the reconstituted freeze-dried cake
b. The hold-up volume of the diluent chamber
c. The hold-up volume for the reconstituted package
d. The deliverable volume

Once these parameters have been determined it is simple to calculate the appropriate fill volume for each chamber using the mathematical equations listed above. Note that other corrections to the fill would be required if there are any significant adsorption losses of the active ingredient to the package surfaces (i.e., to either the glass or the rubber components). It is also important to realize that many of the dual chamber freeze-dried products (especially syringes)