sitting in the middle of the system ("middle plunger"). The liquid drug formulation is first filled in the chamber that starts on top of the middle plunger and that ends at the needle end of the system. Then it is freeze-dried from that chamber. What is left at the end of the process is the freeze-dried cake. The diluent is contained in the second chamber that is confined between the middle plunger that separates the chambers and a second rubber plunger that seals the syringe ("end plunger"). Right before drug administration, the diluent is transferred into the same chamber as where the lyophilized cake is stored. This is done by activation of the end plunger. Exertion of force will not only move the end plunger but by transmission of pressure over the diluent also the middle plunger. This goes on until the chamber with the diluent reaches a bypass in the glass barrel of the system. While the end plunger, always under application of force, keeps on moving forward in the syringe, the diluent in the second chamber will be displaced into the first chamber and the freeze-dried cake will be redissolved. The reconstituted drug is then ready for injection.

Dual-chamber systems are not new. They are in the market since at least 25 years but, in spite of offering distinct advantages, have never generally become first choice administration systems. Nevertheless, efforts are being spent on improving dual-chamber systems. A system that is worth noting in this respect is illustrated in [22]. The claimed advantage of this novel system is that in contrast with existing systems, the diluent is filled first and can be sterilized by autoclaving prior to filling the solution that is going to be freeze-dried in a second step. A further claimed advantage is that after filling the solution, the syringe is fully closed by a specially designed rubber closure, that both has vent openings to allow freeze-drying and also has ribs like a syringe or a cartridge plunger. Between filling and positioning in the freeze-dryer, the ribs serve as sealing elements to close the container. Once inside the freeze-dryer, ingenious use of underpressure in the freeze-dryer and relative overpressure in the chamber with the drug solution allow the closure to move as a plunger over a small distance until the vent openings come free and the pressure in the lyophilizer and in the drug solution chamber of the system equalizes. After this self-opening in the freeze-dryer, the system is ready for lyophilization. At the end of the freeze-drying cycle, the rubber closures will be pushed down again into the syringes by the shelves that are coming down, just as is the case with freeze-dried vials and standard lyophilization stoppers. During the cycle, the diluent that is present between the middle and the end plunger will first freeze and then thaw again. A more extensive discussion of the system is available in [23].

Container/Closure Integrity

It has been emphasized several times before that closure/vial seal integrity for lyophilization vials is not highly robust between unloading of the freeze-dryer and crimping of the cap. This fact has been extensively brought under the attention when in the EU the Annex 1, "Manufacture of Sterile Medicinal Products" to Good Manufacturing Practice Guidelines was in a revision process. The process ended