Until the moment the vials are crimped, underpressure in the vials may get partially or completely lost and care is to be taken for preservation of product sterility until crimping has been performed. For many years, it has been a goal of pharmaceutical packaging component development to design a closure system that is able to put in place a robust seal before the vials leave the freeze-dryer. Such closure system could be in the form of an "integrated closure" where an elastomeric part as primary packaging material is combined in some form with a plastic cap as secondary packaging material, the plastic cap taking over the role of the aluminum crimp cap in the traditional way of working. The idea is that this integrated product is placed on the vial after filling, instead of the rubber stopper only. The integrated product just as a traditional lyophilization stopper has a halfway down position allowing primary and secondary drying. At the end of the freeze-drying cycle, the integrated product is then pushed down until a specially designed feature on the plastic part grips under the collar of the vial, thereby at the same time pushing the elastomeric part into its sealing position on the top rim of the vial. Since it is now a hard plastic part that is in contact with the shelves and not an elastomeric stopper, stickiness to shelves is avoided. The vials then are unloaded from the freeze-dryer already in capped condition, avoiding any risks during further transport. Although the idea looks straightforward, its realization was found to be far from trivial. A number of issues were encountered during development of this type of seals. The first was that the design of the plastic part had to cope with all of the stacked height tolerances of the collar of the vial and of the flange of the stopper. Whereas with traditional flip caps (aluminum/plastic caps) this must be a point of attention when the cap is chosen in the design stage of the packaging, usually there is enough choice in different heights of the aluminum part of the cap so that picking an appropriate cap is not problematic. In the case of the integrated product however, there is only the plastic part to deal with stacked tolerances, and there is little or no flexibility to vary the height of the part once the design is frozen and a mold for the part has been constructed. A second issue was that over a longer time plastic, when fixed on the vial, is subject to stresses that, unlike aluminum, can lead to dimensional changes of the cap ("creep"). Such changes in the worst case lead to an elongation of the cap that leaves so little residual force of the elastomeric part on the vial that the closure/vial seal integrity might be endangered. Eventually however, commercial versions of such plastic caps are offered to the market now [19, 20].

Dual-Chamber Systems

By far, the majority of lyophilized products are freeze-dried in vials. The vial then typically comes with a second vial or with a prefilled syringe that contains the diluent. In a dual-chamber system, both the freeze-dried cake and the diluent are present in the two chambers of the same container. The container can be either a syringe or a cartridge. An illustration of both systems can be found in [21]. During the storage life of the system, the two chambers are separated by a rubber plunger that is