monolayer that is chemically bonded via the hydroxyl groups to the glass. Therefore, it is not available for extraction or leaching into the drug product solution. The second layer is noncovalently associated with the first layer and is enriched in higher molecular weight branched silicone polymers plus a reduced fraction of lower molecular weight silicone. The viscosity of the silicone used for application, the temperature, and the length of curing directly impact the amounts of high and low molecular weight silicones in this second layer (11,12). Heat curing also drives off the stabilizers and water present in the original emulsion. Importantly, it is the second layer of noncovalently bound silicone that can be extracted or leached into the drug product. Additionally, the lower molecular weight silicones have lower vapor pressures and may be volatized during the freeze-drying process (12) and deposited in the frozen solution. If silicone does enter the drug product via leaching and/or deposition of volatile silicones during lyophilization, it may lead to opalescence after reconstitution due to silicone globules refracting light. An additional concern is that exposure of certain protein drugs to silicone has led to protein-related aggregates (13–15). Protein aggregates are considered a potential risk factor for the safety and efficacy of the product (16,17).

Siliconization of the dual chamber package should be optimized for functionality, for example, break-loose and glide force (18). Both break-loose and glide force should be monitored over the lifetime of the product since silicone disposition over the barrel may shift with time and potentially adversely impact compatibility with the device. Wen et al. (19) described spectroscopic and optical methods that can be utilized to monitor silicone disposition in prefilled syringes. These analytical tools could be adapted to monitor silicone disposition after spray-baking in dual chamber package systems. Also, as previously noted, it is important to optimize the siliconization process in terms of compatibility with the formulation.

Extractables/Leachables

Because of the intimate contact of the active and diluent formulations with the syringe barrel and plunger, extractable/leachable (E/L) profiling is important for product development in dual chamber syringes and cartridges. It is especially important to investigate the E/L profile early because low-fill volumes in the syringe or cartridge may lead to high E/L concentrations compared to the same formulation in vial. Notable extractables and leachables may come from the glass, the silicone coating, or the elastomer.

Needle Type

The needle is not affixed to the syringe/cartridge barrel for lyophilized products in dual chamber packaging systems, rather it is attached at the time of use. Lyophilization in a container with a staked needle would not be feasible for a number of reasons, including increased vapor flow resistance during sublimation due to the narrow bore of the needle and the impracticality of sealing the syringe within the freeze-dryer. Additionally, the preferred spray-baked siliconization process for preparation of the syringe barrel would be impossible due to the fact that the adhesive used to affix the needle would decompose during the heat-curing process. Therefore, a pen needle is generally used for a DCC in pen injectors. However, for DCS systems one can utilize either pen needles or