Incompatibilities between glass and product may include the following:

1. Ion exchange of metal ions if the product contains sodium, magnesium, calcium, aluminum, or lithium.
2. Dissolution of glass and resultant particles if the product contains phosphate or citrate.
3. Pitting of glass resulting in particles if the product contains a metal chelating agent such as disodium ethylenediaminetetraacetic acid (EDTA).
4. Adsorption of the active ingredient at the glass surface, a major problem for many biomolecules requiring the use of competitive binding excipients in the formulation.

If any of these problems are found to occur during product development, then treated glass must be used or the formulation modified to remove or reduce the amount of ingredient reacting with the glass surface.

Testing Methods

Glass extractables are always the primary concern and this is reflected in the required compendial test requirements. Test requirements vary depending on the compendia (USP vs. EP vs. JP). All require light transmission, arsenic, and the alkalinity tests (powdered glass or water attack). Other tests include hydrofluoric acid testing (EP), soluble iron (JP), and appearance (JP). The USP and EP require either a crushed-glass test that determines the bulk composition of the glass or a surface test to examine the composition and durability of the glass as a result of the forming process.

Glass syringes present an interesting case where an additional extractable did not directly originate from the glass. The inner needle channel in glass syringes is often formed using a tungsten pin (19,32). Residual tungsten can remain on the glass depending on the processing conditions. The residual tungsten can interact with proteins and lead to aggregation (see later discussion).

RUBBER

In the injectable drug product business, rubber is used for many applications—closures for vials and bottles, seals and plungers for syringes and cartridges, gaskets in manufacturing equipment, and ports on plastic bags and intravenous administration sets (3,33–35).

Basic Chemistry and Composition

The physical properties to be considered in the selection of a particular rubber formulation include elasticity, hardness, tendency to fragment, and permeability to vapor transfer. The elasticity is critical in establishing a seal with the lip and neck of a vial or other opening and in resealing after withdrawal of a hypodermic needle from a vial closure. The hardness should provide firmness but not excessive resistance to the insertion of a needle through the closure, while minimal fragmentation of pieces of rubber should occur as the hollow shaft of the needle is pushed through the closure. While vapor transfer occurs to some degree with all rubber formulations, appropriate selection of ingredients makes it possible to control the degree of permeability.

Depending on how the rubber material will be used (e.g., as a closure, septum, plunger) and properties of the drug product closed by the rubber, other important physical and chemical properties will dictate the best choice of rubber formulation for the product. Examples of specific physical and chemical properties of the rubber closure include oxygen transmission, water vapor transmission, durometer (hardness), pressure to puncture, coring, resealability, breakforce, vacuum retention, and specific leachables/extractables. Typically the rubber manufacturer generates these data although certain functionality tests, for example, breakforce required to begin the movement of a rubber plunger in a syringe or cartridge, is performed by the product manufacturer.

Elastomers

Rubber formulations contain a variety of components. The elastomer determines most of the physical and chemical characteristics of the rubber formulation. The base material for the rubber is the elastomer that is composed of either natural or synthetic rubber. The earliest source of the