Table 12-4 Common Compounding Problems in Sterile Product Manufacturing

- Mistakes in calculations of active ingredient
  - E.g., calculating actual amount of free acid or free base of an electrolytic drug where label claim based acid or base, not salt
  - E.g., calculating correct anhydrous amount of active from hydrated or solvated forms
- Incorrect order of addition of components
- Rate of addition of components too fast, incomplete dissolution
- Not allowing sufficient time or mixing force for complete dissolution of all components
- Problems with pH adjustment
  - Over-shooting or under-shooting pH
  - Increasing ionic strength with excessive addition of strong acid and/or base
- Errors in final QS (Quantity Sufficient) step, making final solution too dilute or too concentrated
- Excessive sampling having effect on final volume
- Errors in sampling or actual measurement of in-process samples
- Components compounded separately, then combined with final product where mistakes are made in calculations, volumes combined, and improper mixing conditions
- Introduction of contamination during aseptic addition of formulation components
- Excessive foaming due to excessive shear force or sloppy technique in component addition
- Errors in weighing of ingredients
- "Down times" excessive, time limits may be exceeded
- Maintaining dose homogeneity during and after compounding for dispersed systems

assessed and selected with the same care as are containers and closures, even though the contact period is usually brief.

All cleaning processes of all containers and closures (and equipment) must be validated for removal of all extraneous chemical materials and all particulate matter. Foreign particulates in final products in majority of the instances originate from the containers and closures. Cleaning validation is not covered in this book because there are many resources for this subject. Suffice to indicate, however, that validation of cleaning processes continues to be a major focus in regulatory inspections in the pharmaceutical industry and many manufacturing companies continue to receive 483 observations and Warning Letters for their problems and failures to prove adequate validation of cleaning processes. More coverage of cleaning of containers and closures can be found in chapter 13.

Glass

Glass containers are cleaned using Water for Injection. Glass sterilization and depyrogenation are accomplished using dry heat, usually with tunnel sterilizers where the temperatures reach 300°C, which is necessary for depyrogenation (see chap. 13). Glass syringes and cartridges need to be siliconized with the siliconization occurring before sterilization procedures.

The following is a typical procedure: Vials are received from the warehouse and part numbers verified as required on the master batch record. Vials are wrapped in shrink-wrap to minimize particulate matter. Vials are washed (actually rinsed, there is typically no detergent used) using washing equipment discussed in chapter 13. After rinsing, the wet vials are placed either in a dry heat oven (e.g., Despatch) or on a conveyor line (e.g., Strunck) for sterilization and depyrogenation.

Generally, glass syringes are prewashed and presterilized and depyrogenated by the manufacturer and come in "tubs," (e.g., Hypak™, see Fig. 7-7) that are ready for filling in the Class 100 clean area. For glass cartridges, the cartridges are loaded onto a conveyor system where they are rinsed, siliconized, sterilized, and depyrogenated, then filled with the product all on the same preparation and filling equipment.

Rubber

Rubber closures are cleaned and depyrogenated by rinsing with copious amounts of Water for Injection. Sterilization of rubber occurs by steam sterilization. Rubber must be "slippery" to move easily during production. Modern rubber formulations contain polymer surfaces that do