SUSPENSIONS AND OTHER DISPERSED SYSTEM FILLING (see also pp. 129–131)

The main issues or potential problems that may occur in the filling of dispersed systems include the following:

1. Maintaining dose homogeneity container-to-container
2. Validation of dose homogeneity especially with higher product viscosities
3. Clogging of filling needles/nozzles
4. Batch size
5. Aseptic additions
6. Particle size reduction under aseptic conditions.

Maintaining dose homogeneity during filling operations is a huge challenge. Dose homogeneity is a function of the ability of recirculation system supporting the filling system to prevent suspension particle settling or emulsion globule interaction and growth.

Suspension products are filled in two ways. The primary way is filling of the recirculated suspension; an alternative although not performed much at all is a two step solution filling where the suspension is formed in situ once the second solution is added to the first. Insulin NPH suspensions are approved to be filled this way where the first solution filled into the container is the insulin solution and the second solution filled contains the complexing agent, protamine, that immediately interacts with the previously filled insulin solution to form a suspension. The amount of protamine in the second fill is precalculated to stoichiometrically bind all of the insulin from the first fill.

CHECK WEIGHING

All filling operations must be checked for accurate dose filling, both prior to the start of the filling operation to make proper initial adjustments and during filling by checking fill volumes periodically to ensure that predetermined volumes or weights are within specifications.

There are a number of check weighing methods (focus on vials) (2).

- Manual check weighing
- Vacuum starwheel check weighing of a full vial set
- Robotic check weighing of a single container
- Robotic check weighing of a full container set
- 100% noncontact check weighing.

Whatever check weighing method is used, control charts are established and monitored during a filling operation (Fig. 19-7). Each filling operation has a target fill volume or weight with upper and lower acceptance limits. Typical fill requirements are $\pm 0.5\%$ of the target fill volume for each and every filling nozzle (1). For example, a target fill weight might be 5.0 g with the upper limit being 5.1 g and the lower limit being 4.9 g. Obviously, for liquid-filled products, the product density (or specific gravity) must be accurately known so that a conversion to weight can be determined. Periodic weight checking is performed and the data recorded on a control chart. Filling precision is calculated using the smaller of the following two calculations:

1. (Upper specification limit—average weight)/3σ or
2. (Average weight—lower specification)/3σ.

where 3σ is three standard deviations from the average (mean) weight value, where 99.73% of all data fall within this range.

STOPPERING

These operations must occur under Grade A/B (ISO 5) clean room conditions.

Ampoules, of course, do not require rubber closures and are sealed with a flame. Vials are closed with rubber stoppers (or, for vials containing solution to be freeze-dried, the stopper is partially inserted into the vial opening) and syringes and cartridges closed with rubber plungers at the distal end (with rubber septa sealing the proximal end except for staked-needle syringes). Rubber stoppers and plungers need to be lubricated either with applied silicone oil or emulsion or with special coatings (see chap. 7) that permit and facilitate rubber units to move easily from the hopper along stainless steel tracks or rails to the openings of the primary