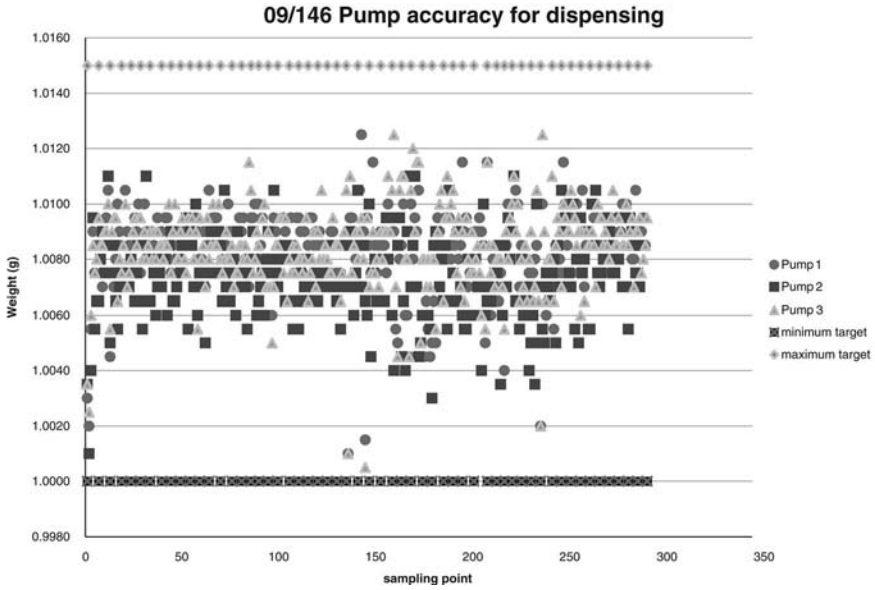

FIGURE 6 Accuracy of fill for typical ampouled reference material with targets set +/− 3CV. Mean fill = 1.0080 g with CV of 0.16%. *Abbreviation*: CV, coefficient of variation.

A minimum of six of the ampoules/vials used are marked and numbered at intervals throughout the fill to determine the dry weight (by weighing before filling and after freeze-drying) of the final material. These samples are used to determine the percentage residual moisture content of the freeze-dried material by the coulometric Karl Fischer method.

Other samples are also taken during/after filling, for assessing the microbial contamination.

Freeze-Drying

The appropriate freeze-drying cycle (see typical cycle from trial lyophilization in Fig. 7), as determined previously, is selected and the freeze-dryer started. When the shelves reach the set temperature (typically either +4°C or −50°C) and filling is complete, the entire batch of steel tins containing the filled ampoules/vials is loaded onto the shelves and the bases of the tins are removed. The position of each tin within the freeze-dryer is recorded on the Product Record and predetermined loading patterns are defined for all sizes of fill.

Resistance thermometers are inserted in one to six of the ampoules/vials (depending on the specified need) and the location of each is recorded on the Product Record. Once the temperature of the thermometers in the ampoules/vials reaches the shelf temperature, the freeze-drying cycle is started. The information gained from these thermometers is used in comparisons between batches and sometimes as an indicator as to the speed of freeze-drying, in the knowledge that the containers with the probes are not typical of the batch.

The freeze-drying parameters are continuously monitored and recorded by the freeze-dryer control system, and are checked and recorded twice daily