

time is sufficiently long to allow all vials to complete this step. If the time to accommodate the lagging vials is not appropriately factored into the cycle, it is possible to cause product collapse when ramping to secondary drying. For particularly labile products such as LVV, vials with the fastest heat transfer coefficients during secondary drying may be exposed to warmer temperatures for an extended period while the slower vials continue to come up to temperature, which may have negative product quality consequences. Large differences in the vial heat transfer coefficients may limit the robustness of the cycle to unanticipated manufacturing deviations. Second, from an operational perspective, significant heterogeneity in heat transfer coefficients leads to longer overall cycles and thus limits facility throughput.

Typical approaches for establishing the effective heat transfer coefficient by vial position include partial sublimation studies under representative load conditions. In these studies, a lyophilization run is simulated using pre-weighed water filled vials. The run is stopped prior to completion of primary drying and the mass sublimed for each vial is used to estimate the effective heat transfer coefficient at that selected location. Significant differences in the effective heat transfer coefficient often exist based on shelf as well as location within a shelf, with differences of 15% not uncommon (Table 4). Many factors contribute to these observed differences, including (1) nonuniform shelf surface temperatures, (2) position-dependent radiation, (3) sizing and design of the condenser, spool piece, port, and refrigeration system, and (4) vial loading approach.

Nonuniform shelf surface temperatures can be caused by design, installation, and operational factors. Heat transfer fluid should be uniformly distributed to all processing shelves with well-designed serpentine flow or baffling systems. Shelf to shelf imbalances in the flow of heat transfer fluid, as well as blocked passages within a shelf, can be detected by a variety of field tests. Multi-shelf temperature mapping studies that include unsteady state conditions, such as transition to new shelf temperature set points, can be particularly useful for start-up of new lyophilizers to confirm proper installation and operation.

Radiative heat transfer effects, which often manifest as edge effects, can be significant contributors to the total heat flow to the product under conditions typically used for primary drying and should be evaluated as part of the scale-up process. Studies have shown that vials in proximity to chamber walls and doors can have considerably different effective heat transfer rates, and hence drying times, than

Table 4 Variations in heat transfer coefficients across laboratories and manufacturing scale lyophilization cabinets

Lyophilization cabinet	H_{center} (W/m ² *K)	H_{corner} (W/m ² *K)	Inhomogeneity ratio
Lab-scale unit 1	5.1	16.4	3.21
Lab-scale unit 2	4.5	13.1	2.90
Lab-scale unit 3	4.7	13.7	2.89
Commercial unit 1 site A	5.6	13.5	2.41
Commercial unit 2 site A	3.7	12.8	3.41
Commercial unit 3 site A	3.7	13.2	3.48
Commercial unit 1 site B	7.7	22.3	2.81