Table 6 Differences in lyophilization cabinets between pilot- and commercial scale

	Characteristics	Pilot plant	Commercial manufacturing
Equipment differences	Shelf area	1 m^2	40 m^2
	Condenser	External	External
	Monitoring end of Primary Drying	Mass Spectrometer	Thermocouple
	Pressure gauge	Capacitance	Capacitance
Operational differences	Batch size	4000 vials	120,000 vials
	Trays	Bottomless	None-automatic loading system (ALS)
	Shifts	One 8-h shift/day	Three 8-h shift/day

choke flow measurement, the apparent heat transfer coefficient (K_v in W m^{-2} K^{-1}) of the various vials types at various location on the shelf, as obtained using gravimetric measurements, were used to correlate the drying in the two lyophilizers and correspondingly the shelf temperature and cycle times were adjusted. For example, an increased K_v for a vial type in moving the product from pilot (approximately 25 W m^{-2} K^{-1}) to commercial scale (approximately 30 W m^{-2} K^{-1}) suggested a drop of shelf temperature by approx. 3 °C. Additionally, the experimental findings were supplemented with a quasi-steady state mono-dimensional model [75], to simulate optimal drying conditions and build the appropriate design space [76]. The model and the corresponding design space were evaluated by correlating the difference in the critical process parameters and its corresponding impact of product. The findings, as measured by calculating the difference between the theoretical and the calculated value, on the pilot scale are presented below in Table 7:

Prior to active runs for process qualification and validation, engineering runs were performed on commercial scale to verify the suitability of the scale-up protocol. In the absence of active runs, appropriate surrogates (as measured by correlating, T_g', T_c, and dry layer resistance using MTM pressure rise method) were used to correlate the two processes (pilot and commercial). Table 8 summarizes various analytical tools to characterize product quality during various stages of the formulation and filling process. Primary drying time, moisture (center vs. edge vials) and cake appearance (i.e., reject rates) were used as the success criteria for engineering batches. Success of the engineering batches (similar moisture, slightly longer PD but within safety margin and acceptable vial reject rates) served as the basis to continue process validation.

Table 7 Illustrative examples depicting differential between theoretical and calculated values

Critical process parameters	Technique	Differential
$T_{product}$	Averaging 5 T-type thermocouple	0.7 °C
	Pressure rise test	0.9 °C
$\Delta T_{end\ of\ sublimation\ time}$	MKS/Pirani gauge	30 min
Δ(maximum rate of sublimation)	TDLAS	0.05 kg h^{-1} m^{-2}
Rejection rate	Cake appearance	0.2%