A scale-down model should be qualified to demonstrate equivalence between manufacturing process and laboratory- or pilot-scale processes in order to support process validation and commercial manufacturing process deviations. The general approach to scale-down model qualification is to run all process parameters at the center of the operating range of the manufacturing process [44]. However, in terms of lyophilization, it is important to compare the product temperature profiles and adjust the conditions of the laboratory-scale cycle to match the product temperature history characteristic of the commercial scale cycle, if necessary. It is recommended to use representative raw materials or process feed streams, preferably from full-scale manufacturing. Also, analytical methods for assessing process performance should be identical between different scales to minimize the potential differences. A well-defined acceptance criterion needs to be established prior to the scale-down runs performed in the laboratory, which can be based on historical large-scale data from engineering runs, process validation, or previous manufacturing runs. The output parameters and process control sensitivity at both scales should be compared. A minimum number of runs are needed at both scales in order to establish the confidence for the comparability [43].

Based on this guidance, the laboratory lyophilizer has been deemed as a suitable scale-down model for the large-scale manufacturing lyophilizer. Based on the prior knowledge for the product, the most important product CQAs for this product were selected from the release assays list. These CQAs include cake appearance, moisture, reconstitution time, aggregation, activity, concentration, purity, oxidation, etc. In addition, characterization assays such as glass transition temperature, protein secondary and tertiary structure, subvisible and visible particle counting, and SSA were performed on the product to evaluate the lyophilization process impact. The product temperature profile must be assessed and compared at both scales. A risk assessment was also performed for the lyophilization process, and risk factor number is calculated for each process parameter as the product of frequency, severity, and detectability. Through this exercise, several lyophilization process parameters including primary drying temperature, secondary drying temperature, and chamber pressure and freezing rate were identified as “potential” CPPs.

Experimental Studies for Process Characterization

The primary drying temperature was first investigated in order to establish the failure point imposed by the product. Based on the modeling approach, a shelf temperature robustness range was determined (between –25 and –20 °C) as shown in Fig. 4, and a maximum shelf temperature of – 20 °C was obtained. In order to understand the quality attributes of the product for more aggressive condition, shelf temperature of – 15 °C was examined. An acceptable cake structure was observed from the resulting vials, and further analytical tests showed that product quality attributes were well within the acceptable range and aligned with the historical trend. Thus, it is possible to expand the design space for this product. Several shelf temperatures higher than – 15 °C were also tested. At a shelf temperature of – 5 °C, micro-