a higher load of water vapor, an un-optimized condenser design and nonuniform vapor flow over condenser coil reduce the "effective" surface area for vapor condensation and limits the capability of the equipment.

After thermal characterization of the formulation for $T_g'$, $T_c$, and other thermal events (crystallization, melting, etc.), target freezing conditions (freezing ramp rates, annealing conditions, and ramp rates) and product temperature are selected. A conservative cycle is designed, that yields a good cake appearance of the product. The primary aim of the conservative cycle is to estimate $\widehat{R}_p$ (using product temperature data, MTM or TDLAS). Note that cycle optimization is not the goal for this first cycle. Conservative freezing conditions (hold times, temperature, and ramp rates) are selected based on prior knowledge and mDSC, FDM characterization studies. Conditions for primary drying are selected based on predetermined $K_v$ values for the vials (using TDLAS or gravimetric measurement), equipment capability, and a hypothetical value of $\widehat{R}_p$, corresponding to higher mass transfer resistance. Data and guidelines described by Tang et al. [13] can also be used for selection of primary drying conditions. The primary drying end point should be estimated using a method that yields the gas composition inside the chamber such as TDLAS and/or a Pirani gauge [23]. Conservative conditions for secondary drying are used (slow ramp rate, extended hold time, temperature based on literature data on $T_g$ of the components and formulation). Lyophilized samples from this initial study should be characterized for $T_g$, crystallization temperature, and melting temperature. It is also advised to conduct small-scale stability testing of the samples. The stability data from initial time points can serve as an important indicator of the lyophilization process feasibility. The information generated during this first study is used to construct a design space for a particular formulation and lyophilization process.

## Lyophilization Design Space for Primary Drying

Steady-state heat and mass transfer equations as described by Pikal [10, 24, 25] can be used for construction of the process design space. Figure 3 shows a graph of the sublimation rate as a function of chamber pressure used to construct the design space for the primary drying stage. The area "choked flow regime" represents the equipment limitation to support the "maximum" mass flow during primary drying [21] and therefore shelf temperature and chamber pressure conditions generating mass flow of water vapor in the "choked flow regime" should be avoided. In cases where the condenser design is the limiting factor in achieving the target mass flow, the choked flow regime is replaced with the "condenser overload regime."

The product temperature ($T_p$) during primary drying is a function of shelf temperature ($T_s$) and chamber pressure ($P_c$). A general representation of steady-state heat and mass flow during vial-based freeze-drying is useful for the selection of shelf temperature and chamber pressure is presented in Eq. 1:

$$\dot{Q} = A_v \cdot K_v \cdot (T_s - T_p) \tag{1}$$