be routinely tracked and analyzed. It is useful to categorize time for each product and dryer in the following manner:

- Manufacturing (matrix of the following for each product)
  - Loading
  - Equilibration
  - Freezing
  - Annealing (if applicable)
  - Primary drying
  - Secondary drying
  - Re-cooling (if applicable)
  - Stoppering
  - Unloading
- Turnaround
  - Defrosting
  - Cleaning
  - Sterilization
  - Vacuum testing
- Maintenance
  - Planned/routine/preventive
  - Unplanned
- Idle time

Any variability in time required for any of the above steps can also have a negative impact on overall throughput. Reduction in variability allows planners to cut planning "cushions," driving higher throughput by scheduling more batches and reducing idle time.

A key aspect of this analysis is to include a metric for time spent on failed batches or maintenance that was not effective. For a failed production batch, the impact extends to the additional time spent on turnaround for that batch as well. This will help justify the costs of improving expertise within the organization and the quality control improvements.

Another impact on throughput is the extent of freeze-dryer loading. If each freeze-dryer is not being fully loaded with each product, it may be worth examining the reasons and increasing to a full batch size. If the limitation is due to freeze-dryer capabilities, note that this chapter's case study also considers partial versus full loading of two of the freeze-dryers.

PRIMARY DRYING DESIGN SPACE

The "design space" is defined by International Conference on Harmonization (ICH) Q8 as "The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality" (2).

For primary drying, the process parameters constituting the design space are chamber pressure and shelf fluid inlet temperature.

Outputs are the resulting product temperature, product drying rate, and all product quality attributes. One important *caveat* is that other input variables that can affect performance during primary drying are the choice of vial and stopper, choice of formulation, and processing conditions for freezing and annealing (3). Particulate levels present in the vials during freezing can also be a factor (4).