the dryer is under load. Heat flows only where there is a pressure difference; therefore, when supporting a high load such as freezing or early primary drying there must necessarily be a significant difference between the shelf fluid inlet temperature and the shelf surface temperature just under the product.

- Track and analyze step times, product quality attributes, and process measurements for each product.
- Know the drying rate that each product will be generating when it is at its maximum—early in primary drying. These can be measured in small-scale freeze-dryers.
- Understand the "design space" for your process (2). This chapter defines it for significant parts of freeze-drying. For primary drying one will find that the design space gets smaller at higher drying rates.

ACKNOWLEDGMENTS

I wish to acknowledge and thank Professor Ted Randolph at the University of Colorado, and the following people from Eli Lilly & Co. for their contributions to this work: David Lowndes, Steve Nail, Gordon Livesey, Adam Scott, Ted Tharp, Keith Glad, Rebecca Elliott, Robert Bell, Lisa Rathburn, Rick Owens, Carmel Egan, Ralph Riggin, Sandrine Favre, and Bob Cole.

REFERENCES

1. Lienhard JC IV, Lienhard JC V. A heat transfer textbook. 3rd ed. Cambridge, MA: Phlogiston Press, 2008. Available at: http://web.mit.edu/lienhard/www/ahtt.html.
2. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Pharmaceutical development q8(r1). ICH Harmonised Tripartite Guideline 13 November 2008.
3. Searles J, Carpenter J, Randolph T. Annealing to optimize the primary drying rate, reduce freezing-induced drying rate heterogeneity, and determine tg' in pharmaceutical lyophilization. J Pharm Sci 2001; 90(7):872–887.
4. Searles J, Carpenter J, Randolph T. The ice nucleation temperature determines the primary drying rate of lyophilization for samples frozen on a temperature-controlled shelf. J Pharm Sci 2001; 90(7):860–871.
5. Chang BS, Fischer NL. Development of an efficient single-step freeze-drying cycle for protein formulations. Pharm Res 2001; 12(6):831–837.
6. Searles JA. Observation and implications of sonic water vapor flow during freeze-drying. Am Pharm Rev 2004:58–69. Available at: http://americanpharmaceuticalreview.com/ViewArticle.aspx?ContentID=27.