liquid ammonia and unable to be brought to room temperature unless they are freeze-dried from their frozen solution at −120°C.

Organic solvents: Many organic solvents are susceptible to be eliminated by sublimation from their frozen solution, for example, dioxane, diethyl amine, chloroform, cyclohexane, dimethylsulfoxide, and benzene. We showed that they could be used for the preparation of delicate biochemicals (like phospholipids). In that case, however, the main problem is the residual amount of solvent that can be found in the final dry product and this, of course, is a redundant issue for the whole pharmaceutical industry. For that reason the use of pure organic solvents in freeze-drying has not really been developed. However, their application as partial constituents in mixed aqueous solutions has given rise to most interesting new processes. This is the so-called cosolvent issue that is dealt with in details further in this book by Dirk Teagarden, who has been pioneering in that field for a long time. It is expected that this approach will find more and more new applications in the future.

Continuous Operations

For more than 65 years freeze-drying has been almost exclusively done within the pharmaceutical and biological industries as a batch-type operation. The starting liquid solutions are distributed in vials or filled in trays, frozen, dried, and then handled as one single batch. To the contrary, the food industry, which had to face large productions, has progressively shifted from batch to semi-continuous and even purely continuous operations. The results are a substantial increase in productivity and a more homogeneous product.

To my feeling, it is ample time for the pharmaceutical and biological industries to take up that challenge and enter the process analytical technology (PAT) constraints with better monitoring and control of their operations.

Indeed, any chemical engineer dreams of a continuous process because it is easy to control and gives manufactured products a standard equal quality. In food areas freeze-drying has not escaped this trend and, as early as in the 60s, semi-continuous to continuous equipments have been designed and built. Leybold was among the very first to do it, and Oetjen developed the continuous quality controlled (CQC) process into an industrial reality for milk products. The operation was, indeed, sequenced into several phases. The frozen products, most often under granular form, were loaded on trays placed on a special carrier, hanged to a monorail that traveled all along the freeze-drying tunnel between heating plates in successive steps through vacuum locks closed by sliding gates. The total cycle time from the entrance lock to the outlet was of the order of several hours.

An alternative to this system was introduced by Atlas who pioneered the so-called "Conrad" system in which the loading of the frozen goods was done tray by tray through a small side lock. Not only coffee and milk, but also vegetables, fish fillets, and meat have been successfully treated in this way.

Quite obviously this technology worked but it was still a semicontinuous process and food industry was eager to develop a fully automated continuous operation for one of its leading products on the international market, that is, instant coffee. I had the opportunity to live this development very closely, and I can tell you that it has been very difficult since most steps of the instant coffee processing had to be revisited.