Harry Meryman, Christopher Polge, Peter Mazur, and others. We had the privilege of living this exciting period together with all these people since 1954, and most of them were present in Lyon in 1958 when Charles Mérieux and I opened the first International Course on Lyophilization, with the sad exception of Earl Flosdorf who had agreed to deliver the opening address but died tragically a few weeks before the conference.

Today, 56 years later, we are pleased to see that freeze-drying still holds a remarkable place in our multiple panel of advanced technologies, more particularly in the pharmaceutical field.

BASIC FREEZE-DRYING

Lyophilization is a multistage operation in which, quite obviously, each step is critical. The main actors of this scenario are all well known and should be under strict control to achieve a successful operation.

The product, that is, the "active" substance, which needs to keep its prime properties.

The surrounding "medium" and its complex cohort of bulking agents, stabilizers, emulsifiers, antioxidants, cryoprotectors, and moisture-buffering agents.

The equipment, which needs to be flexible, fully reliable, and geared to the ultimate goal (mass production of sterile/nonsterile drugs or ingredients, experimental research, technical development).

The process, which has to be adapted to individual cases according to the specific requirements and low-temperature behavior of the different products under treatment.

The final conditioning and storage parameters of the finished product, which will vary not only from one substance to another but also in relationship with its "expected therapeutic life" and marketing conditions (i.e., vaccines for remote tropical countries, international biological standards, etc.). In other words, a freeze-dryer is not a conventional balance; it does not perform in the same way with different products. *There is no universal recipe for a successful freeze-drying operation*, and the repetitive claim that "this material cannot be freeze-dried" has no meaning until each successive step of the process has been duly challenged with the product in a systematic and professional way and not by the all-too-common "trial-and-error" game.

The Freeze-Drying Cycle

It is now well established that a freeze-drying operation includes the following:

The ad hoc *preparation of the material* (solid, liquid, paste, emulsion) to be processed, taking great care not to impede its fundamental properties.

The freezing step during which the material is hardened by low temperatures. During this very critical period all fluids present become solid bodies, either crystalline, amorphous, or glass. Most often, water gives rise to a complex ice network, but it might also be imbedded in glassy structures or remain more or less firmly bound within the interstitial structures. Solutes do concentrate and might finally crystallize out. At the same time, the volumetric expansion of the system might induce powerful mechanical stresses that combine with the osmotic shock given by the increasing concentration of interstitial fluids.