The overall efficiency and consistency of the entire process, as well as ensuring high quality of the products, largely depends on the nucleation temperature. This temperature directly affects the size of ice crystals and in turn determines the pore size distribution and the pore network of the porous freeze-dried matrix.

The temperature difference between the equilibrium freezing point and the ice nucleation point is known as *supercooling*. A lower nucleation temperature, or a higher degree of supercooling, results in more ice nuclei and smaller ice crystals. On the other hand, higher nucleation temperature, or a lower degree of supercooling, results in fewer ice nuclei and larger ice crystals forming pores and pore networks. Larger pores enable higher sublimation rates, hence shorter drying cycles, as well as reduced reconstitution times and improved finished product attributes. It is also important that all vials nucleate at the same temperature, to ensure consistency of the product morphology, resultant cake structure and appearance, as well as uniformity of the product.

Due to its spontaneous and stochastic nature, uncontrolled nucleation occurs over a wide range of temperatures and a lengthy amount of time, which results in nonuniform ice crystal structure. To overcome such ice nucleation heterogeneity, the process known as annealing is commonly used, during which larger ice crystals are formed at the expense of smaller ones (Ostwald ripening phenomenon) [2]. Annealing can in itself be a time-consuming process; therefore, the potential benefit of reduced drying time may result in little or no overall cycle time reduction.

Therefore, the freezing step is one of the most important steps in the lyophilization process. Handling it in a “controlled” versus “uncontrolled” or “random” fashion, results in a number of benefits to the product manufacturers as well as end users.

Products that could benefit from implementation of controlled nucleation include: biological products like protein and peptide formulations, vaccines, liposome, and small chemical drugs susceptible to physical and chemical degradation, as well as other injectables, which must remain effective from manufacture to patient administration [2]. Due to the rapid growth in biological therapies, the demand for freeze drying has never been higher. This trend is expected to continue for the next decade [3].

Recently, Linde has introduced a novel ice-fog technology, called VERISEQ® Nucleation, which was developed in cooperation with IMA Life North America [4]. This patented cryogenic technology enables controlling the parameters of the nucleation process by using a sterile ice “fog”, produced using liquid nitrogen and water vapor and offers a new degree of control over freeze-drying process as well as the ability to develop more robust lyophilization cycles. VERISEQ® Nucleation technology can be implemented on virtually any freeze-dryer from laboratory lyophilizers to commercial-scale units, as well as aseptic and nonaseptic units, and new as well as retrofits, regardless of pressure rating. The technology is adaptable to both container-based and bulk freeze-drying [5].