ing the vapor port into the product chamber maintained at a lower pressure than the condenser chamber. According to the developers of this technology, such ice crystal injection enables uniform and rapid nucleation of the product in different areas of the product chamber. Furthermore, the technology allows the crystal structure to be consistently created, monitored, and controlled by producing a consistent and repeatable ice formation, which results in a highly uniform finished product with reduced primary drying times.

The depressurization technique used by Praxair's ControLyo™ nucleation on-demand system, involves pressurization of the freeze-dryer chamber with an inert gas, such as nitrogen or argon to pressures ranging from 18 to 28 psig, followed by reducing the product temperature in all vials to a selected value. When thermal equilibrium between the vials has been achieved, the excess pressure is released rapidly [9]. With this method, nucleation is induced at essentially the same time for all vials in the batch. However, the technique does involve pressurization, which requires the use of pressure-rated freeze-dryers, and could be problematic when working with laboratory units, which are typically not pressure rated. This could also represent a challenge when retrofitting existing units.

Nevertheless, the developers believe that depressurization technology can be successfully used from laboratory to manufacturing scale. The ControLyo™ nucleation on-demand technology developed by Praxair was licensed to SP Scientific exclusively for use on dryers with shelf areas of less than 1.0 m^2. According to reports, the Lyostar™ 3 pilot freeze-dryer with ControLyo™ technology introduced by SP Scientific was the first commercially available freeze-dryer with the control nucleation capability.

VERISEQ® Nucleation Technology: Background, Technical Approach, Scale-Up

The VERISEQ® Nucleation technology, developed by Linde Gases Division of the Linde Group in cooperation with IMA Life North America, offers a commercially viable technique for cryogenically generating a uniform dispersion of microscopic ice crystals (or ice fog). The ice fog is a result of contact between liquid nitrogen (produced from sterile-filtered gaseous nitrogen) and water vapor in a mixing device outside the lyophilization chamber. Upon introduction into precooled vials, containing the product to be freeze dried, these ice-fog crystals serve as nucleation sites. This causes a rapid and uniform nucleation of the product in a vial as well as between vials of the same batch at very low degrees of supercooling [10].

A key challenge for the commercial implementation of VERISEQ® Nucleation technology was to generate a sufficient amount of ice fog to fill the chamber, and to ensure its penetration inside the vials given various lyophilizer volumes, as well as container/closure geometries. Efficient ice-fog generation and distribution were achieved using an ejector assembly, which provides an extremely efficient method of quickly forming the ice fog and circulating it throughout the freeze-dryer chamber.