Overview of Current Technologies Offering Controlled Nucleation

The challenge of providing a solution to enable controlled nucleation of the liquid preparations in terms of nucleation temperature and time greatly depends on its scalability. A number of proposed techniques that work well in laboratory conditions, however, are difficult or sometimes impossible to implement at a production level [6].

Technologies utilizing ice crystals as nucleation sites are commonly referred to as "ice-fog" technologies. The first ice-fog method was demonstrated in 1990 by introducing a cold gas into a humid freeze-dryer chamber to produce a vapor suspension of small ice particles [7]. This method was further combined with reduced pressure to achieve more rapid and more uniform nucleation [8].

Additional laboratory approaches to controlled nucleation include the following [2]:

- *Vial pretreatment* by producing surface defects or glass particles (for example, by scoring, scratching, or roughening the internal vial walls) to provide nucleation sites and accelerate ice nucleus formation. However, this method does not ensure any control over nucleation temperature and time, and may result in undesirable contamination of pharmaceutical products.
- *Ultrasound treatment* to cause nucleation as a result of ultrasonic vibrations. However, implementation of this method in a commercial-scale freeze-dryer without compromising the ability to clean the equipment is challenging.
- *Utilization of additives*, such as silver iodide, *Pseudomonas syringae* bacteria, and adventitious environmental particulates, to introduce artificial nucleation sites. However, the presence of additives is generally unacceptable and this approach does not provide sufficient control over nucleation parameters.
- *Electro-freezing* by delivering relatively high electric fields (~0.01 V/nm) either continuously or pulsed between narrowly spaced electrodes immersed in the solution to be freeze-dried, in order to induce nucleation in subcooled solutions. However, such method is generally impractical for use in commercial pharmaceutical applications and is sensitive to ionic molecules (for example, NaCl).

The two main techniques currently offering the potential of achieving controlled nucleation in the commercial scale are ice fog (e.g., Millrock's FreezeBooster nucleation technology and Linde's VERISEQ® Nucleation technology) and depressurization (ControLyo™ technology, developed by Praxair).

Millrock's patented FreezeBooster™ controlled nucleation technology, combined with the company's patent pending AccuFlux™ technology works by first cooling the chamber to the desired temperature below the equilibrium freezing point, say −5 °C, reducing the chamber pressure creating a predetermined volume of condensed frost on an outer surface of the coils inside a condenser chamber separate from the product chamber, and then rapidly introducing ice crystals, formed by breaking down the condensed frost due to gas turbulence created as a result of open-