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1. **What are the main considerations when selecting a freeze dryer?**

   For the sake of this discussion, we will focus on freeze dryers with fluid filled shelves, which does not include low-end manifold or heat only shelf freeze dryers.

   The most important consideration is making sure the freeze dryer is fit for today's application and future needs. An understanding of the available features of a freeze dryer also helps.

   Some considerations:
   Shelf Size: square meters
   Shelf style: bulk or stoppering
   Condensing Rate: liters per hour
   Condensing capacity: liters
   Condenser location: Internal or external
   Material: 304 vs 316SS
   Advanced features:
   - Vacuum instrumentation
   - Isolation valve
   - Sterilization
   - 21 CFR Part 11 compliance

   The freeze dryer manufacturer will also want to know what space is available for the freeze dryer and what utilities, such as: electrical, air, chilled water, and air conditioning are available.

   Freeze dryer selection falls into several categories; first is laboratory versus production and the second is non-sterile versus sterilizable.

   Laboratory freeze dryers are used for a large variety of applications which range from simple removal of solvent from a material to Phase 1 clinical trials to protocol development for scale-up production. A typical laboratory system will have a shelf area from 0.1 sq meters up to 1 sq meter with a condensing capacity of up to 30 liters.

   Laboratory style systems can be simple where temperature and pressure control are provided or they can be complex where additional instrumentation and features are added to aid in developing optimized freeze drying cycles (protocols). Standard features include a pirani gauge for vacuum level measurement and thermocouples for temperature monitoring. Advanced features include a capacitance manometer for vacuum measurement, proportional vacuum control for fine vacuum control, an isolation valve between the product chamber and condenser for pressure rise testing, liquid nitrogen traps for organic solvent trapping, and additional product thermocouples for monitoring product temperature.

   Pilot and Production systems offer shelf areas from 1 sq meter up to and over 40 sq m. Production systems are used for Phase 2 and Phase 3 clinical trials and tend to be used for the

same or a limited number of products in high volume production. Recently, there is a shift from 10ml to 50ml vials, to smaller volume high potency biotech and protein related products, in 2ml and 5 ml vials. The result is smaller freeze dryers with expensive payloads.

The type of processing will determine whether stoppering is required. Bulk applications can have fixed-in-place shelves, while vial applications require stoppering where the shelves move and are squeezed together to press the partially inserted stoppers into the vial.

Pharmaceutical and other applications may require sterilization between cycles. Sterilizaton can add significant complication and cost to a freeze dryer. A freeze dryer is normally rated for vacuum and the most common method of sterilization is pressurized steam, which requires the freeze dryer chambers to be certified pressure vessels rated to 2 atmospheres at 131C.

An alternative sterilization technique uses Hydrogen Peroxide. Hydrogen peroxide (H2O2)sterilization is growing in popularity for Laboratory and small production systems. H2O2 does not require a pressure rated vessel, which keeps the cost down.

2. Are there any common 'oversights' regarding the selection process and if so what are they?

The most common oversight is the concept that ‘all freeze dryers are the same’. The choice of components, materials, construction and instrumentation create a wide variety of cost versus performance.

Older systems tended to have undersized compressors/condensers and restrictions between the product chamber and the condenser which limited the rate of freeze drying and often caused the freeze drying process to be extended. Today, freeze dryers are much better designed to accommodate the maximum load that may be placed in the system and the freeze dryer is not the limit to the process.

As an example, compressor reliability has significantly improved compared to systems made 15 years ago. In small freeze dryers the use of scroll compressors has virtually eliminated the failures that are common with reciprocating compressors.

Advanced freeze dryers are ‘built to order’ since there are so many possible variations in size and features. As our knowledge of freeze drying grows, the designs and features that can be built into the equipment grows.

The end user must understand their application requirements and work with the freeze dryer manufacture to get a system that meets their needs today and in the future.

3. How have demands in freeze dryers and their features changes in recent years?

The most current demand on freeze dryers are validation and the ability to meet 21CFR Part11 compliance as required by the FDA. These are now a significant part of the cost of pharmaceutical processing freeze dryers.

For validation a full component catalog must be supplied. An IQOQ (installation qualification, operational qualification) document is generated which outlines the proper validation process and an FAT (factory acceptance test) and SAT (site acceptance test) are implemented to verify that the system is supplied as ordered and performs within the specifications required.

To aid in 21 CFR Part11 compliance, the software must encrypt all data to prevent tampering and must log every change and entry on the computer control system using user log-in's and password protection.

4. What advantages are associated with the various options?

The following are a few of the many examples of the various options:

304SS vs 316SS stainless steel – 304 can be used on food grade and industrial applications. 316 is used on pharmaceutical and biotech applications.

Cylindrical vs Rectangular product chambers – A cylindrical product chamber is less expensive than a rectangular chamber, however, it may take up more floor space depending on the configuration of the shelf assembly.

Internal vs External Condenser – An internal condenser is less expensive and provides unrestricted vapor flow. An external condenser is supplied with an isolation valve to separate the product from the condenser. This protects the product from reconstitution during power loss and keeps the condensate out of the clean room environment.

Pirani vs Capacitance Manometer – Pirani's, the least expensive vacuum measurement device, read the relative vacuum inside a freeze dryer since they are affected by vapor. The more vapor present, high the pressure reading.

A capacitance manometer reads the absolute vacuum level. The reading is not affected by vapor pressure. Most production systems use a capacitance manometer for measurement and control of vacuum level.

The best method for determining the 'end of primary drying' (EOPD) is to compare a pirani reading to a capacitance manometer reading. When they 'read the same', there is no vapor present and therefore the product is dry. A quick test can be done by lowering the vacuum level to see if the pirani reading tracks the capacitance manometer. If water is present the capacitance manometer will drop faster. If no water is present, they will drop at the same rate.

Proportional vacuum control – the least expensive vacuum control system bleeds gas into the chamber using a solenoid valve. This technique provides +/-10mT stability at 100 mT. For better stability a proportional vacuum controller can be used which regulates the gas bleed through a proportional valve. The result is +/- 0.5 mT or better control.

5. Have there been any recent innovations in freeze dryer technology and if so, what are they?

Using Thermal Analysis and freeze drying microscopes with now have a much better understanding of the critical temperature of the product being freeze dried. The critical temperature of a product is the temperature at which the product may collapse or melt-back. This knowledge provides the information required to produce a robust and efficient freeze drying cycle.

Classic freeze drying control is open loop; the shelf temperature and chamber pressure are controlled based on a predetermined profile and it is assumed that the temperature of the product stays below its critical temperature. The result is a reproducible, but very conservative and long freeze drying cycle.

Closed loop control of the shelf temperature is required to both prevent collapse and minimize the length of the freeze drying cycle. The latest control systems use the critical temperature information to dynamically control the shelf temperature, which both protects against collapse and melt-back while optimizing the freeze drying cycle.

Methods using an average measurement of the product in the chamber, such as calculated via pressure rise testing, adjust the temperature of the shelves a few times through the first half of the primary drying process. This process is limited to only the first half of primary drying and only provides a conservative protocol, but is not optimized and does not take into account variations inside the chamber.

The latest control system, Auto-Dry™, takes into account both average and specific measurements to ensure that there is no melt-back and constantly controls the shelf temperature throughout the entire cycle to produce a user selectable conservative or aggressive protocol.

6. How do you see freeze dryers developing during the next 10 years?

More advanced closed loop control systems that provide better process control. Today most of the applicable measuring instruments, such as: TDLAS, NIR, and Mass Specs, are expensive and provide only marginal process improvement and therefore are not economically feasible for process control. As instrumentation and techniques advance, they will be incorporated into real-time process control systems.