

Reducing compliance costs in the life sciences industry

Eurotherm[®]

Freeze drying process

Eurotherm[™] provides a range of products, digital engineered solutions and services throughout the world. Our expertise in life sciences allows us to supply solutions that suit the scale of your manufacturing requirements, while helping to maximize efficiency, productivity, and ultimately your return on investment.

Our solutions support regulatory compliance and help create a safer world.

Compliance

We empower our customers to help maintain regulatory compliance and minimize audit costs by providing a Data Integrity layer with open IoT platforms that support the digital transformation to Pharma 4.0.

Safer world

Specialists in managing critical data and contextual metadata to efficiently manage the quality, safety and authenticity of manufactured goods.

We have application expertise in:

- Control and sequencing
- Recipe management
- Batch control and reporting
- Setpoint programming
- Graphics based on situational awareness concepts
- Alarm management
- FDA 21 CFR Part 11 and EudraLex Annex 11 compliance
 - Electronic signatures
 - Electronic records
 - Audit trail
- Data Integrity ALCOA+ concept
- ISPE GAMP[®] 5 guidelines
 - Good engineering practice (GEP)
 - Qualification practices
 - Risk based approach
 - Quality management
- System lifecycle support services

Freeze drying overview

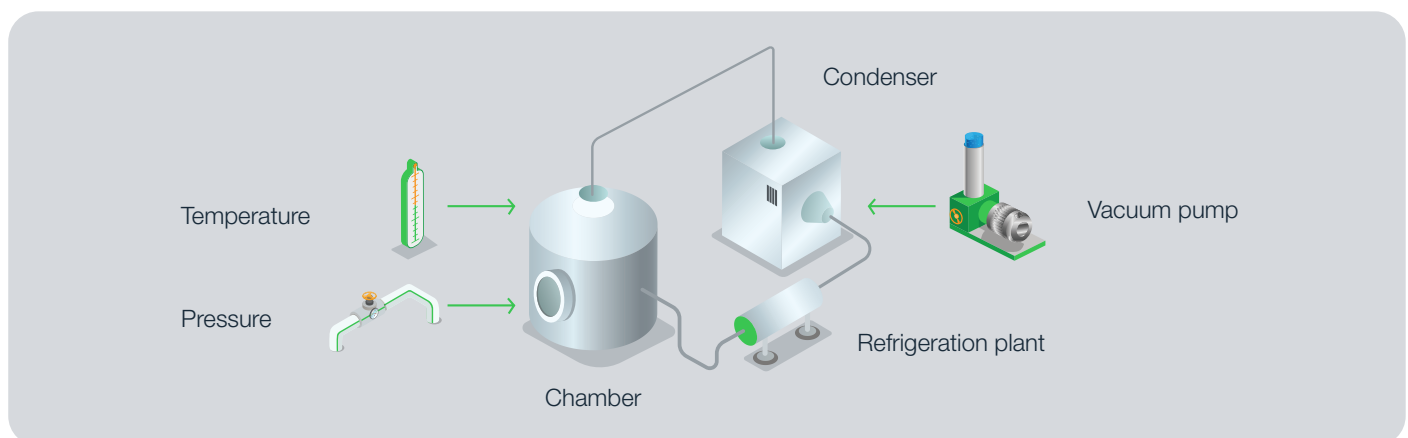
Freeze drying (also known as lyophilization or cryodesiccation) is a slow batch process used in pharmaceutical and biotechnology industries (such as diet food production) to extract dry product from an aqueous solution. The resulting powder material can be easily stored, shipped, and later reconstituted for use in products such as solid dose tablets and soluble solutions. Freeze drying works by freezing the material, then reducing the pressure and adding heat to allow the frozen water in the material to sublime at the water triple point condition.

For example, injectable medicines are usually situated in glass vials placed on shelves in a vacuum chamber, which is first controlled down to freezing temperature and then evacuated to create the vacuum. The shelves are then warmed up very slowly, to sublime the liquid, whilst the chamber is continuously evacuated through a cold condenser. Once above zero degrees, the chamber isolation valve is closed and a 'pressure rise test' is performed to indicate that appropriate drying conditions have been met.

As cryodesiccation is a high energy process, it is important to develop economical drying cycles suitable for large scale production. Also, the vacuum and refrigeration units require regular extensive maintenance if they are not used effectively. Therefore, an efficient process automation control system is required to manage the freeze dryer machine.

Freeze drying design and control

There are many different arrangements for freeze dryers but the basics are outlined here:



Temperature can either be controlled electrically using heating mats on the shelves, or by circulating oil through pipes welded to the shelves in the chamber. The temperature of the chamber, shelves (and/or heating oil), plus condenser form part of the control and monitoring variables also known as critical process parameters (CPPs). There are usually separate sensors for sterilization, which also require monitoring.

The vacuum pressure can be measured with a pirani gauge. Control is achieved either by an analog needle valve or coarse and fine admittance valves. A change-over valve is used to switch the refrigeration plant from freezing the chamber to freezing the condenser. In the final drying stage, the vacuum may be allowed to go as low as it can to encourage desorption of the material, or it can be controlled to protect the product from too much dehydration. Freeze drying is typically carried out in four steps:

- Pretreatment
- Freezing
- Primary drying
- Secondary drying

This full process is characterized by long stabilization periods. For example, in the freezing step, the shelf temperature is reduced to between -50°C (-58°F) and -80°C (-112°F), usually in several steps (sometimes in more complex profiles than a simple ramp), converting most of the water into ice.

The critical and longer phase is the primary dry heating phase (sublimation drying), where the rate at which the water sublimates must be slow enough not to damage the product. During this phase, the vacuum is held constant to give consistent conditions. The temperature ramp must be held if the vacuum rises too much, as it indicates that the product is subliming too fast.

At the end of the primary drying heat ramp, a pressure rise test (PRT) is performed. Once the product has been heated, all the water should have been driven off. The actual temperature depends on the product but will be above ambient. To check the dryness, a PRT (usually automated), is performed. This checks that there is no more evaporation by sealing the chamber and looking for a pressure rise.

After the PRT, the secondary drying phase takes place to ensure absolute dryness. The product is brought up to or just above ambient temperature. The machine usually requires sterilization after the process. This is achieved by an alternative strategy within the control system using steam or gases (such as ethylene oxide – ETO, EtO, EO).

Eurotherm solution:

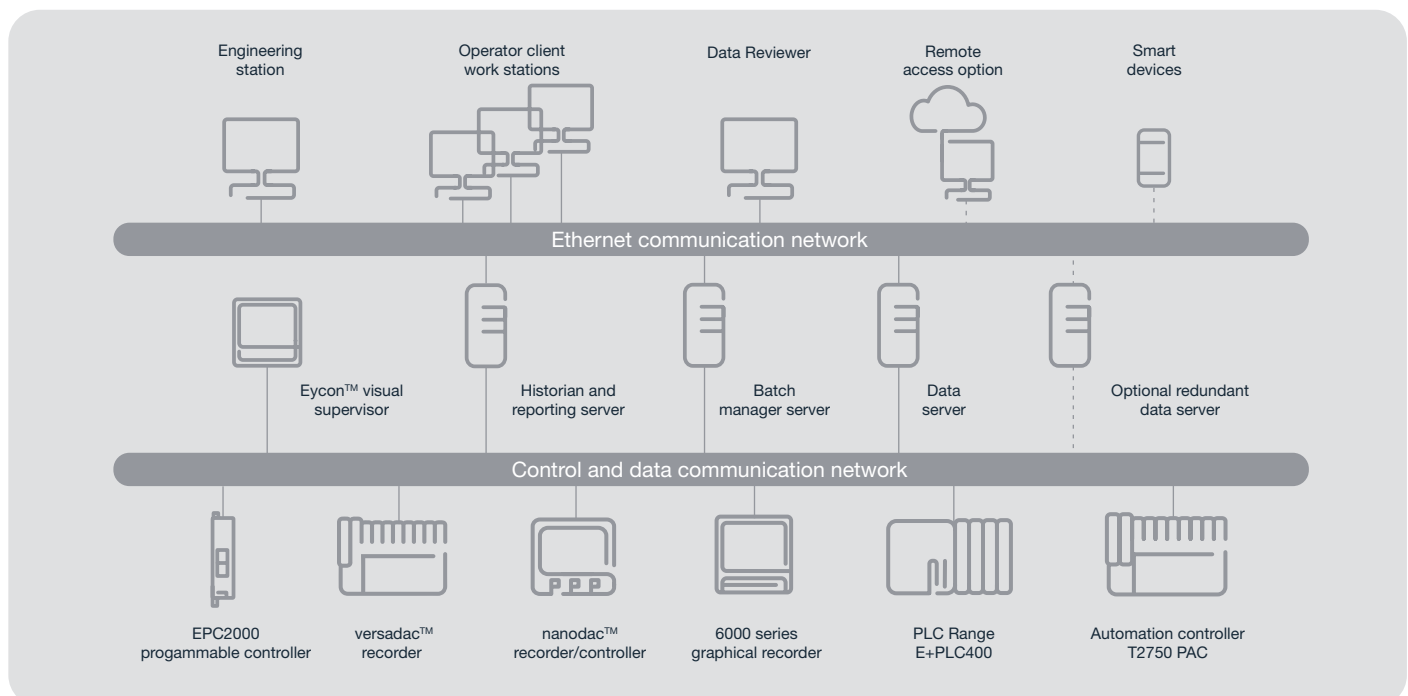
- Distributed control system with configuration lock
- Fast acting control accuracy, and process repeatability
- Batch/recipe management
- Data management based on ALCOA+ principles
- Power control for electric heaters
- Local HMIs to full SCADA solutions
- High availability architecture (redundant solutions and 'Store and Forward' feature)
- Data analysis
- Historian and reporting server
- Reporting

FDA 21 CFR part 11 and EU EudraLex Annex 11 regulations compliancy

As an automation and information technology leader our solutions meet the Electronic Record and Electronic Signature requirements as defined by the US and EU regulatory bodies.

Data Integrity ALCOA+ guidelines

To make sound decisions, you need to trust your data. Key regulatory bodies (FDA, EMA, WHO) and some advisory bodies (PIC/S, ISPE) have agreed on the Data Integrity related ALCOA+ concept. ALCOA+ defines that data should be Attributable, Legible, Contemporaneous, Original, and Accurate + Complete, Consistent, Enduring, and Available. As an experienced solution supplier, well established in life science processes, Eurotherm is a main supporter of that vision and contributed to the definition and the revision of some of these guidelines.



A 21st century risk-based approach

Business investments should be future-proof and audits hassle free. Eurotherm has developed and widely applied a set of good engineering practise (GEP) qualification documents based on ISPE GAMP 5 guidelines to assist with achieving these goals. Qualification documents can be maintained in electronic format. Industry is progressing from manual standard operating procedure (SOP) based manufacturing operations to a digitalized paperless quality systems approach based on FDA and ICH guidelines.

Quality by design

In a quality by design (QbD) approach, product quality is continuously monitored and controlled at the earliest stages, rather than waiting for a process to end. Pharmaceutical manufacturers need to focus on identifying, controlling, and validating process variables that could cause a non-compliant result. This is accomplished by managing the quality target product profile (QTPP), the critical quality attributes (CQA), and the critical process parameters (CPP). As defined by the process analytical technology (PAT) approach, Eurotherm can assist with measurement and performance analytics on CQAs and help manage CPP deviations, providing time-stamped evidence for correlation of parameter behaviors at their occurrence.

Pharma 4.0 ready technology

Eurotherm control and data recording solutions are IoT ready, providing a data integrity layer within open IoT platform system architectures and aiding the digital transformation to Pharma 4.0 technology.

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