

*Epsilon*

Production and Pilot Freeze-Drying Systems  
Project Engineering



**CHRIST** 

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**CHRIST** 





## The Products

Our unique and comprehensive range of freeze dryers, vacuum concentrators and accessories provide a system for every application.

Freeze dryers for industrial production

Pilot systems for process development or optimization

Freeze dryers for research and development

Rotational vacuum concentrators, available in 4 sizes, covering the gamut from solving routine laboratory problems to evaporation in high-end pharmaceutical research

Freeze dryers for routine laboratory use





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## Dear reader,

You may already know Martin Christ Freeze Dryers GmbH as a leading manufacturer, with over 50 years of experience, in the demanding field of freeze drying. Today we would like to introduce you to the very core of our company in which our knowledge and experience meet. I am referring to the manufacturing of pilot systems for process development and optimization as well as the construction of customer-specific systems.

The individually configured Epsilon series freeze-drying systems embody our research and development efforts and our experience, providing freeze-drying solutions for each particular need. For example, when assembling and positioning a system-configuration we consider the space in which it will reside as well as providing individual vacuum, cooling and interface concepts. The development and implementation of automatic loading and unloading systems and the use of additional peripheral units are an important part of our customer-specific service. All Martin Christ freeze-drying systems conform to current international regulations such as the guidelines set by the FDA and GMP and fulfill the highest safety requirements. Our staff is active on several national and international committees involved with, and keeping informed about, the latest technological innovations in the field.

This is why we can ensure that our present systems will remain compatible and adaptable to future developments. An additional aspect of our products is our modern user-friendly interface and software which allow for accurate process reproduction. Using our extensive knowledge in this field, we have developed an innovative product-weighing technique and a wireless product temperature measuring technique, mainly designed for use within the increasing demands of Process Analytical Technologies (PAT). Last, but not least, comes our commitment to customer service: we not only provide support throughout the installation, operation and training process, but also during the entire time a system is being used.



We invite you now to acquaint yourself with our company and services in more detail in the following pages. Take part in the excitement of this innovative and fascinating technological field. Should you have any further questions, please do not hesitate to contact us. We would be happy to personally assist you.

Sincerely,

Martin Christ

**CHRIST** 

## Clever, and with a Passion for Detail

Rules, regulations, guidelines - an incomprehensible number of controls govern the production and use of pharmaceutical equipment. You are probably familiar with the most important guidelines including the ISPE, GMP, and GAMP, the norms EN/ISO 13408 and EN/ISO 14644 or government approvals such as the FDA Aseptic Guide, the EMEA and the EG-GMP.

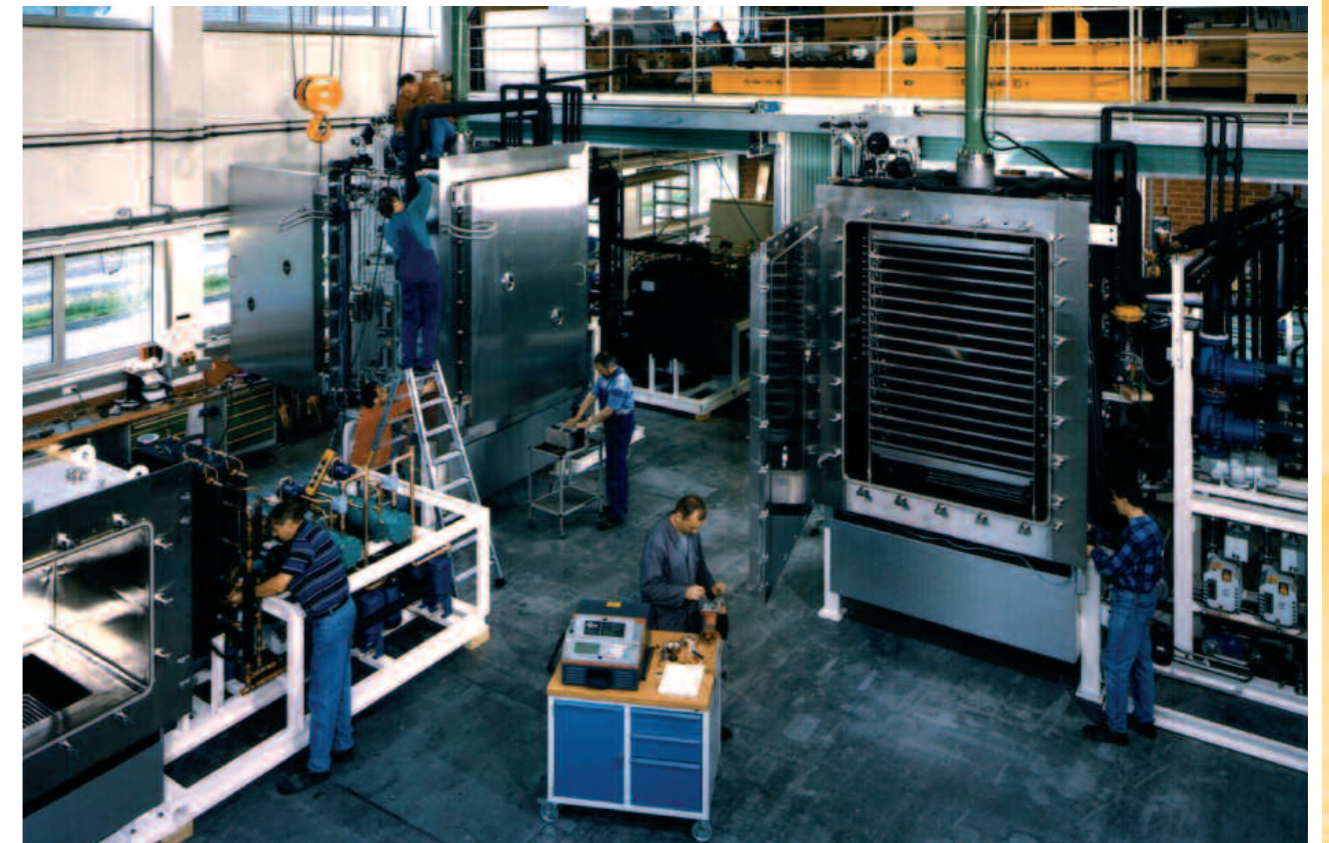
The staff at Martin Christ participate on many committees so that they can advise our clients on the various guidelines and regulations that need to be complied with while using freeze-drying systems. Presence on committees also allows us to contribute to the development of new regulations. We are currently on a national committee on the ISO/TC 198/WG9 and in the German ISPE work group PAT.

This involvement provides us with valuable first-hand information that we pass on to our clients, adding further efficiency to the planning phase of a new system.



## An Overview of Martin Christ Performance Features

- patented system design with technical advantages such as compact design and optimized vapour flow
- systems are produced compliant with current GMP, FDA, ISPE guidelines
- provider of systems such as loading/unloading systems, CIP modules, isolator
- user-friendly interface for manual, automatic and program-controlled freeze-drying processes
- SCADA software LPC (Lyophilization Process Control) for the documentation and control of batch and process data
- highest safety standard through risk-analysis and optimal product-safety with use of Lyocontrol
- interface for data export into commonly used programs for spread sheets, allowing further computing of process information
- measurement of product temperature and resistance for determination of freezing point and process control
- pressure increase tests and weight measurements allow for determination of the end of the drying process
- SIP - automatic sterilization (121° C to 134° C) with cooling and vacuum test
- optional CIP (Clean in Place) equipment
- inline integrity test of sterile aeration filter
- project engineering
- project management
- validation (Qualification of systems)
- training and seminars



5.1.: Production hall



## Production Freeze Dryers: the Single-Chamber System

The Martin Christ single-chamber units are the system of choice for high drying capacity processes at low investment and energy costs. These efficient systems guarantee years of reliable and economic operation.

These units fulfill a range of requirements with their variable distances between shelves. The shelf sizes are available in standard sizes with areas measuring from 1.8 m<sup>2</sup> to 16.2 m<sup>2</sup>

and ice condenser capacities of 20 kg up to 180 kg. Modern and ecological refrigerants and heating systems achieve shelf temperatures ranging between -60°C to +50°C.

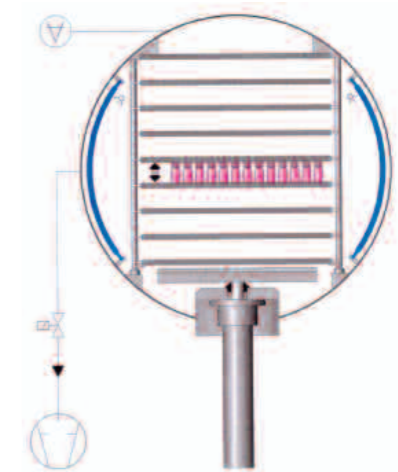
Single chamber units can be supplied as a cabinet or can be built into a wall. The switch cabinet, containing the controls, can either be installed next to the drying chamber (with controls facing the front) or to its side.



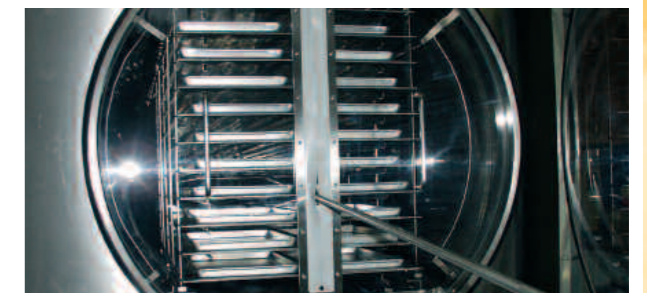
6.1: Production freeze dryer with single-chamber system

### Advantages of the single-chamber system

- simple and user-friendly operation (LSC or Siemens PLC combined with SCADA software LPC)
- high efficiency and short drying periods due to the placement of the ice condenser alongside the shelves
- ability to observe ice layer development during drying and defrosting
- simple cleaning of drying chamber and ice condenser chamber, also available with CIP
- short 20 to 30 minute periods for the defrosting of the ice condenser
- high operational safety
- minimal use of seals, valves and moving parts reduces servicing and maintenance costs
- electro-hydraulic sealing device and variable distances between shelves available upon request
- compact construction, usually within a single frame, saves space and eases transport and installation
- CFC-free refrigerant, using LN<sub>2</sub> as alternative
- the largest standard model Epsilon 2-90/90 has two product chambers that run simultaneously. Specially equipped systems, for example, ones with more powerful cooling and heating systems for the production of special inorganic materials, are available when required



7.1.: Principles of the single-chamber system



7.2.: System with additional inner door for loading within inert gas atmosphere



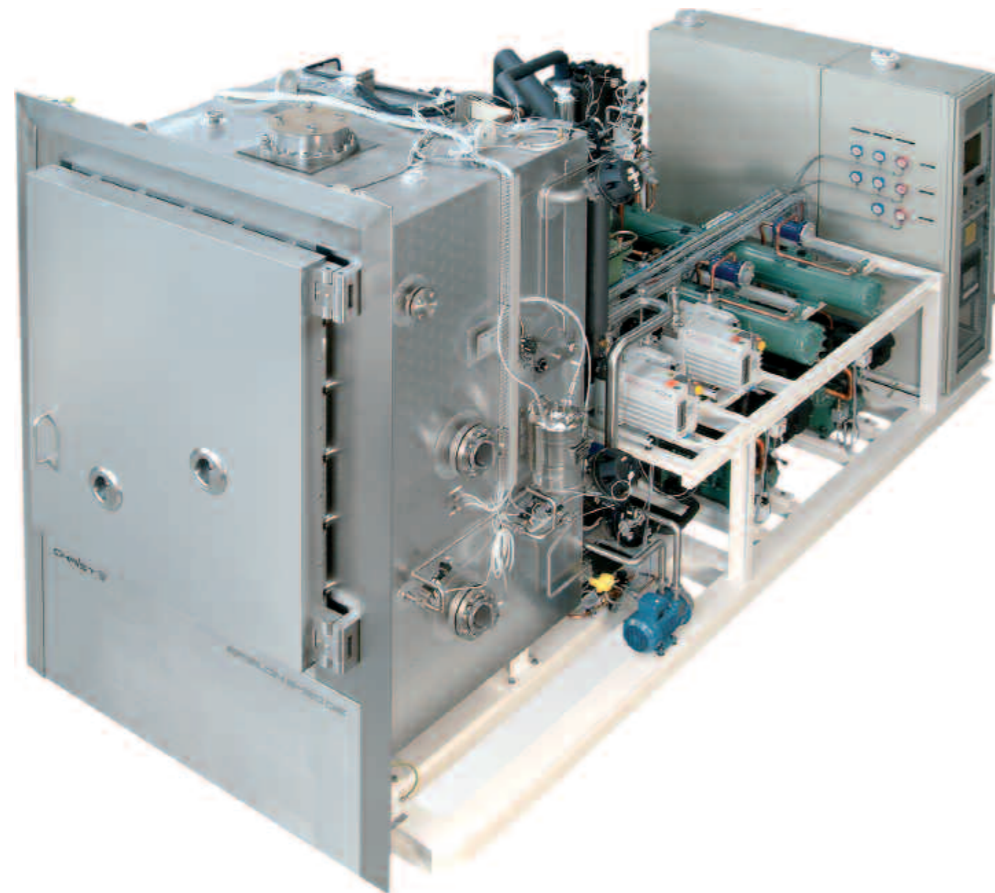
7.3.: Epsilon 2-90/90 with 16.2 m<sup>2</sup> shelf and 180 kg ice capacity

## Production Freeze Dryers: The Double-Chamber System with Patented Design

Martin Christ has developed a pioneering freeze dryer where the ice condenser is positioned directly under the drying chamber (see fig. 9.1). The advantage lies in the large opening that provides the ideal cross section for the dissipation of water vapor. When coping with the enormous vapor quantities produced during drying, avoiding a high pressure difference between the drying and ice condenser chambers is crucial. This is only possible when a sufficient cross section is available. With this in place, the efficiency of the unit's operation is greatly increased. Also, temperature sensitive materials can be dried close to their melting points with the double-chamber system. This ensures shortest drying times.

It is also possible to position the ice condenser next to, or behind the product chamber. Here, a rectangular sealable plate with a built-in electro-hydraulic cylinder creates strong draughts.

The systems are extremely compact due to the integrated drying chambers and ice condensers. Systems equipped with steam sterilization are built into walls, other systems can either be built-in or in cabinet form.



8.1.: Production freeze dryer with double-chamber system (14.5 m<sup>2</sup> shelf area, 160 kg ice condenser capacity, equipped with steam sterilization)

Smaller systems are provided with acrylic glass doors, allowing for observation of the product during the entire freeze-drying process. Systems equipped with steam sterilization have illuminated view ports within the steel doors.

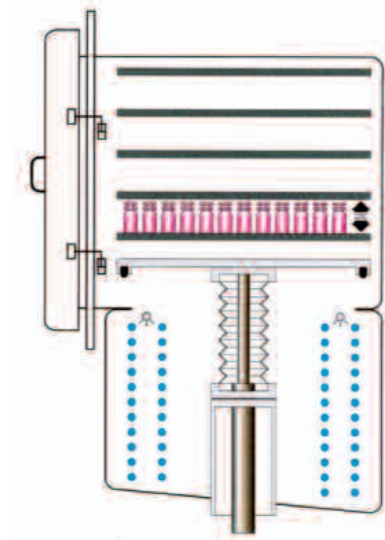
When there is abundant space, the system can be assembled on one frame. This way all component installation can be done prior to delivery. This simplifies the validation process once the system is in place. When necessary, the machine frame can be separately installed from the product chamber and ice condenser. It can also be placed on a different floor.

The sealing of the ice condenser chamber, during defrosting or when determining the end of the drying-phase, can be achieved manually or automatically using the electro-hydraulic sealing mechanism. This eliminates the need for additional intermediate valves and vacuum tight lead throughs. The hydraulic cylinder can be operated from the top or bottom.

Constant loading (where the loading height is constant) is made possible when the hydraulic cylinder is placed on top. In this case a "pizza door" is normally used, although the use of large loading doors can also benefit from this set-up.

The testing of sterile aeration filters in simple non-pharmaceutical processes can be achieved using separate testing equipment. Pall® or Sartorius® tabletop and trolley equipment are compatible. The water necessary for the test can be produced in a vessel inside the freeze dryer or will be provided from the test trolley. The test analysis is then completed by the peripheral device.

In order to fulfill highest pharmaceutical regulations, a fully integrated WIT-system (water intrusion test) is available as well.



9.1.: Principles of the double-chamber system

### Advantages of the double-chamber system

- ice condenser chamber is easy to access and control through the chamber door
- large cross-section between drying chamber and ice condenser chamber; water vapor flow is optimized
- efficient unit operation due to short water vapor distance
- drying of sensitive and low eutectic substances possible due to minimal pressure difference between the ice condenser and drying chamber
- drying and ice condenser chambers are easy to clean
- minimal use of sealing devices facilitates service and maintenance
- simple to validate



## Further Equipment Features of Double-Chamber Systems D and DS (Steam Sterilization)



10.1.: View of ice condenser chamber (with CIP steam sterilization)

### The cooling system

The freeze dryers, depending on their size, are equipped with up to six independent cooling systems. The cooling requirements determine whether the systems function using the ice condenser or the shelf cooling system. Large systems, starting with the Epsilon 2-65D/DS, use the full redundant cooling system while smaller systems have an option to do so.

Freeze-drying systems with an ice capacity of up to 24 kg are equipped with air cooled systems, but can also be provided with water cooled ones. Larger freeze dryers use only water cooled systems.

Production freeze dryers with an ice capacity above 800 kg can be favorably equipped with screw compressors. Central cooling systems for several freeze dryers are also available.

### Water chilling systems

Chilled water for water-cooling systems is, in most cases, provided externally. Systems with ice capacities up to 100 kg can be supplied with compact water coolers. A location where the exhaust can easily be ventilated out of the building must be selected when installing the cooler. The cooler can also be installed outside when covered by a roof.

The use of liquid nitrogen ( $LN_2$ ) as an alternative cooling substance

The advantages of liquid nitrogen-use include high-speed freezing, very low ice condenser temperatures ( $<-100^\circ\text{C}$ ) and quiet operation.

Possible variation:

- shelves and ice condenser can be cooled exclusively with liquid nitrogen
- shelves and ice condenser can be cooled with liquid nitrogen, when conventional cooling is out of order ("emergency cooling")
- liquid nitrogen can be used as a booster to conventional cooling

Further advantages using liquid nitrogen:

- low shelf temperatures
- high control accuracy
- constant ice condenser temperature even at maximum load
- low electrical power requirements
- low maintenance costs
- ecological

### The ice condenser

The ice condenser consists of several bundles of metal tubes each operating from independent cooling systems. The high capacity of each single system adds to the safety of a process. The ice condenser can be sealed off by the pressure plate when defrosting with warm water or steam. The unit can then be charged during the defrosting process.

### The temperature-control system

The temperature-control system for the liquid-cooled shelves of the Epsilon models is filled with low-temperature silicon oil. Electric heating elements are used for the warming phase. These can be replaced without having to drain the heat transfer fluid. In order to avoid the contamination of the product with the oil, there are no movable system connections within the drying chamber. The construction of the vacuum tight leadthroughs allows shelves to be individually retrieved during maintenance.

Steam operated heating systems are recommended for the temperature regulation in case higher energy input is required. We especially recommend them for systems using steam sterilization

### The vacuum systems

The Epsilon freeze dryers are supplied with double stage, rotary vane vacuum pumps. A second vacuum pump is installed beginning with the Epsilon 2-65D/DS dryers to guarantee full redundancy. Smaller units can also be equipped in this way upon request.

The rotary vane pumps can also be replaced by dry vacuum pump systems. The roots pumps used in the larger systems are already running oil-free.



11.1.: Product chamber with shelves in lower position and stainless steel hoses for heat transfer fluid



11.2.: Redundant cooling system



11.3.: Redundant vacuum system

## Optional and Customized Equipment



12.1.: Customized Ice condenser of an industrial unit, arranged sideways



12.2.: Small production freeze dryer with vaporized hydrogen peroxide sterilization

Our specialty is custom-built systems following client specifications. Martin Christ offers expertise, competence and flexibility in providing both standard and customized systems of every dimension. Here are some examples:

### Sterilization SIP (Sterilization In Place) with steam

The sterilization process involves the drying and ice condenser chamber, including all product related parts. Sterile steam is externally provided. Smaller systems can be equipped with an internal steam generator. The sterilization procedure can be programmed to the client's specific needs (for example: 3-pulse evacuation).

The optional cooling system for the drying-chamber walls and door can decrease process time by several hours. This system can also be used for the cleaning with condensation. The chamber walls are cooled during the sterilization phase. The large amount of condensation washes the interior walls and shelves.

### Sterilization of the freeze-drying system with vaporized hydrogen peroxide (VHP)

The last few years have seen an increase in the use of vaporized hydrogen peroxide ( $H_2O_2$ ) when decontaminating the system, alongside steam sterilization and manual disinfection with isopropanol and other substances. VHP is advantageous when the installation of steam sterilization equipment is too costly, but the advantages of a reproducible procedure are needed. A generator of VHP is attached to the dryer through connectors and tubes that feed the gas directly into the freeze dryer. The mobile generator can be used on a variety of equipment.

### The filter integrity test

The Water Intrusion Test (WIT) is used to regularly test the function of the sterile aeration filter. The Martin Christ freeze dryers with steam sterilization have an automatic filter test integrated within the control system. Water for the test is captured within the dryer from steam and the test results are documented on the LPC process-control system.

### Chamber door latch

The Epsilon freeze dryers with steam sterilization have automatic latching systems on the drying chamber doors. The doors' closing mechanisms are located on the unsterile side of the chambers, allowing for easy maintenance.

### Automatic chamber doors

There are instances when hinged doors on freeze dryers are less convenient. Automatically loaded freeze dryers or those assembled in confined spaces may benefit from sliding or slot doors ("pizza doors"). The sliding doors developed by Martin Christ are driven electro-hydraulically on sealing claws and sliding rails. These automatic doors require a minimum use of components within the sterile interior and no greased bearings. System and interface controls are located on the unsterile machine room side of the chamber.

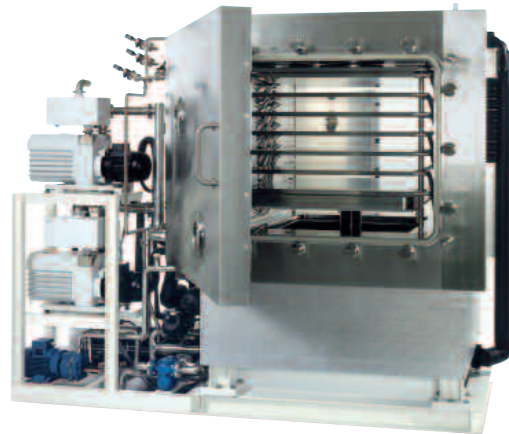


13.1.: System with sliding door

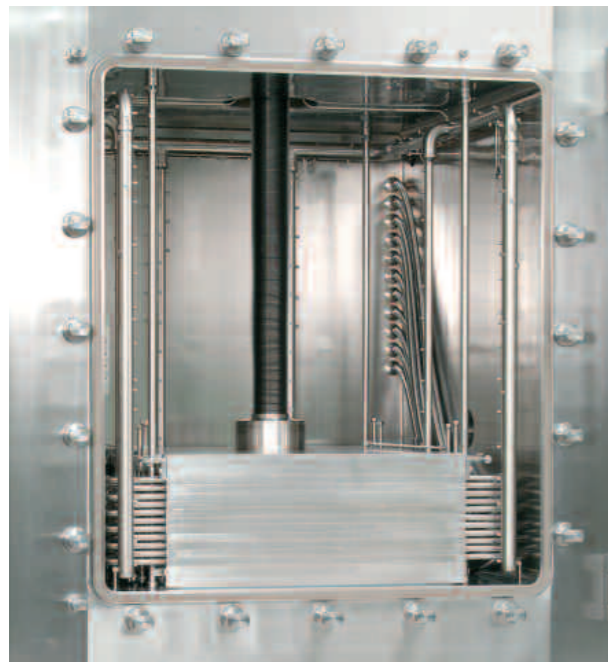


13.2.: Slot or "pizza door" on the Epsilon 2-400 DS with steam sterilization





14.1.: Double door system with separate machine frame



14.2.: Epsilon 2-160 DS with automatic chamber door closures and CIP system

#### Double-door systems

The drying chamber can, when requested, be provided with doors on both front and back of the chamber. The Martin Christ freeze dryers are well suited for this arrangement due to their close connection between the ice condenser and drying chamber.

#### Clean-In-Place (CIP)

Clean In Place is a validated automatic cleaning process. The pharmaceutical industry usually uses Water for Injection (WFI) for cleaning. Acids and alkaloids can also be used. The CIP method can be achieved in a number of ways:

**Spraying of the cleaning agent:** the cleaning agent is sprayed into the chamber through nozzles and valves. The ice condenser, shelves and chamber walls are cleaned effectively and the waste is drained away.

**Sequential spraying of the cleaning agent:** the chamber interiors are sprayed as above, although the nozzles are activated sequentially. This allows for the use of less cleaning solution, but the process takes longer.

**Circulation of the cleaning agent:** the ice condenser chamber is partially filled with cleaning agent prior to cleaning. It then gets sucked out using a CIP pump and sprayed back into the chamber. The waste is drained away after the shelves, ice condenser and chamber walls get sprayed clean.

**Circulation of the cleaning agent using the CIP buffer tank:** the cleaning agent is circulated through the system as above. Meanwhile, the attached buffer tank gets filled. A final rinse is performed when the tank sprays its contents into the chamber. The waste is drained away.



15.1.: Production freeze dryer Epsilon 2-220 D with lateral ice condenser placed next to the drying chamber (30 m<sup>2</sup> shelf area, 220 kg ice capacity)

Systems that can not be steam sterilized must have their chambers dried after the CIP process. A chamber can be dried with a liquid ring pump when a cleaning agent above 70°C is used. Should there only be cold cleaning agents available, then the chamber walls and shelves need to be re-heated in order to dry. This can be done either electrically or with unsterile steam.

#### CIP tank

Depending on the selected CIP-pocedure, an external CIP buffer tank may be necessary. They are in trolley form and come in sizes ranging from 500 L to 3000 L. The tanks are also available, upon request, with their own CIP cleaning (CIP-CIP) and drying system.

## The EPSILON Control Systems



16.1.: LSC-Controller with system diagram for smaller pilot systems



16.2.: Screen showing values



16.3.: Program editing screen

The both Martin Christ LSC or Siemens control systems are tailored to the needs of pilot and production freeze dryers. Many years of experience in the manufacturing of systems of all sizes have contributed to the success of this combination, the result being the development of an uncompromising interface, configuration and communication capability needed for the pilot and production series.

### The attributes of the LSC interface

This type of interface comes with pilot and production systems without steam sterilization if only few custom made features have to be included.

This intuitive, simple to control interface has the following features:

- 1/4 VGA LC display
- graphic user interface with turn and push one-button interface
- clear overview of important process data
- up to 30 freeze drying programs can be entered in tabular form (optional)
- recording of process data using documentation Lyolog LL-1 software
- SCADA-System LPC as Windows software available

Larger pilot and production freeze dryers use an integrated touch-screen with an LPC process control system (see p 18).

The ease in setting product-specific drying profiles on a PC as well as a comprehensive process documentation is very helpful. It can simulate conditions on large production systems (process optimization, scale-up).

### Advantages of the Siemens control system

The most current Siemens industrial interface programs are put to use in conjunction with our LPC software, in all our custom-made freeze dryers and dryers with steam sterilization.

- this combination fills the complex demands on the setting and control of the freeze-drying process, as well as satisfying the safety aspects. It is also very flexible, adaptable to individual customer's needs.
- easily validated SCADA-software LPC
- choice between manual, automatic or program-controlled operation
- universal interface (e.g. RS-232 / RS-485) for data transfer to computer networks, such as the LPC process-control system developed by Martin Christ for the supervision of up to 16 freeze dryers
- reproducible freeze-drying results due to the setting and display of the maximal allowed difference of temperature between freezing and drying (target value/actual value comparison for shelves and product temperatures)
- software controls for process parameters are incorporated into the interface
- vacuum regulation with pressure control valve, air or N<sub>2</sub> injection optional for heightened drying results
- process-specific control of shelf temperature with pressure-sensitive heat setting to avoid partial melting of material
- communication and saving of real time data needed for each process step
- Lyocontrol LC-1 sensor can be connected to determine exact freezing point of a material, improving in-process control of ice/liquid phase of the product
- Programming module for creation, saving and executing of freeze-drying recipes
- automatic aeration, closing and storing of vials
- automatic determination of drying-phase completion through measurement of pressure increase
- immediate calculation and display of set temperature and actual temperature (°K) in pressure (hPa=mbar) and vice-versa according to a material's eutectic point
- warning system that can be connected to a central supervisory control system
- fully automatic steam-sterilization process with display of each phase
- broad production-oriented configuration possibilities with preselection of unit-operation to save energy; integrated display of maintenance needs



17.1.: Industrial PC with SCADA software LPC for system control



17.2.: Additional control panel with manual controls (redundant)

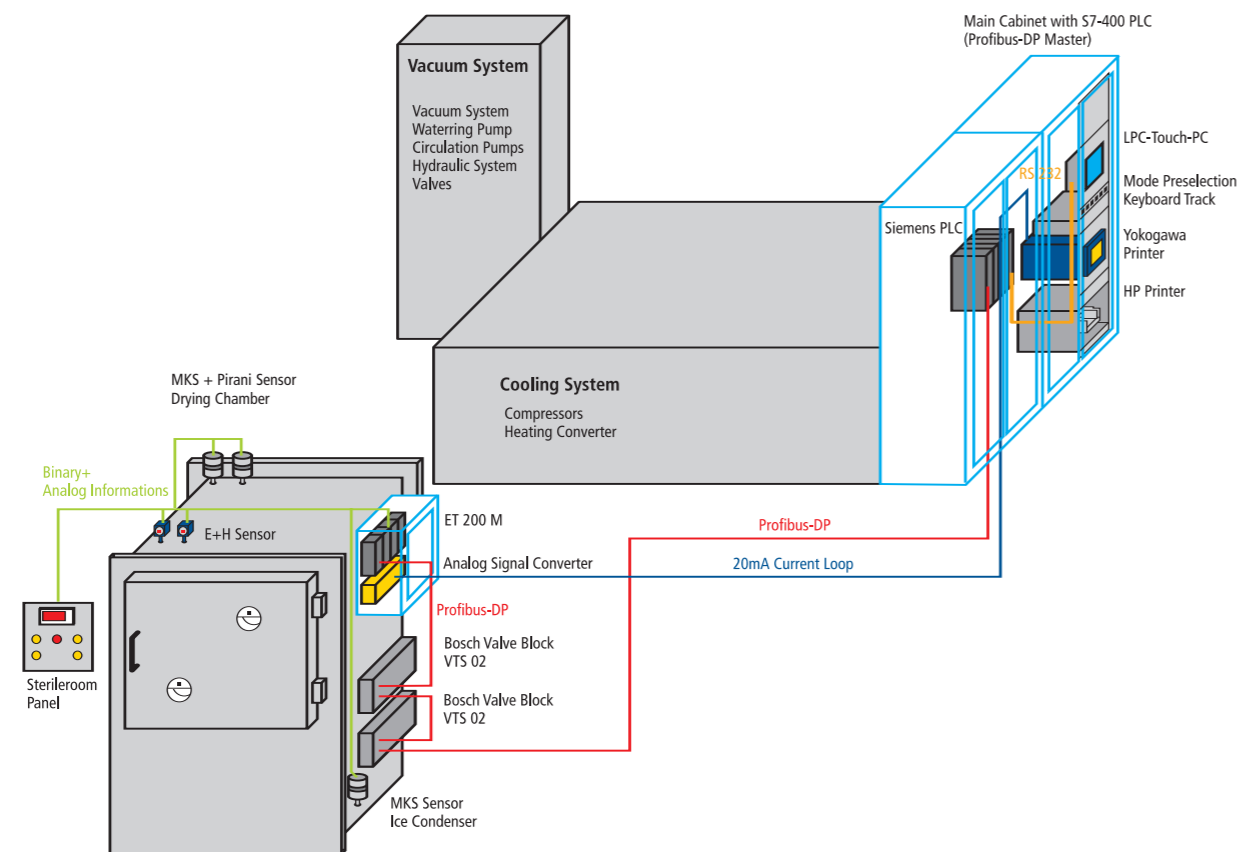


## The Martin Christ LPC Process Control System

The LPC (Lyophilization Process Control) process visualization and control system was specially developed by Martin Christ for the use, supervision and documentation of freeze-drying processes. It is used in complex industrial processes involving large freeze-drying units and complies with the GAMP and CFR guidelines.

LPC is compatible with different system components (e.g. LSC, Siemens-PLC) and with several PC software systems.

The illustration below depicts an example of an interface concept as used by a production system with separately positioned components. Several functions can be controlled within the sterile room. The full process, however, is controlled by the production manager in the operating room or on another remote PC within the network. Communication between the user and the Siemens-SPS is made possible by the SCADA-software LPC.



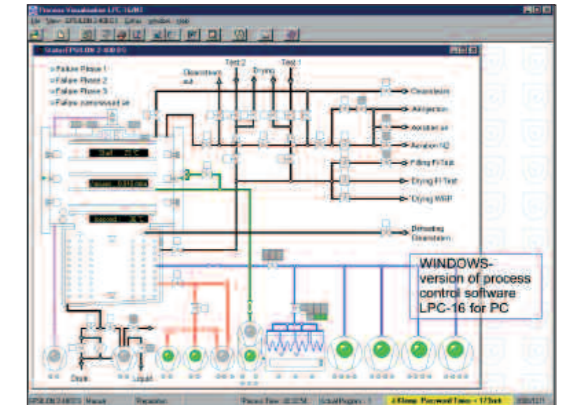
18.1.: Process control concept for an Epsilon 2-500 DS freeze dryer with machine frame located on a separate floor

### An overview of important LPC features

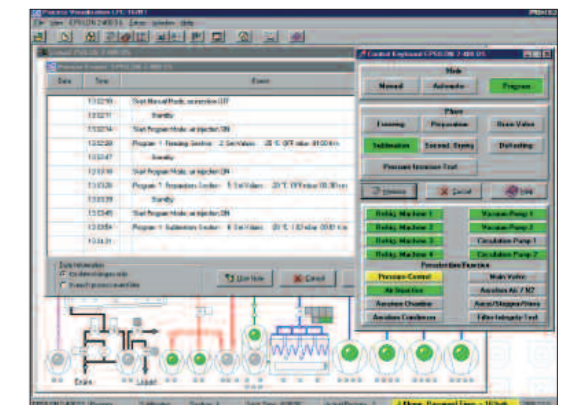
- transparent interface
- graphical display of system's current activity
- graphical display of process with free selection of measurement values and zoom functions
- tables illustrating current status of ongoing process (log book)
- graphic supported creation of drying programs (recipes)
- input of batch-related information
- archive and process documentation including data export (e.g. into Excel)
- plausibility control and user-code checks at data entry
- avoidance of unauthorized entries, configuration changes and program changes
- system security due to different access levels
- optimal data integrity through the use of binary formats that can not be manipulated
- recording of single assigned process file (audit trail)
- data storage through networks or on portable media
- process control from a distance over remote PC
- process information in SMS form can be sent to cell phone

### Custom designed interface

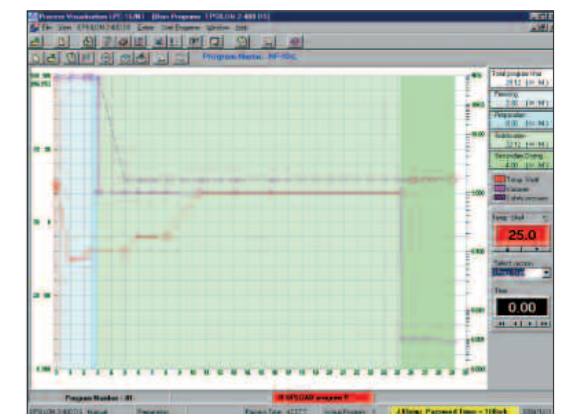
Customer specific interface solutions can be developed, in addition to the freeze-drying system interface and the LPC process control offered by Martin Christ. The LPC process control could be integrated, for example, within another process control system at a plant (factory management).



19.1.: LPC screenshot system flow chart



19.2.: List of process events and user panel



19.3.: Graphic support for FD program creation (recipes)

## The Martin Christ Loading Systems

The previously mentioned ISPE, GMP and GAMP regulations, the EN/ISO 13408 and EN/ISO 14644 norms, the FDA Aseptic Guide guidelines or the relevant EMEA paper have a strong influence on the use of pharmaceutical production plants.

GEP, Good Engineering Practice, is the pivotal term used when planning and running pharmaceutical production facilities. The level of process-automation is an aspect that needs to be addressed right at the beginning of the conceptual planning of a plant, as it influences construction in terms of containment strategies and, therefore, the actual building.

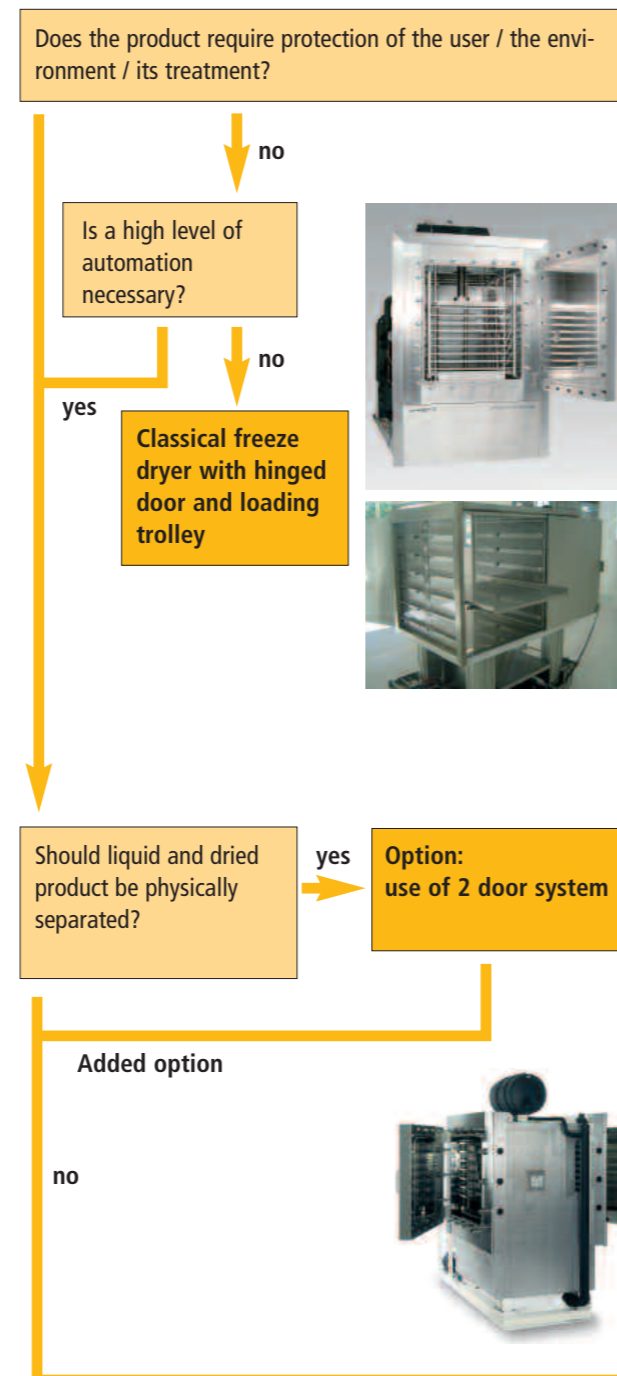
Freeze-dryer loading requires thorough and precise preparatory work. The Martin Christ risk analysis evaluates all the factors that may influence the process, such as the effect the environment has on a material and vice-versa, from the handling and loading of a product up to the capping machine. The precise process and budget information gained from the analysis allows for the creation of a perfectly suited Epsilon system.

### Martin Christ provides the solution!

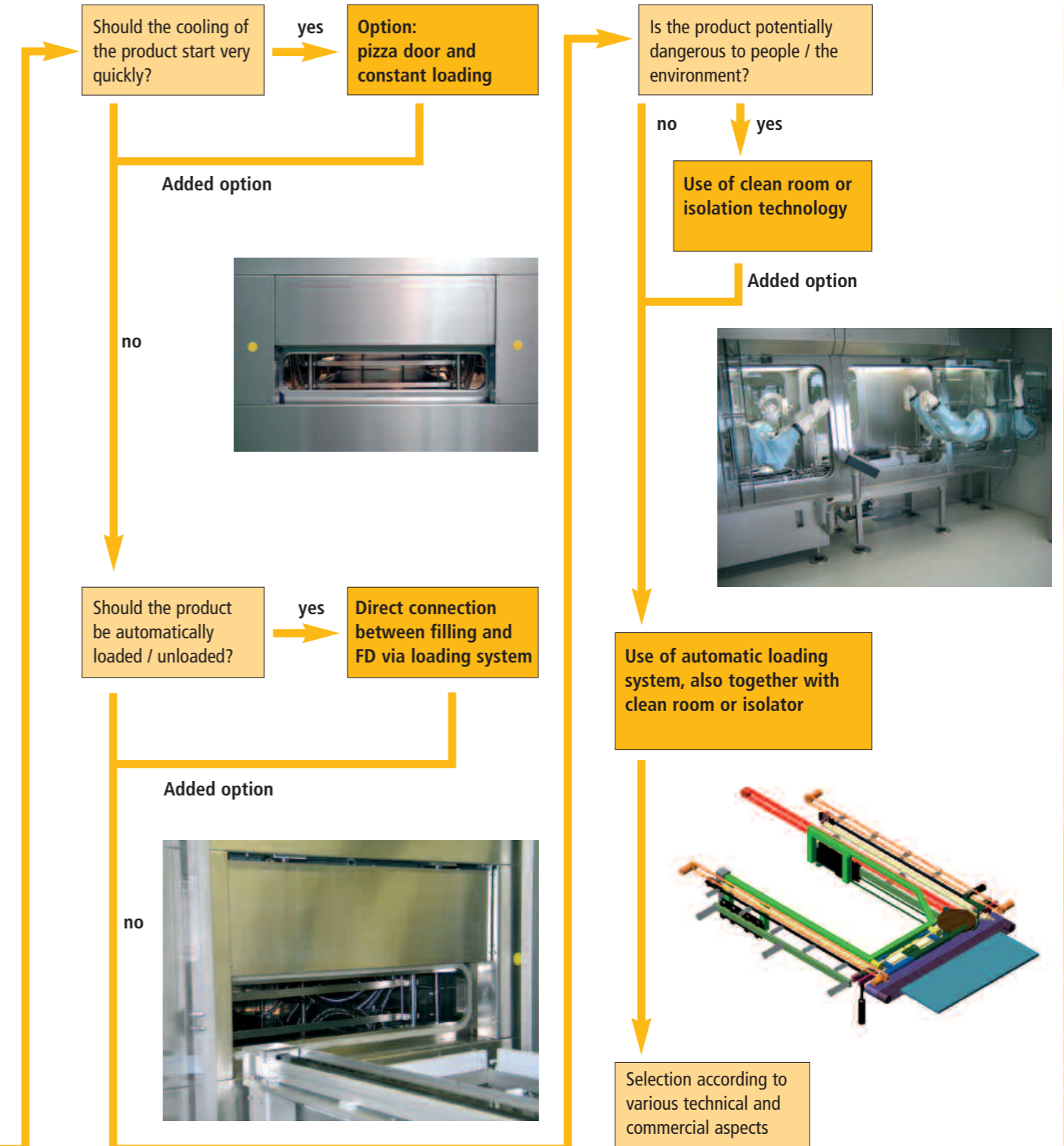
Clean room, RABS or isolator - the balance between the most effective protection and the most economic procedure is difficult to achieve. The cooperation between the ISPE and FDA concerning the definition of RABS (Restricted Access Barrier System), did, however, establish technical clarity for the different strategies. Further components are described in the EN/ISO 14644 and EN/ISO 13408-6:2005.

We provide the analysis, planning and choice of system components, including the perfect combination of the freeze-dryer, cleaning and loading systems. Our many years of successful collaboration with leading manufacturers of additional technologies needed for freeze-drying systems (such as loading systems and isolators) provide us with the ability to offer you the most innovative as well as cost-effective solutions.

We plan and realize the appropriate technical loading and unloading solution following a risk-analysis of your freeze-drying needs, the product and the people behind production.



## The Selection of the Appropriate Technology





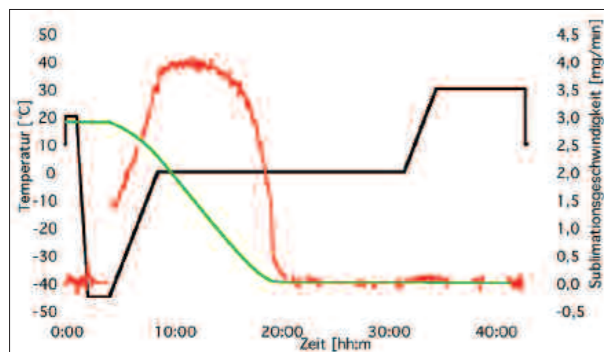
## Process Optimization / Monitoring

### The Martin Christ weighing system for determining the sublimation speed and end of drying

The drying speed should be continually monitored during process test runs. The variable process parameters, vacuum and shelf temperature, should be adjusted until the optimal process is achieved. The weighing system monitors the weight of a substance throughout the entire freeze-drying process, recording precise information on sublimation and process completion.



22.1.: Martin Christ weighing system specially designed for freeze drying



22.2.: Measurement of sublimation speed with the weighing system

This is why Martin Christ, together with a leading manufacturer of precision scales, has developed and patented a compact weighing cell for freeze dryers. It functions according to electromagnetic force compensation, providing an extremely accurate reading. Its small dimensions allow it to reside on any shelf within a pilot or production freeze dryer and it remains there throughout the entire process. The weighing cell uses an arm that is adjusted to the height of the specific vials in order to weigh the substance. The bottle is lifted, weighed and returned to its spot at regular intervals established by the user. As weighing occurs within seconds, the freeze-drying process remains unaltered.

The typical temperature range for the weighing cell lies between a shelf temperature of  $-40^{\circ}\text{C}$  to  $+40^{\circ}\text{C}$ . Resolution at up to 50g is 0.001g. The weighing cell can be used at temperatures between  $-50^{\circ}\text{C}$  to  $+40^{\circ}\text{C}$ . It comes with its own software with which it is used and results are transmitted.

#### Advantages of the weighing cell:

- able to function in a vacuum and under extreme temperatures, remains in the freeze dryer throughout the entire process
- the sample remains on location next to the other vials on the shelf, insuring accurate results
- continual measurements allow for determining sublimation speeds during the process
- easy determination, through weight loss, of the end of drying process

### Lyocontrol LC-1 and Lyolog LL-1

The freezing range of a substance can be determined with the Lyocontrol measuring system. The measured readings, product temperature and electrical resistance provide information about the product's reaction to freeze drying, allowing a safe set of parameters to be determined for the process. The direct integration of data into the automatic process control is possible.

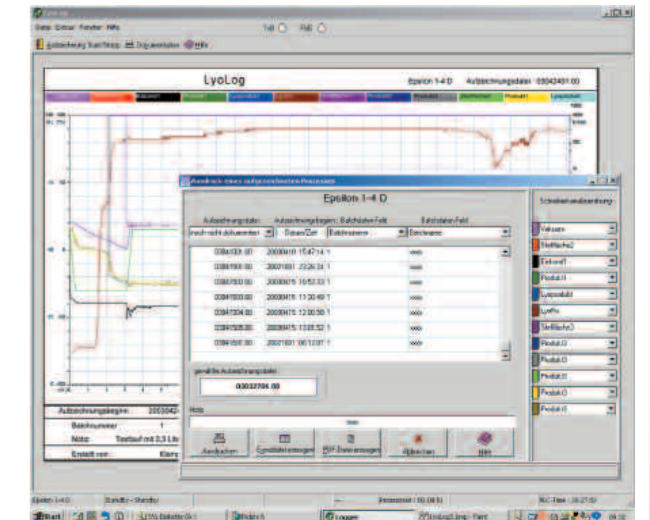
Freeze dryers with the LSC interface system can be directly connected to external hardware including PC's. Our Lyolog LL-1 documentation software allows for direct and precise documentation of batch data and process results (T,p,Rx-curves).

#### Foam drying process

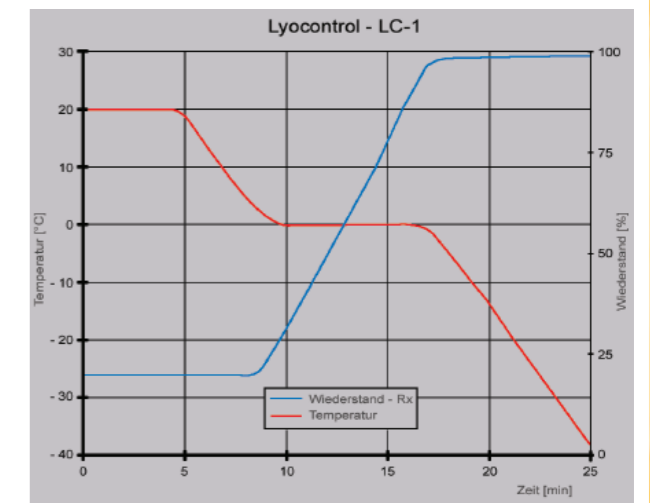
Martin Christ has been involved in a European R&D project of alternative freeze-drying methods. The result is the development of the foam drying process, an alternative method to the classical sublimation process and an additional option for our clients. The foam drying process cuts the freeze drying time by at least half and uses 40% less energy. A freeze dryer equipped for this process needs a special interface as well as a stronger cooling system to cope with the larger water vapor quantities. The liquid nitrogen cooled ice condenser has proved to be a good choice for foam drying.

#### Comparative pressure measurement

The parallel use of two vacuum sensors with different measuring methods can supply process information in addition to the information acquired through conventional product temperature readings and pressure increase tests. The Pirani sensor shows higher absolute pressure values from the start of the main drying phase, as it measures specific gases and is influenced by the large amounts of vapor during sublimation. A capacitive pressure measurement provides a measurement unspecific to particular gases. The intersecting point of both values determines the end of the drying process.



23.1.: Documentation software Lyolog LL-1



23.2.: Determination of freezing point and process monitoring using Lyocontrol LC-1

## Pilot Systems of the Epsilon series



24.1.: Freeze dryer Epsilon 2-6 D for freeze-drying out of solvents



24.2.: System with steam sterilization for scale-up processes and for the production of clinic samples, with an integrated flange for a sample retrieval system (manipulator)

### The highest level of research and process development for successful products of the future

Martin Christ has set the standard for high quality and productive pilot systems with the Epsilon 1-6 to the Epsilon 2-16 D models. These freeze dryers look and function in a very similar way to the large production freeze dryers. The Epsilon models 1-6 D and 2-6 D have the ability to dry on a maximum of six shelves with a total area of 0.42 m<sup>2</sup>. The distance between shelves can be as little as 75 mm when using three shelves. Shelf temperature control with a closed silicone oil loop and the use of stainless steel fulfill the highest pharmaceutical and biotech industrial specifications. Epsilon 2-10 D, Epsilon 2-12 D and Epsilon 2-16 D have areas from 0.6 m<sup>2</sup> to about 1.2 m<sup>2</sup> with up to 10 shelves.

New cooling concepts allow shelf freezing temperatures of -55°C (Epsilon 2-6 D / 2-10 D) and -60°C (Epsilon 2-12 D / 2-16 D) in the very compact double chamber system. This allows for the freeze drying of very sensitive material from the genetic/biotech and pharmaceutical industry, such as substances with amorphous structures and low glass transition points. These systems can be provided with partial or complete liquid nitrogen cooling for special processes. The standard equipped system comes with the pioneering Martin Christ interface LSC (Lyo-Screen-Control) and the Lyolog LL-1 data recording software. Optionally, they can also be supplied with the more powerful Windows based LPC software for PC process control and documentation. This allows for simple creation of process specific drying profiles (recipes). The cGMP guidelines, such as ease of cleaning, smooth high quality product related surfaces and reproducible process parameters, are adhered to. The systems can, if required, be provided with H<sub>2</sub>O<sub>2</sub> sterilization capability and also be delivered with an installation/operation qualification as well. They are sure to stay up-to-date with the future rising standards of the cGMP guidelines. All pilot units are very flexible and are available with additional equipment such as stoppering devices for vials and manifolds for the lyophilization in round bottom flasks.

### Pilot system customized configurations and optional equipment

#### The manipulator

Single vials sometimes have to be retrieved from the freeze dryer at regular intervals during the freeze-drying process. This is in order to measure and record various attributes when analyzing the process during the research and development phase. The retrieval can be simply achieved, without interruption of the freeze-drying process, with the use of the Martin Christ developed manipulator installed on the door of the freeze dryer. A grasping device takes hold of the vial and transports it to an interim vacuum sluice gate where individual vials can be closed. The sample can be retrieved from this site and examined while the freeze-drying process still continues.

#### The glove box

Some freeze-drying processes involve substances that are harmed by or are harmful to the environment. Sometimes the effect on the environment is unknown, sometimes toxic substances are being used. These cases require a drying chamber to be completely sealed from the surrounding room. A mobile glove box docked on to the freeze dryer allows the substance to be manipulated.

Many situations require the combination of glove box and manipulator. The manipulator is then mounted to the side of the machine to avoid collision with the frame and gloves of the box. A video camera assists the handling of the manipulator.

#### Freeze drying with solvents

Lyophilization out of solvents, as opposed to aqueous substances, has become more widespread especially in the pharmaceutical industry. The following solvents all have freezing points that are technically feasible: DMSO (freezing point +15°C), tertiary butanol (+25.5°C), dioxan (+12°C), and acetonitrile (-45°C). Freeze dryers for solvents must be chemical-resistant. Valves and seals must be modified, special vacuum pumps need to be installed and a specially adjusted cooling system needs to be used.



25.1.: Manipulator (Sample thief)



25.2.: Glove box

Leading international pharmaceutical companies use Martin Christ freeze dryers for this purpose. The advantages of solvent freeze drying are the improved structure of the end product, the reduced amount of solvent in the end product and a more gentle drying process.



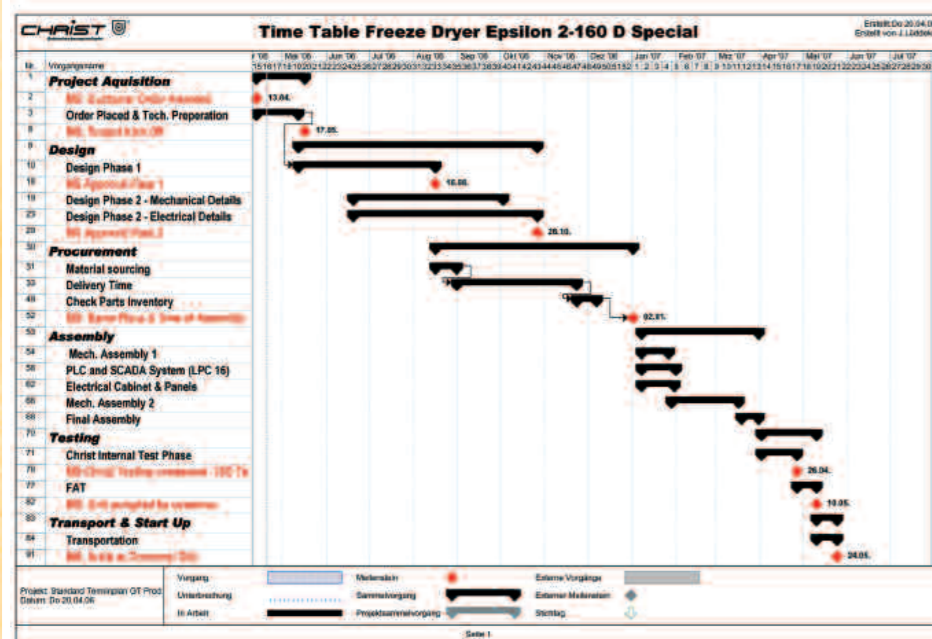
## Martin CHRIST Project Management

As every client, project and task is unique, every Martin Christ Epsilon system is different. However, the paramount end result for us is always the same: Our customer's satisfaction. We can guarantee this satisfaction thanks to our modern project management and efficient planning and executing of complex freeze-drying systems.

Technical dependability and product-specific parameters are always important factors, but the business requirements based on efficiency, speed of production and general flexibility are equally important. This is where the management of investments plays an important role in realizing all the technical, safety and product relevant requirements.

Martin Christ has developed a project management capability based on its many years of experience in the complex field of customized manufacturing. A detailed plan is created right at the start of the negotiations with a client. This plan spells out the exact delegation of tasks and the conditions with which a freeze-drying system can be achieved. It comprises many stages, punctuated by milestones at which progress can be checked. The procedure can be modified should changes be required, and an on-time completion of the project is ensured.

It is very important to maintain continual cooperation and communication with our clients, along with the monthly project-realization reports that we issue to them. This permits quick reactions in the change-control-process of a project. Our focus is on achieving the deadline and remaining within the budget of a given project. The Martin Christ project management accompanies all the phases of system installation from our in-house testing (FAT) to installing, testing and running the system together with our client at its final location (SAT).



26.1.: Excerpt from a project schedule

## Documentation / Validation / Computer Validation

Martin Christ has many years of international experience in the field of system qualification. We provide all the information needed for a safe and smooth operation of a complete freeze-drying system. We will also collect the necessary readings and document them for the IQ (Installation Qualification) and OQ (Operational Qualification), when needed.

The Martin Christ Standard Documents (qualified documentation in the form of cooling plans, electrical plans and technical data) meet the high standards set by the various authorities such as the FDA, PIC, etc. These documents are continually updated to cover new regulations. We also provide customer specific qualification documentation.



27.1.: Our specialists compiling qualification documentation



27.2.: Software Qualification

## Training and Seminars

The Martin Christ company headquarters has the facilities to conduct seminars and other educational events. Sample freeze-drying procedures and other practical exercises can be demonstrated and taught in our research laboratory. Specialists from the pharmaceutical and biotech fields are also available for seminars and lectures.



28.1.: Drying experiment in our application lab

### Applications Seminar

#### Day 1: arrival by 18:00

- All participants meet
- Group discussion with dinner

#### Day 2, begin at 8:30

- Purpose and fields of freeze drying
- Sublimation - physical attributes
- Behavior of substances in vacuums
- Freezing (crystallization / amorphous solidification of substances)
- Preparation of sample materials
- Concept and function of freeze-drying systems
- Process control and choice of parameters
- Establishment of drying process
- Freeze drying of microorganisms and pharmaceutical products (with external speakers)
- IQ/OQ validation
- Practical trials
- Guided tour of company

seminar ends at 16:00

### Operation and Service Seminar:

#### Day 1: arrival by 12:00

- Use of freeze-drying processes, introduction to systems
- RVC 2-18, RVC 2-33, ERROR system, practical exercises
- Control System LSC /LD Plus, sensor calibration, ERROR systems, practical exercises
- Dinner

#### Day 2, begin at 9:00

- Control System LSC/LD Plus, actualization
- Control System LPC 32, use and practical exercises
- Sensor adjustment
- Corrective measures against vacuum, cooling and mechanical problems
- Control Systems (LSC + Siemens)
- Control System LMC3, practical exercise

#### Day 3, begin at 9:00

- Control Systems, practical exercises
- Documentation, general questions

seminar ends at 13:00

## Quality Management

"Focused on quality" - This is more than a slogan for our company: it is the job, commitment, and responsibility of all the employees at Martin Christ. Our excellent reputation amongst laboratories and within the freeze-drying industry is thanks to our self-imposed high quality standards.

The successful implementation in the 1990's of our quality management guarantees our meeting the commitment to provide optimal structures and procedures. Our quality management does not only apply to us internally, but also to those companies with which we cooperate and with whom we share many years of experience. The intensive work relationship with our partners relies on their equally high commitment to quality and service.

The proof of our success in this matter is best illustrated by the certifications we receive, most recently the DIN EN ISO 9000:2000. The auditors of the TÜV e.V. certify us over and over again as a company whose quality management is on the highest international level.

The most important element of our mature level of quality management is, however, our close contact with our clients. Practical experience shows us directly in which areas we need to implement our Continual Improvement Program. We collect continual feedback from the development and manufacturing managers using the Factory Acceptance Test as well as from the final users of our systems.



29.1.: TÜV certificate



29.2.: Final inspection and test of a pilot freeze dryer



## Service Representatives

The Martin Christ freeze-drying systems are successfully used worldwide. An international network of representatives exists to provide assistance and service. Specialists directly from our company are available within Germany for assistance.

Our hotline is always accessible, 24 hours a day, 365 days a year



### Location of selected Martin Christ international representatives

Please check [www.martinchrist.de/contact/distributors](http://www.martinchrist.de/contact/distributors) for a detailed list of Martin Christ representatives.