

2019 PDA EUROPE TRAINING

Freeze Drying in Practice



25-29 MARCH 2019
OSTERODE (HARZ), GERMANY

Overview

Freeze drying, also termed lyophilization or sublimation drying, is a gentle drying technique. It has been used in the pharmaceutical industry for many years to improve the stability of medications.

Biopharmaceuticals in particular require an especially gentle manufacturing process due to their complex and thermosensitive molecular structure. In this regard, freeze drying represents the method of choice for improving storage stability of biopharmaceuticals, which is insufficient in the liquid formulation. While presently already approx. 60% of these products are freeze dried, a further increase in this percentage is to be expected in the coming years.

A freeze drying process is divided into three stages: freezing process, primary drying and secondary drying. The freeze dryers necessary for this are complex, computer-controlled systems. The main components are a vacuum chamber with vacuum pump and ports for attaching the product as well as the cooled condenser, where deposit of the subliming steam from the product occurs on its surfaces. Automated cleaning and sterilization units complete the range of functions. Production freeze dryers are integrated into process lines and equipped with automatic loading and unloading systems to satisfy both aseptic requirements and higher product throughput while at the same time decreasing error rates.

Learning Objectives

You will be thoroughly familiarized with the freeze drying process. The structure and operating principle of freeze dryers are introduced and the interaction of the different functional groups is explained.

You will get to know the regulatory requirements of the freeze drying process. Fulfillment of these requirements and the sequential process steps will be introduced by means of examples.

Emphasis is placed on technical support, calibration of the most important sensors, qualification of the system and preventative maintenance. You will learn how to identify and remedy the most frequently occurring system malfunctions. Understanding the maintenance plan rounds off your skills of servicing a freeze drying system.

Cleaning and sterilization requirements are discussed intensively and their technical application will be demonstrated on the freeze dryer. Technical concepts are introduced for automatic loading and unloading.

Interactive training elements, exercises and experiments in the laboratory and production areas constitute a large part of the course. After you have been familiarized with the theoretical background, you will carry out a freeze drying process to completion under the guidance of experienced experts. The results are examined, potential errors and their avoidance are discussed thoroughly. You will obtain insight into the procedures for cleaning and sterilization and will also carry out these processes yourself.

The practical character of the meeting is furthermore supported by the fact that you may pose questions from your everyday work, which will then be discussed collectively. You will receive advice from the experts and have the opportunity to exchange with the other course participants.

Who Should Attend

This training course is geared to operators of pharmaceutical freeze drying systems. It particularly addresses employees in the areas of

- Production
- Technology
- Qualification/Validation
- Quality Assurance who are responsible for the planning, purchasing, operation, usage and qualification/validation of freeze drying systems.

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Monday, 25 March 2019
12:00-21:00
12:00 Reception and Welcome Snack
12:30 INTRODUCTION

- Collection and clustering of the questions contributed by the participants

13:00 THEORY 1 – INTRODUCTION TO FREEZE DRYING PROCESSES

- Why lyophilization?
- History and Development
- Examples in daily life and pharmaceutical industry
- The freeze-drying process
- Freeze-drying equipment
- Pros and Cons for Lyophilization

13:45 THEORY 2a – BASIC PRINCIPLES OF FREEZE DRYING PROCESSES

- Basic principles of freeze-drying processes
 - › Physical understanding
 - › Critical process parameters
 - › Controlled nucleation
- Product attributes for designing lyophilization cycles
 - › Differential scanning calorimetry
 - › Freeze-drying microscopy

THEORY 2b - FORMULATION DEVELOPMENT OF LYOPHILIZATES

- Development and composition of a (biological) formulation
- Primary packaging components
- Analytical characterization of lyophilizates including solid state characterization
 - › Residual moisture (Karl Fischer, NIR)
 - › Reconstitution time
 - › Thermodynamic state (X-ray powder diffraction)
 - › Specific surface area (BET)
 - › Cake appearance at different levels (visual inspection, 3D scanning, PDMS embedding, SEM, μ CT)

15:00 Coffee Break
15:15 PRACTICE 1 - PREPARATION OF SOLUTIONS

- Compounding of formulations
 - › Calculation of composition
 - › Compounding
- Filling
- Stoppering
- Freezing experiment with distilled water under vacuum to develop a general understanding of the critical temperature

17:15 Transfer to the recommended Hotels
18:00 Transfer from the recommended hotels to the Networking Dinner
18:30 Networking Dinner
21:00 Transfer to the recommended Hotels

Tuesday, 26 March 2019

8:30-17:45

08:30 **Transfer from the recommended hotels to Martin Christ facility**

09:00 **Recapitulation and Summary of Day 1**

09:10 **THEORY 3 - DEVELOPMENT OF A FREEZE-DRYING PROCESS**

- Development of a lyophilization cycle
 - › Which are the most important parameters?
 - › How to choose them?
 - › What happens if they are not chosen adequately?
- Simulation tools
- Finalization of cycles
- Discuss loading scheme

10:30 **Coffee Break**

10:45 **THEORY 4 - PROCESS CONTROL TOOLS**

- Thermal resistance measurement (Lyo-RX)
- Comparative pressure measurement (Pirani/capacitive pressure measurement)
- Barometric temperature measurement (BTM/MTM)
- Wireless temperature measurement (WTM)
- Desorption rate measurement (DRM)
- Conductance sensor
- Inline camera (LyoCam)

11:45 **PRACTICE 2: PROGRAMMING**

- Programming the freeze dryer with the programs developed in Theory 3

12:45 **Lunch Break**

13:45 **PRACTICE 3: FREEZING BEHAVIOR**

- Loading of the shelves
- Positioning of the thermo couples
- Start of the lyophilization program

14:45 **PRACTICE 4:**

- Introduction to the LyoCam technology
- Play-back and discussion of prepared/available video sequences
- Discussion on the correlation of the video sequences with the process parameters using the process graphs
- Time lapse mode for identifying process advancement

15:00 **Coffee Break**

- 15:30** **THEORY 5 - OPERATING PRINCIPLES OF THE FREEZE DRYER**
- Overview of different operating and construction principles of freeze dryers
 - Construction principle of the freeze dryer and its device modules
 - Performance figures (port sizes, condenser sizes, evacuation times)
 - Chamber system
 - Cooling & vacuum systems
 - Filter systems
 - CIP/SIP
 - Interaction of the device modules in the freeze-drying process

- 16:15** **THEORY 6 - LYO QUALIFICATION**
- Explanation of the sequence DQ-RA-IQ-OQ-PQ
 - Measures for maintaining the qualified state

- 17:00** **PRACTICE 5 - A GLANCE AT FREEZE DRYERS**
- Discussion of the current status of the process
 - What is evident/what is not yet evident

17:45 **Transfer from Martin Christ facility to the recommended hotels**

Wednesday, 27 March 2019

8:30-18:15

- 8:30** **Transfer from the recommended hotels to Martin Christ facility**

- 9:00** **Recapitulation of Key Learnings from Day 2**

- 9:10** **PRACTICE 6 - TOUR OF THE PRODUCTION ROOMS OF MARTIN CHRIST**
[Coffee Break included]
- Introduction to the different size classes of freeze dryers
 - Introduction to the functional modules of the freeze dryer
 - Visualization of the basic analogy of the functional modules across the size classes
 - Explanation of the step-by-step production process for freeze dryers

- 11:30** **PRACTICE 7 - INTRODUCTION TO THE GENERAL ORDER OF EVENTS IN OPERATION**
- Brief explanation of all workstations
 - Explanation and instruction on the logistics

- 12:00** **PRACTICE 8**
- **Discussion of the current status of the process in the freeze dryer**

12:30 **Lunch Break**

- 13:30** **PRACTICE 9: WORKSTATION OPERATION SEQUENCE 1**
- Calibration of pressure sensor/vacuum sensor
 - Calibration of temperature sensor
 - Shelf temperature mapping
 - Roughness measurement

14:15	CONTINUATION PRACTICE 9: WORKSTATION OPERATION SEQUENCE 2 <ul style="list-style-type: none">• Calibration of pressure sensor/vacuum sensor• Calibration of temperature sensor• Shelf temperature mapping• Roughness measurement
15:00	CONTINUATION PRACTICE 9: WORKSTATION OPERATION SEQUENCE 3 <ul style="list-style-type: none">• Calibration of pressure sensor/vacuum sensor• Calibration of temperature sensor• Shelf temperature mapping• Roughness measurement
15:45	CONTINUATION PRACTICE 9: WORKSTATION OPERATION SEQUENCE 4 <ul style="list-style-type: none">• Calibration of pressure sensor/vacuum sensor• Calibration of temperature sensor• Shelf temperature mapping• Roughness measurement
16:15	Coffee Break
16:30	THEORY 7 - MAINTENANCE AND FAULT CORRECTION <ul style="list-style-type: none">• Introduction to the most frequently occurring faults<ul style="list-style-type: none">› Diagnosis› Most probable causes› Correction• Introduction to a preventative maintenance concept• Presentation of examples of defective components with explanation of the causes
17:30	PRACTICE 10 <ul style="list-style-type: none">• Discussion of the current status of the process in the freeze dryer
18:15	Transfer from Martin Christ facility to the recommended hotels

Thursday, 28 March 2019**8:30-21:00****8:30** **Transfer from the recommended hotels to Martin Christ facility****9:00** **Recapitulation of Key Learnings from Day 3**

9:15 **THEORY 8 - CIP & SIP**

- Inspection of CIP & SIP systems
- Cleaning validation
- Sterilization qualification
- Turn-around concept

10:00 **Parallel Practice Sessions**
[Coffee Break included]

PRACTICE 11

- Simulation of major faults with freeze driers
- Diagnosis (and simulation) of the correction of major faults

PRACTICE 12

- Explanation of conductance sensor
- Inspection and explanation of the CIP/SIP-functional modules in an industrial freeze dryer
- Riboflavin practice

11:45 **PRACTICE 13**

- Discussion of the current status of the process in the freeze dryer

12:15 **Lunch Break**

13:00 **THEORY 9 (including equipment demonstration)**

- Introduction to the functioning and operation of the RM measuring instrument
- Presentation of theory, function and purpose of the most important analysis techniques for lyophilizates
- Introduction to the measurement of residual moisture

14:00 **THEORY 10 – CONTROLLED NUCLEATION****15:00** **Coffee Break**

15:15 **PRACTICE 14**

- Discussion of the current status of the process in the freeze dryer
- Visual control – examples

16:15 **THEORY 11 – AUTOMATION**

- Loading and Unloading

16:45 **Transfer to the recommended hotels****18:00** **Transfer from the recommended hotels to dinner location****18:30** **Farewell Dinner****21:00** **Transfer from dinner location to the recommended hotels**

Friday, 29 March 2019

8:30-12:00

8:30 **Transfer from the recommended hotels to Martin Christ facility**

9:00 **PRACTICE 15**

- Unloading the freeze dryer
- Evaluation of the process chart
- Determination of reconstitution time
- Visual Inspection
- Assessment of the different results

10:00 **Q&A and conclusions**

12:00 **End of Course**

Faculty



Andrea Allmendinger, PhD, Senior Scientist, Hoffmann-La Roche Basel

Andrea Allmendinger is a pharmacist by training and conducted her studies at the University of Heidelberg in Germany and at the University College London. She holds a PhD in Pharmaceutical Technology from the University of Basel. Andrea joined Hoffmann-La-Roche Basel in 2010, where she currently holds the position as Senior Scientist in the Late-stage Pharmaceutical and Processing Development Department for parenteral products. Andrea is specialized in highly concentrated monoclonal antibody formulations and in particular in the development of freeze dried, parenteral formulations, as well as process development, optimization and transfer of lyophilization cycles. In addition to her role at Roche, she is lecturer at the University of Freiburg in the department of Pharmaceutical Technology and Biopharmacy since 2015.



Klaus Hudel, PhD, Business Development Manager, Martin Christ GmbH

After his studies of chemical engineering at the University of Dortmund, Klaus held a position as test engineer in a public water and waste association. His following position at the well-known German RWTH Aachen University consisted in practical industrial projects. After achieving his PhD in engineering about a thermal treatment topic, he moved to the appropriate industry where he worked as project engineer for big scale drying equipment. For almost 20 years now, Klaus works for in Martin Christ Gefriertrocknungsanlagen GmbH. In his current position as business development manager he is not only responsible for market perspectives and key customer relations, but is also busy in seminars and workshops about freeze drying.



Sascha Pfeiffer, Managing Director, Lyo Engineering

Sascha Pfeiffer is a Pharma Quality Engineer with over 10 years of experience in Pharma Engineering in the area of API Fill Finish. Sascha founded Lyo Engineering in 2013 and holds the role as Managing Director. Lyo Engineering is a Consulting Company in the Areas Management, Freeze Dryer Process Engineering and Quality Issues (Quality Assurance, Qualification and Validation). Sascha is specialized in Quality Assurance Engineering and in technical Transfers, as well as plant process optimization.

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Please bring flat and solid shoes for hands-on sessions.

