

LYOPHILIZATION 2005

March 17-18, 2005 • Brussels Marriott • Brussels, Belgium

Barnett International's Annual Conference on Freeze-Drying

LYOPHILIZATION 2005

Strategies for Successful Formulation, Cycle Development and Optimization, Regulatory Compliance, Validation, and Scale-Up

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Learn from the Real World Experience of Industry Members Working in Formulation, Cycle Development, and Manufacturing!

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KBI BioPharma, Inc.
SP Industries-VirTis & Hull Brands
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Drying Technology
Regeneron Pharmaceuticals*

In-Depth Industry Case Studies and Workshops:

Pre-Conference Workshop on Fundamentals: A College Level Review of Lyophilization

Narlin Beaty, PhD, Sublimation Science

**An Empirical Approach to Developing
an Optimized Lyophilization Cycle:
Formulation and Process Strategies**

*J. Jeff Schwegman, PhD,
Baxter Pharmaceutical Solutions, LLC*

**Understanding the Key Considerations
for Successful Cycle Development and
Process Control**

Pascal Vacus, PhD, Aventis Pasteur

**Comprehensive Process Validation &
Use of Microbalance to Develop a
Freeze-Drying Cycle**

Yves Mayeresse, GlaxoSmithKline Biologicals

**Successful Scale-Up from Pilot Scale to
Production Scale & Selecting a
Contract Site**

Samir U. Sane, PhD, Genentech, Inc.

**Knowing and Fully Utilizing
Your Freeze-Dryer's Maximum
Throughput Capability**

Jim Searles, PhD, Eli Lilly and Company

**Developing a Scientifically Sound
Formulation and Optimizing the
Lyophilization Process**

Frank Bedu-Addo, PhD, KBI BioPharma, Inc.

**Determining Product Performance:
Strategies for Stability Testing**

Karen Bossert, PhD, Regeneron Pharmaceuticals

**Understanding the Various Issues
Relating to Stopper Selection for
Freeze Drying Applications**

Dr. Mike Schäfers, West Pharmaceutical Services

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DAY ONE, Thursday, March 17, 2005

7:30 Conference Registration and Morning Coffee

8:00 Chairperson's Welcome and Opening Comments
Edward H. Trappier, President, Lyophilization Technology, Inc.

Fundamentals: A College Level Review of Lyophilization

8:15 **OPENING WORKSHOP**

Narlin Beaty, PhD, Principal, Sublimation Science

Lyophilization involves diverse academic areas. Yet most of the topics involve physical transformation and phase change rather than chemistry. This review covers a little physics, chemistry, history, and math (very little). In particular, we will review the multiple steps of pharmaceutical lyophilization (just how many are there?), and provide a launch point for further pursuing individual topics in greater depth. Fundamentals which will be reviewed include:

- Formulation excipients – what, when, and why
- Freezing, annealing, enthalpy, refrigeration
- Sublimation, primary drying, vacuum technology
- Desorption, secondary drying, moisture analysis, endpoint determination
- Closures, hydraulics, leaks
- History

9:30 **Understanding the Key Considerations for Successful Cycle Development and Process Control**

Pascal Vacus, PhD, Head, Center of Expertise in Lyophilization, Aventis Pasteur

Comprehensive cycle development requires a solid technical frame coupled with modern tools to allow developers to support and document the cycle rationale. In addition, final success requires investigating cycle robustness and process control to cope with scale-up and routine operation issues. Detailed steps are proposed:

- Consider the critical specifications of freeze-dried products
- Understand how the different cycle steps affect the finished product
- Determine the critical product temperatures (eutectic point, glass transition, collapse, etc.) by using thermal analysis technologies (DSC, microscopy, etc.)
- Establish acceptable ranges for proven process robustness by conducting rationale studies at time/temperature/pressure boundary combinations
- Anticipate scale-up and routine operation issues by checking practical limits on operating conditions
- Recognize the key factors of successful lyophilization process control, their main limitations, and how to maintain them at an acceptable level

10:30 *Mid-Morning Break*

10:45 **Developing a Scientifically Sound Formulation for Optimal Lyophilization**
Vicky Kett, PhD, School of Pharmacy, Queen's University of Belfast, and Kevin R. Ward, BSc, PhD, MRSC, Director of Research and Development, Biopharma Technology, Ltd.

- Understanding product formulation specifically for lyophilization – use of excipients and lyoprotectants
- How will excipients affect the freezing and drying behaviour of the formulation?
- Impact of excipient behaviour on the final product qualities
- Product analysis prior to lyophilization using freeze-drying microscopy and thermal methods
- Importance of formulation characteristics for devising new freeze-drying cycles and “optimizing” old cycles
- Thermal analysis of lyophilized products for stability prediction purposes

11:45 **Use of Microbalance to Develop a Freeze-Drying Cycle**

Yves Mayeresse, Freeze-Drying Manager, GlaxoSmithKline Biologicals
Sublimation rate is a key parameter to develop and optimize a freeze-drying cycle. For instance, product probes are classically used to estimate end point of the primary drying during a cycle; now the microbalance can give the precise value. Moreover, the drying rate can be followed and interpreted during the whole primary drying. The desorption phase can be started with a known quantity of residual moisture avoiding collapse due to a not adapted heat input. By varying the parameters of your cycle and formulation, you can evaluate the impact on each of them on the optimization of your cycle. During the presentation, the following points are addressed:

- Principle of a microbalance *in situ* measurement
- Influence of pressure, temperature, and concentration of excipients on freeze-drying rate for a model formulation
- Statistical analysis of the obtained curves
- Interpretation of the values obtained in respect of freeze-drying theory

12:30 *Luncheon*

1:45 **Developing a Scientifically Sound Formulation and Optimizing the Lyophilization Process**

Frank Bedu-Addo, PhD, VP Process Development and Biopharmaceutics, KBI BioPharma, Inc.

The presentation will address important issues to be considered when developing a lyophilization process for a biological formulation. The advantages and disadvantages of various excipients and their effect on product integrity will be discussed. Common mistakes in developing such products will also be addressed. A case study will be presented.

- Consider important factors when developing a lyophilized biotech product
- Avoid committing common mistakes
- Understand the use of biophysical characterization tools in developing lyophilized biological products
- Maximize success in the development of lyophilized products

2:30 **Determining Product Performance – Strategies for Stability Testing**
Karen Bossert, PhD, Vice President, Regeneron Pharmaceuticals

The process of lyophilization is done specifically to stabilize a compound and/or a product. However, how do you really know that the product is stable? And how long will it remain stable? This session examines the regulatory requirements for stability of lyophilized products and provides training on the tools and techniques available for assessing stability.

- Examining stability requirements worldwide
- Characteristics of lyophilized products monitored on stability
- Analytical techniques for assessing stability

3:15 *Mid-Afternoon Break*

3:30 **Successful Scale-Up from Pilot Scale to Production Scale**
Samir U. Sane, PhD, Senior Process Engineer, Genentech, Inc.

Implementing a robust lyophilization process on production scale is a critical step to ensure reliable manufacture of a product for clinical or commercial supply. The implementation can be especially challenging if it is performed at a contract site. This session will discuss the key considerations involved in scaling up lyophilization processes from pilot-scale freeze-dryers to production-scale freeze-dryers. For example:

- Approaches to process characterization and development studies
- Selection of surrogate formulation
- Impact of equipment and facility differences
- Selection of process tolerances
- Process monitoring – pressure rise testing

The presentation will also include a case study describing lyophilization process scale-up for a pharmaceutical protein at a contract site. Considerations involved in selecting a contract site will also be discussed.

4:15 **Examining Current Trends in Lyophilization Cycle Control – Vapor Pressure Induced Pressure Rise, Product Temperature Profiles, Case Study Implementation of PV/CM and BE in Freeze-Drying**
Lawrence Ulfik, Director, Sales Laboratory Products, SP Industries-VirTis & Hull Brands

This session looks at current trends in lyophilization cycle control, and how and when the various methods can be used to maintain consistency in lyophilization cycles. The presenter explores the benefits and drawbacks of each technique, and offers strategies and a case history describing pitfalls and successes. Your instructor provides an understanding of how barometric endpoint and Pirani/Capacitance differential can be used during primary and secondary drying to assist in endpoint determination. In addition, the presentation covers regulatory/cGMP guidelines as they apply to lyophilization and cycle control.

- Exploring the role of shelf surface temperature and shelf inlet temperature in the freeze-drying cycle
- Learning how a temperature sensor reacts in product during freeze-drying, and use of special TC probes
- Knowing how shelf edge effects can be minimized using thermal-guard trays and chamber wall heating and cooling to minimize edge effects
- Understanding how time based controls function in some lyophilization control systems

5:00 *End of Day One Main Sessions, and Half Hour Break*

Communication Link: An Open Forum sans PowerPoint

5:30 **INTERACTIVE FORUM Begins in Marriott's Lounge**
Facilitator: Narlin Beaty, PhD, Principal, Sublimation Science

This session will provide a forum for discussion of lyophilization issues that haven't been addressed in the formal meetings. It is an opportunity for you to get the opinion of experts about your concerns. Your questions can be brought up at the session, submitted prior to the session, or submitted with your registration. Issues for discussion might include the following:

- Leak rates and leak testing – what to do?
- Do you need solid-state collapse temperatures?
- What about pressure rise endpoint determination?
- How should lyophilized products be visually inspected?
- What is the correct chamber pressure for stopper placement?

Your facilitator: Narlin Beaty, PhD, is the Principal at Sublimation Science, a service organization to the parenteral pharmaceutical industry specializing in lyophilization commissioning, cycle development, and both machine and product cycle validation. He retired from a career as the Chief Science Officer at Chesapeake Biological Laboratories, Inc., in Baltimore Maryland. Dr. Beaty has 22 years of experience in diverse areas of sterile manufacturing, engineering related to fill and finish of pharmaceuticals, sales, and contracts. Over the past two decades, he has been closely involved in the transfer of scores of processes from the development lab to commercialization. In addition to lyophilization projects, Dr. Beaty is knowledgeable in test method development and testing validation; sterile process design and manufacturing validations; preparation of clinical trial materials; container-closure system design; and accelerated and ongoing stability studies. He holds BS and MS degrees from the University of Texas at Austin, and a PhD in Biological Chemistry from the University of Michigan at Ann Arbor. His current professional associations include the American Association for the Advancement of Science, and the American Chemical Society.

7:30 Morning Coffee

7:45 Chairperson's Welcome and Opening Comments
Karen Bossert, PhD, Vice President, Regeneron Pharmaceuticals

A Two-Part In-Depth Case Study Presentation

8:00 **Case Study** **An Empirical Approach to Developing an Optimized Lyophilization Cycle: Formulation and Process Strategies**
J. Jeff Schwegman, PhD, Research Scientist, Baxter Pharmaceutical Solutions, LLC
The goal of the formulation/process development scientist when designing a lyophilization cycle is to produce a stable, safe product in the shortest amount of time, using the most robust cycle. By taking an empirical approach to freeze-drying through thermal analysis studies and targeted pilot studies, it is possible to significantly reduce overall cycle time by eliminating the number of pilot runs, and by maximizing the sublimation rate by working closer to the critical temperatures. Specifically:
Part I – Pre-Lyophilization: Formulation and Thermal Analysis Techniques

- Understand how to use, and the importance of using, thermal analysis techniques to characterize the properties of a frozen system
- Understand the technique of annealing, how it can benefit/stabilize formulations, and how to determine if your formulation requires an annealing step
- Learn about the common excipients added to lyophilized formulations and how to choose them
- Evaluate case studies in failed products/cycles, and learn how to diagnose and prevent these problems in the future

Part II – Lyophilization Cycle Development, Dried Solids Characterization, and Stabilization of Problematic Formulations

- Understand how to use targeted pilot studies in a lab-scale dryer to develop an optimized freezing, primary drying, and secondary drying protocol
- Understand the various techniques used to characterize the final freeze-dried solids and why these techniques are important in development
- Learn formulation tips and techniques that can be used to help stabilize problematic formulations (specifically biological formulations)
- Evaluate case studies in failed products/cycles, and how to diagnose and prevent these problems in the future

9:00 **Understanding the Various Issues Relating to Stopper Selection for Freeze-Drying Applications**
Dr. Mike Schäfers, Director, Scientific & Technical Customer Services Europe/Asia Pacific, West Pharmaceutical Services Deutschland
This presentation will discuss selection criteria and technologies that have to be taken into consideration in order to meet the increasing requirements of pharmaceutical and biopharmaceutical companies for lyophilization stoppers. Excellent machinability, protection of the drug against volatiles or leachables from the elastomeric closure, and protection of the drug against moisture and oxygen permeation through the closure, are just a few features of a modern lyophilization stopper. The improvements made in the area of rubber formulas, but also special coating technologies to meet these requirements will be presented. In addition, case studies will summarize experiences and recommendations concerning appropriate stopper selection for freeze-drying applications.

9:45 Mid-Morning Break

10:00 **Control of Residual Moisture Content of Vials During the Freeze-Drying Processes**
Dr. Dietrich Gehrman, CEO, Drying Technology, former Head of "Drying Technology" of Bayer Technology Services
Control of residual moisture content is one of the important tasks of guiding freeze-drying processes. Due to the differences of lab scale, pilot, and production freeze-dryers, the analytical signals (temperatures, system pressure, partial pressures of gases) have different significance. Based upon the knowledge of the freezing and drying processes in freeze-dryers, the classic and new possibilities of controlling the residual moisture content of vials are described.

- Determination of the freezing and drying behaviour of freeze-drying equipment (lab, pilot, production scale)
- Quantification of this behaviour
- Assessment of different control methods
- Conclusions

10:45 **Knowing and Fully Utilizing Your Freeze-Dryer's Maximum Throughput Capability**
Jim Searles, PhD, Senior Research Scientist, Global Parenteral Commercialization Technology Center, Eli Lilly and Company
The throughput of a freeze-dryer can be defined as the number of vials of a given product that it will produce in a year. Higher throughput represents a more effective use of this capital asset, and provides more medicine manufactured at a lower cost. This enables more patients to receive the medicine, and frees up capital for use in discovering and developing new pharmaceuticals. Your session leader will present the results of a comprehensive effort at Eli Lilly to characterize the maximum drying rate capability of all of our freeze-dryers, and show how these findings provided critical input into a freeze-drying cycle optimization project that was taking place at the same time. The dryer capability and cycle optimization projects will improve Lilly's freeze-drying throughput by over 20% worldwide. Your presenter will also cover the factors controlling the maximum drying rate capability, including Lilly's recent discovery of choked water vapor flow in freeze-drying. This session will feature an extended opportunity for Q&A.

11:45 **NCCW: In-Line Non-contact Inspection with NMR Presents New Opportunities and Challenges in Process Control**
Jos Corver, Senior Scientist, BOC Edwards Pharmaceutical Systems
BOC Edwards develops in-line measurement equipment to determine the product quality of every single product dosage. This fits well within the PAT framework as defined by FDA. One of the first deliverables of this development is the Non-Contact Check Weigher (NCCW) based upon NMR. Besides 100% weight measurement, it is clear that with a filling system the feedback of the measured results improves the filling accuracy significantly. The session will illustrate some of the background, and will identify potential other applications especially on moisture determination of the freeze-dried product.

- Understand the working principle of this new measurement technique
- Identify the applicability of the technique for product quality improvement
- Define next steps to implement this technology in the production environment

12:30 Luncheon

1:45 **Using Smart Freeze-Dryer™ Technology as a Process Analytical Technology (PAT) Tool**
Joseph F. Brendle, Director, Technology and Business Development, FTS Systems, Inc.
Smart Freeze-Dryer Technology provides process information not previously available to those involved in developing and troubleshooting freeze-drying processes. This session will present an overview of Smart Freeze-Dryer Technology, and show how the data available from the system may be used to better understand the effect of process parameters and process parameter changes on the freeze-drying process. The data and analysis can be applied as a part of a company's overall PAT initiative.

- Become familiar with the fundamentals of Smart Freeze-Dryer Technology
- Understand the data available from Smart Freeze-Dryer Technology
- Learn examples of how to apply Smart Freeze-Dryer Technology as a PAT tool

2:30 **Comprehensive Process Validation**
Yves Mayeresse, Freeze-Drying Manager, GlaxoSmithKline Biologicals
Three parameters need to be optimized to obtain a successful product: the formulation, the freeze-drying cycle, and the freeze-dryer. This session focuses on the last one. A deep knowledge of the freeze-dryer obtained through validation helps you to better interpret your results at R&D level, to scale-up easily your product, and to implement it in production freeze-dryers. Specifically, this presentation covers the following topics:

- Strategies for validation of the freeze-dryer from the DQ to the PQ
- Establishing the link between product, freeze-dryer, and freeze-drying cycle
- Adding value to your process with a rational validation approach
- Increasing your knowledge of the freeze-dryer to better improve your freeze-drying cycle

3:30 Afternoon Break

Risk Assessment and Root Cause Analysis in the Lyophilization Process

3:45 **Workshop Begins**
Process excursions of critical process parameters warrant a deviation investigation as to the root cause, and an assessment of the impact on finished product qualities. Consideration of excursions includes relative magnitude compared to a proven acceptable range (PAR) of processing parameters. This session will review establishing such ranges for PAR during development. Events that can occur outside a PAR will also be discussed relative to the risk assessment and impact on finished product quality. Illustrations of abhorrent processing conditions and product abnormalities will be used during this interactive workshop to develop possible root causes and assessment of the impact on finished product qualities. Examples of events and observations include:

- Examining potential issues in freeze-drying – Critical verses non-critical excursions
- Understanding what is and is not a problem – What constitutes a cycle deviation? How conservative do you need to be?
- Using PAR to minimize cycle deviations
- Variations in finished product attributes – What causes them and what can be done? i.e., physical appearance (melt back, collapse, etc.) and residual moisture
- Strategies for reviewing cycle data to identify potential root causes of the problem

About the Workshop Leader

Edward H. Trappier is President and Founder of Lyophilization Technology, Inc., a contract research and technical services firm dedicated to freeze-drying. He has over 25 years experience in lyophilization that ranges from product development to equipment application engineering. He received his Bachelor of Science degree in Chemistry at The College of New Jersey. His experience in the pharmaceutical industry includes product development, toxicology supply preparation, clinical manufacturing, and parenteral production.

5:00 Close of Conference

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VENUE INFORMATION

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