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Lyophilization

*Optimizing the Lyophilization Cycle through
Strategic Application, Processes and Technologies*

JUNE 25-26, 2007 • RADISSON-PLAZA WARWICK • PHILADELPHIA, PA

***Featuring Case Studies and Lessons Learned from Industry Experts from
Multiple Scale-Up and Cycle Development Projects!***

- Explore Current Methods in Cycle Development and Control
- Developing a Lyophilization Process that is Beyond Trial and Error
- Excipient Selection and Thermal Analysis of Formulation and Finished Product
- Chamber Considerations for Primary and Secondary Drying
- *Comprehensive Coverage!*
Understanding Container and Closure Needs for Lyophilized Drug Products

Featuring In-Depth Regulatory Coverage:

Understanding FDA Requirements for Lyophilized Products

Karen A. Bossert, Ph.D., R.Ph., Vice President, Lyophilization Technology, Inc.

Global Regulatory Requirements for Sterile Lyophilization

Douglas Stockdale, President, Stockdale Associates, Inc.

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Monday, June 25, 2007

8:30 **Chairperson's Welcome and Opening Remarks**
Karen A. Bossert, Ph.D., R.Ph., Vice President, Lyophilization Technology, Inc.

CASE STUDY

8:45 **Developing a Lyophilization Process that is Beyond a "Trial and Error" Method**
Lisa M. Hardwick, Associate Research Scientist, Baxter BioPharma Solutions

This presentation will stress the benefits of a systematic and simultaneous development of formulation, container/closure, processing conditions, and lyophilization cycle to efficiently bring a product to market. The following will be discussed:

- Excipient choice
- Thermal analysis of formulation and finished product
- Appropriate vial size and product fill volume
- Best choices for rubber closures
- Effect of product contact materials during processing
- Chamber conditions for primary and secondary drying

10:00 *Refreshment break*

10:15 **Lyophilization of Biopharmaceuticals: Considerations During Scale-up and Process Validation**
Shan Jiang, Ph.D., Principal Development Scientist, BioProcess Development, ZymoGenetic, Inc.

The manufacturing of lyophilized biopharmaceutical products requires the development of robust and efficient lyophilization cycles, to ensure effective transfer/scale-up. Typically, lyophilization cycles are developed using small-scale lyophilizers in an uncontrolled environment.

The efficiencies and capabilities of commercial-scale freeze-dryers may not match those used during development. Likewise, the processing environment can affect the lyophilization process and product characteristics. As such, challenges are often encountered during process transfer/scale-up. Meanwhile, laboratory scale studies can provide reasonable scientific approximations of manufacturing-scale operations and are useful for conducting process validation/characterization studies that would be impractical to perform at manufacturing scale.

This presentation will introduce some challenges and problem resolution experiences with lyophilization cycle transfer/scale-up, and summarize the strategy and practical approach of process validation.

- Troubleshoot challenges during cycle transfer/scale-up
- Developing a process validation strategy that includes a practical approach
- Acceptable operating range studies of lyophilization cycle

11:00 **Clinical vs. Commercial Manufacturing – Considerations for Lyophilized Drug Products**
Karen A. Bossert, Ph.D., R.Ph., Vice President, Lyophilization Technology, Inc.

Lyophilized drug products are sterile, solid dosage forms which are manufactured using unique processing technology. As drug products evolve from initial design through early phase clinical manufacturing, to late phase clinical manufacturing, final scale-up and commercialization, many aspects of the dosage form may also change. This talk examines various aspects of lyophilized drug products, including cycle definition, interpretation of cycle data, validation, sampling and testing, and scale, and their impact on acceptability of finished product. Also included are case studies which highlight potential issue with site and scale changes required when moving from clinical to commercial manufacturing.

12:00 *Luncheon*

REGULATORY UPDATE: FDA AND GLOBAL REGULATORY REQUIREMENTS

1:30 **Understanding FDA Requirements for Lyophilized Products**
Karen A. Bossert, Ph.D., R.Ph., Lyophilization Technology, Inc.

Lyophilized drug products are sterile, solid dosage forms which are manufactured aseptically using unique processing technology. The regulatory requirements for lyophilized products are a challenging combination of those designed for applications other than just lyophilization, including manufacturing facilities, equipment, characterization of solid materials, aseptic processing, and sterilization validation. This talk examines applicable regulations and reviews relevant 483 observations for lyophilized drug products.

2:15

Global Regulatory Requirements for Sterile Lyophilization

**Douglas Stockdale, President,
Stockdale Associates, Inc.**

The global regulatory requirements for sterile lyophilized medicines are extensive for this unique manufacturing process. This presentation will encompass:

- Global licensing requirements
- Equipment qualification and validation
- Product Design Qualification
- Regulatory inspection areas of concern

“The scale-up and change of lyophilization cycles, including the freezing procedures, have presented some problems. Studies have shown the rate and manner of freezing may affect the quality of the lyophilized product.”

— FDA’s “GUIDE TO INSPECTIONS OF LYOPHILIZATION OF PARENTERALS”

3:00

Refreshment Break

CASE STUDY

3:15

Case Study: Key Considerations in Lyophilization Selection and Scale-Up
Scott A. Harris, Senior Manager of Aseptic Production, Pharmaceutical Products Division, Abraxis BioScience

There are many challenges that must be overcome to starting a Lyophilization Department, particularly within the confines of a mature pharmaceutical plant. Careful consideration must be paid to the location of both the mechanical room and the connection of the chambers to the existing aseptic complex. Access from both the high-level and low-level sides will pay major dividends during installation and validation of each lyophilizer. An evaluation of the cost benefit of installing one lyophilizer

at a time or installing the lyophilizers in groups must be assessed. A thorough analysis of potential product transfers and new products must be considered in selecting the size, design and ancillary systems of the lyophilizers. An appropriate transfer method from the fill room to the lyophilizer must be developed that fits within the confines of the existing aseptic complex. Once the lyophilizers begin arriving; equal attention must be given to the organization, training and support equipment of the department to ensure successful validation and subsequent production of lyophilized products.

This presentation will discuss the key factors in designing a Lyophilization complex, selecting the right lyophilizers, including:

- Additional items and utilities that should be included in a Lyophilization complex. (WFI ports, Central HEPA filtered Vacuum, Alarm system)
- Identifying necessary design features of the lyophilizers for current and future products. (Compressor or LN2, # of shelves, shelf height)
- Using IQ and OQ data to demonstrate equivalency of the different lyophilizers to the FDA.
- Organization, training and equipment required for a Lyophilization department

4:45

Chairperson’s Closing Remarks and Close of Day One

Tuesday, June 26, 2007

8:45

Chairperson’s Day Two Opening Remarks

CASE STUDY

9:00

Development, Robustness Studies, and Scale-up of a Lyophilization Cycle for a High-Concentration Protein Formulation and Challenges when Transferring to a Contract Fill-Finish Site

**Linda M. Maldonado
Bioprocess Associate IV, Team Leader,
Human Genome Sciences**

A 2-day freeze dry cycle was developed for a high-concentration protein formulation lacking any crystalline bulking agent and containing disaccharide as the principle excipient. DSC and freeze-dry microscopy were used to characterize the frozen system. Product concentration had a larger impact on collapse temperature than on Tg'. Primary drying with a product temperature above Tg' had no apparent impact on cake appearance, reconstitution

“The sterilization of the lyophilizer is one of the more frequently encountered problems noted during inspections.”

— FDA’s “GUIDE TO INSPECTIONS OF LYOPHILIZATION OF PARENTERALS”

time, post-reconstituted protein structure (by FTIR), or stability. Therefore primary drying was set under conditions where product temperature was above T_g but below collapse temperature in order to reduce overall cycle time. A design of experiment study (using JMP software) was used to assess cycle robustness, and the cycle was transferred to a contract site. This case study will take you through the developing and optimizing of a robust lyophilization cycle and the challenges faced when scaling up at a contract site.

9:45

Recent Advancements for Improved Lyophilization Productivity

Speaker: Balazs Hunek, Ph.D., Manager, Pharmaceutical and Biotechnology Applications Group, Praxair, Inc.;

Contributing authors: Alan Cheng, Ph.D.; Robert Sever, Ph.D.; Barb Jordan, Praxair, Inc.

Lyophilization is a leading option to gently stabilize pharmaceutical and biopharmaceutical products and intermediates during manufacture. Successfully operating a large commercial freeze-dryer with high productivity remains a significant challenge. Continuing advancements in freeze-dryer capabilities are needed to meet this challenge. Not only do most modern lyophilization cycles require ultra-low temperature refrigeration below -50 °C, but the refrigeration load is also extremely variable, often requiring a system turn-down in excess of 10:1. Both of these key characteristics favor cryogenic refrigeration - using liquid nitrogen (LN₂) and/or gas nitrogen (GN₂) - over mechanical systems. In general, key benefits of cryogenic LN₂/GN₂ refrigeration systems include increased flexibility in terms of operating temperature range and cooling rate capability; higher reliability and lower maintenance requirements; comparable cost of ownership; plus less footprint and environmental impact. Pros and cons of using cryogenically chilled

heat transfer fluid versus direct cryogen expansion in condensers will be summarized. Novel means for reducing drying time up to 30-40%, improving product uniformity, and better preserving product activity will also be discussed.

10:30

Refreshment Break

SPECIAL COVERAGE: CONTAINER CLOSURE CONSIDERATIONS FOR LYOPHILIZATION

10:45

Examining Container and Closure Needs for Lyophilized Drug Products

Jeff Smythe, Manager, West Pharmaceutical Services

A great deal of time, effort and research go into the formulation and preparation of lyophilized drug products. Often, the selection of packaging materials is considered late in the development cycle. The processing and selection of packaging materials, in particular, the elastomeric closures play a critical role in preserving the lyophilized product over the intended shelf life. Factors to consider include the migration of residual moisture from the elastomeric closures to the lyophilized product over time, the processing parameters and the resulting total moisture in the closures. Different elastomeric closure formulations and configurations possess different chemical, physical and functional characteristics. Choosing the right closure for your lyophilized product is critical. During the presentation, we will review these formulations, configurations and processing parameters. In addition, we will review one study where various elastomeric formulations and configurations of lyophilization closures were tested for moisture content before and after typical steam sterilization and drying cycles. These stoppers were dried using three different cycles and then placed on filled vials containing a lactose solution and then lyophilized. The moisture content of the closures and the resulting lyophilization cakes was measured over time. The data demonstrate that residual moisture from the elastomeric closures can pass from the closure into the lyophilized cakes over time. Careful selection of appropriate closures and optimization of processing cycles can help reduce product development time and yield more robust packaging solutions

- Factors to consider when choosing a closure for lyophilized products
- Factors affecting seal integrity and vacuum retention
- Role of the lyophilization process in vacuum retention

11:30 **Container & Closure Development for Sterile Lyophilization**

Douglas Stockdale, President, Stockdale Associates, Inc.

The container and closure system are critical components for the sterile medicines that are manufactured by sterile lyophilization, and the elastomeric closure can create the most potential issues. In this session we will address:

- Sterile lyophilizer design and the container-closure interface
- Basics of container design for lyophilization
- Basics of elastomer closure design for lyophilization
- Container-closure qualification and validation overview

12:15 *Lunch*

1:30 **Determining Best Practice Protocols for Freezing, Primary and Secondary Drying**
Shailaja Rambhatla, Senior Research Scientist, Centocor R &D/Johnson & Johnson

The primary objective of lyophilization process development is to minimize process times while maintaining product quality. In practice, chamber pressure and shelf temperature during primary drying and secondary drying are determined by trial and error. This seminar will address heat and mass transfer principles pertinent to the lyophilization process that would assist in developing protocols for primary drying and secondary drying. The freezing stage is an important part of the process and the impact of freezing parameters on the primary drying process will also be discussed.

2:15 **Lyophilization Primary Drying Endpoint Detection**

Paul Young, Manager for Instrumentation, Alcatel Vacuum Products

The endpoint of primary drying in a lyophilization cycle is sometimes difficult to determine. There are several technologies that are used with various levels of success, including vial temperature sensors, microbalances, differential pressure readings and Residual Gas Analyzers (RGAs). We propose a new technology, a plasma sensor that creates a cold gas plasma with a

sample of the effluent from the lyophilization chamber. This sensor analyzes the spectrum of light from this plasma and calculates the moisture content of the gas. The data from this sensor is compared to other methods of primary drying endpoint detection, on accuracy of detection as well as other factors such as cleanability, ease of use, and ability to integrate onto an automatically loaded production freeze dryer. The use of the application as a Process Analytical Technology (PAT) will also be discussed.

3:00 *Refreshment break*

3:15 **Examining Current Freeze Drying Technologies and Qualification Requirements**
Heikki Hyttinen, Business Unit Manager, Lyophil Freeze Drying Applications, Niro Inc.

Fueled by the increasing demand and availability of modern pharmaceutical and biotechnical medicines as also engineered delivery vehicles for drugs and diagnostic agents Lyophilization continues to prove its significance as an effective technology for the conservation of sensitive formulations which remain instable in liquid form. This session will address the general principles of the lyophilization process, the design of the process equipment, current methods for monitoring and controlling the process as also technologies to increase the process efficiency and reliability. Furthermore, we will address the current qualification requirements including a presentation of a systematic approach to minimize risks and assure the success of qualification.

4:00 *Panel Discussion:*

Examining Current Technologies and Lyophilizer Selection Strategies: Current Developments and Considerations

During this interactive discussion, hear faculty members discuss new developments and technologies available that have recently changed industry approaches to lyophilization. Key considerations including scale-up, cycle development and regulatory considerations will be addressed.

4:30 **Chairperson's Closing Remarks and Close of Conference**



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VENUE INFORMATION:

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