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

DECEMBER 10-11, 2007 • RADISSON FISHERMAN’S WHARF • SAN FRANCISCO, CA

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.

Featuring Representation from Leading Companies:

Abraxis BioScience
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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.

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 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.

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.
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

“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”

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.
“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”

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 ºC, 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.

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
The 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.

3:00 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.

3:45 Refreshment break

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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