Lyophilization Forum, 2013

Formulation, Cycle Optimization, & Regulatory Compliance

November 7-8, Racquet Club of Philadelphia, PA

Featured Speakers:

With Case Studies and Lessons Learned from Industry Experts!

- **Secondary Drying Optimization for Proteinaceous Drug Formulations**
  - Presented by Lisa Hardwick, Baxter

- **QbD Principles in the Lyophilization Process: A Collaborative Project with NIPTE & FDA**
  - Presented by Vinay Radhakrishnan, Pfizer

- **Technology Transfer in Lyophilized Vaccines—From Lab to Production**
  - Presented by Jeffrey T. Blue, Merck

- **Use of Thermal Methods in Formulation Selection for Biologicals**
  - Presented by Paul Matejtschuk, NIBSC

- **PAT and Preformulation in Process Scale-Up and Cycle Optimization**
  - Presented by Dushyant Varshney, Novartis

- **Stabilization of Lyophilized Nucleic Acid-Based Therapeutics During Storage**
  - Presented by Marion Molina, Cureport

- **Impact of Excipient State and Freeze-Drying on the Stability of Bio-pharmaceuticals**
  - Presented by Matthew Brown, Genzyme

- **Spotlight on Controlled Nucleation**
  - Presentations by Mark Shon, SP Scientific, and Karen Bossert, Lyophilization Technology, Inc.

And Many More! Including Special Coverage On:

* **Recent Innovations in Spray Drying**
* **Formulation Considerations for Lyophilized Products**
* **Validation & Regulatory Compliance of Lyophilizers and Container Closure Systems**

Featuring Representation From:

Pfizer
Novartis
Merck
Steris
Genzyme
Baxter
SP Scientific
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Cureport
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Thursday, November 7, 2013

8:00 *Complimentary Breakfast & Chairperson's Welcome and Opening Remarks*

Best Practices for QbD in the Lyo Process and Cycle Optimization—Collaborative Project with NIPTE & FDA, and Secondary Drying Optimization

8:30 **Application of QbD Principles for the Development of the Lyophilization Process for a High Concentration Monoclonal Antibody Formulation: Collaborative Project with NIPTE & FDA**
Vinay Radhakrishnan, Ph.D., Associate Research Fellow and Group Leader Pfizer, Inc., Division of Biotherapeutics Pharmaceutical Sciences

A series of studies were designed to use quality by design principles to develop the lyophilization process for a high concentration monoclonal antibody formulation. The principles of quality by design were applied including definition of the target product profile, quality attribute definition and ranking, and process flow definition, risk assessments were preformed. Based on prior knowledge and published information, appropriate experiments were defined. These experiments as well as in silico modeling were performed to assess the interaction of the process parameters with quality attributes. Based on these results, risk assessments were redone and important process parameters were identified that can potentially impact product quality. The experiments as well as key results will be presented during the presentation.

9:15 **Secondary Drying Optimization for Proteinaceous Drug Formulations**
Lisa Hardwick, Research Scientist, Baxter BioPharma Solutions

The secondary drying phase of a lyophilization cycle can be critical for protein-containing products. This case study will focus on methods used to find the optimal residual water content for the finished product, as well as acceptable ramp rates and shelf temperatures for the freeze dry cycle.

10:00 *Mid-Morning Break and Exhibit Viewing*

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Formulation Considerations, Part I—Preformulation, PAT, and Impact of Excipient State

10:15 **The Impact of Excipient State and Lyophilization on the Stability of Biopharmaceuticals**
Matthew Brown, Ph.D., Development Scientist, Genzyme, a Sanofi Company

Determining the impact of excipient state on the structure of biologics is critical for understanding product stability. Excipient state is fundamental for maintaining protein structure upon lyophilization via glass dynamics and biochemical interactions. Formulation and process improvements provide better control of excipient state, facilitating conservation of native protein structure and improved stability. Application of protein and thermal characterization provides industry with the understanding to optimize manufacturing processes.

11:00 **Preformulation and PAT Methods in Developing a Lyophilization Process**
Dushyant Varshney, Ph.D., Senior Project Manager, Novartis

Recent advances in Process Analytical Technologies (PAT) have significant implications for companies seeking process optimization and scale-up to market of new products. This session examines the challenges inherent in preformulation, phase transitions during lyophilization, and offers case studies involving multi-component freeze-dried systems. Presentation highlights include:

- Preformulation approaches in investigation of phase transitions of formulation components during lyophilization.
- Advances in Lyo PAT technologies for process scale-up and optimization.
- Case studies of high sensitivity & rapid data collection methods for multi-component freeze-dried systems.

11:45 **LSNE - WHY WE ARE THE RIGHT FIT FOR YOUR LYOPHILIZATION NEEDS**
Christine Palus, Vice-President of Sales & Marketing, Lyophilization Services of New England, Inc.

In this sponsored presentation, LSNE will present a corporate overview of their services ranging from process development to aseptic vial filling and lyophilization to bulk lyophilization. The presentation will go through the company's history beginning in 1997 as well as summarizing their proven regulatory background. LSNE will highlight the advantages of working with one CMO from development through commercialization including reducing your time to marketing and minimizing risks. The company's experienced development, project management, quality and operations groups work together with

their clients to handle each client's individual needs to make sure your project receives the highest priority and all milestones are met successfully and on time. LSNE has an extensive history providing process development services to clients with challenging compounds and a case study will be included to show methods LSNE has used in the past to approach compounds that have been proven to be difficult to work with.

12:05 *Complimentary Lunch Sponsored by Lyophilization Services of New England, Inc.*

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1:15 **Critical Factors in Designing Formulations for Lyophilized Products (with Case Studies)**
J. Jeff Schwegman, Ph.D., CEO, AB Bio Technologies

Lyophilization, or freeze drying, is a very common means of extending the shelf life of molecules that are otherwise unstable in the aqueous, solution state. Companies producing pharmaceuticals, diagnostics, vaccines, food, etc., all utilize this technology in a wide range of products to make them viable for years instead of days, weeks, months, or in some extreme cases, hours. Unfortunately, many of these companies view lyophilization as the simple task of placing their product in the freeze-dryer after the formulation has been developed, and getting a stable, pharmaceutically elegant product back out of the dryer in a few days. In some cases, this approach works; however in many cases, this is the point when companies first find out that their product is either very difficult to freeze-dry and takes an extremely long time, or cannot be freeze-dried at all. Additionally, many of the new molecules coming out of discovery (proteins, monoclonal antibodies) are easily damaged by freeze drying, unless the formulation has been properly developed.

This presentation will begin with a discussion on the proper approach to use when developing a formulation, to ensure that the product can be dried successfully, have long-term stability, and produce a pharmaceutically elegant product. Several case studies in failed lyophilized products will be discussed.

Benefits of this presentation include:

- Understanding the thermal properties of your formulation before freeze-drying
- Understanding that all excipients are not created equal when developing a product to be freeze-dried
- Understanding the special considerations for freeze-drying biological
- Discussing case studies of failed cycles and formulations

Critical Issues: Spotlight on Controlled Nucleation

2:00 **ControLyo™ Nucleation On-Demand Technology. Moving from Lab to Production: A Case Study**
Mark Shon, Vice President, Technology Development, SP Scientific

Controlled nucleation is quickly becoming an important step in the freeze-drying cycle. Development scale research has shown numerous benefits including: reduction in primary drying time, improved cake appearance, reduction in protein aggregation, elimination of vial breakage and vial to vial uniformity, consistent with the FDA's QbD initiative. In order to realize these benefits, the technology needs to be scalable to production freeze dryers and ideally can be retrofitted on existing dryers. This presentation reviews the technology and benefits and presents a case study where ControLyo™ Technology was retrofitted on a 28 square meter production dryer and controlled nucleation was demonstrated on a fully loaded dryer with 8700 vials of various sizes and fill volumes.

2:45 *Afternoon Coffee Break and Exhibit Viewing*

3:00 **Combining Nucleation Technology and Aseptic Processing: The Impact of ControLyo™ on the Viability and Performance of Process Simulation Media Fills**
Karen A. Bossert, Vice President, Scientific Affairs, Lyophilization Technology, Inc.

Lyophilized drug products are sterile solid dosage forms manufactured aseptically through a series of unit operations. During lyophilization, to improve batch uniformity and ensure reproducibility batch to batch, recent advances in control of nucleation during freezing have been developed. One new technology, ControLyo™ Nucleation On-Demand, pressurizes and depressurizes the freeze-dryer product chamber to induce controlled (simultaneous) nucleation during freezing for materials contained within the product chamber.

To accurately assess the use of the technology during aseptic processing, the ControLyo™ technology must be incorporated into the processing of media-filled containers within the lyophilizer during a media fill. However, this requires an understanding of the viability of various types of organisms in the environment during pressurization/depressurization, as well as development of a method for conducting the media fill which depicts

an accurate use of the technology, while not interfering with the possible outcome of the media test.

The impact of the technology on the viability of organisms potentially present in the lyophilizer is examined. As well, the methodology and considerations for assessment of aseptic processing while utilizing the technology are discussed.

Take-home Benefits

1. Understanding of the new technology available for controlling nucleation of ice during manufacture of lyophilized drug products.
2. Understanding of the role of the new technology in the design of media fills.
3. Understanding of the impact of the new technology on the viability of microorganisms typically found in an aseptic manufacturing environment.

Session Objectives

1. Discuss new technologies available for manufacture of lyophilized materials.
2. Define an approach for conducting media fills for lyophilization processes.

3:45 **New Developments in Controlled Nucleation: Commercializing VERISEQ® Nucleation**

Joe Azzarella, Development Laboratory Technician, IMA LIfe & Eugene Wexler, PhD, Senior Project Manager, The Linde Group

For the past few years, the topic of controlled nucleation has been one of great interest to the bio-pharm community. The potential benefits of enhanced process control, process repeatability, and cycle time reduction are exciting to both manufacturing and quality groups. One means of achieving control of the nucleation process is the injection of sterile ice fog into the product vials.

The details of the ice fog nucleation technique are briefly discussed. A summary of tested products will also be presented, along with data to support the safety of the process with respect to product. The focus of the presentation however will be to share test data from the first commercially integrated unit. This will include performance data as well as data from sterilization verification studies.

4:30 ***End of Day One***

Friday, November 8, 2013

8:00 ***Complimentary Breakfast & Chairperson's Opening Remarks***

Technology Spotlight—Recent Innovations in Spray Drying

8:30 **Formulation Strategies for Successful Spray Drying and Case Studies**

Tarun K. Mandal, Ph.D., McCaffrey/Norwood Professor & Director, Center for Nanomedicine & Drug Delivery, Xavier University College of Pharmacy, New Orleans, LA

In the pharmaceutical industry, Spray Drying is typically used as a method for removing water or other liquid from a solution or dispersion of drug and/or excipients. In this process, the liquid is dispersed as fine droplets into a moving stream of hot gas where they rapidly evaporate before reaching the wall of the chamber. The formed dried particles carried by the gas current and gravity flow into a collection chamber. The size, shape, morphology, density, and flow properties of the particles can be controlled by optimizing several formulation and processing factors. Most important among all the factors that can be controlled is the size of the atomizer nozzle. Smaller nozzle produced smaller size particles. Few other important factors that must be controlled to prepare particles with desired characteristics are the (a) inlet air temperature, (b) outlet temperature, (c) liquid flow rate, (c) liquid viscosity, and (d) solid content. Particles that are formed by careful selection of the formulation and processing parameters possess excellent flow properties, higher water solubility, and ideal aerodynamic diameter. For example, spray dried lactose has been known for decades as an excellent excipient for direct compression tableting because of its superior flow characteristic compared to regular lactose powder. We have successfully developed spray dried chitosan/lactose as direct compression tableting excipient. We have increased the solubility of poorly soluble drugs 4- to 20-fold by a laboratory spray dryer. These spray dried formulations achieved higher water solubility and bioavailability because of their sub micron particle sizes. We have also prepared low density or hollow particles for pulmonary delivery of pDNA vaccine. Spray Drying improved the pulmonary delivery efficiency by reducing the aerodynamic diameter of the particles. Benefits of spray drying include:

- reduces the total drying time
- produces particles with smaller aerodynamic diameter
- enhances solubility of poorly soluble drugs
- produces microcapsules/nanoparticles for various pharmaceutical applications

9:15 **General Comparison of Spray & Freeze Drying Technology, with Case Studies**
Sune Klint Andersen, Principal Scientist, Novo Nordisk

When is spray drying a cost effective alternative to freeze drying? This presentation will provide answers through case studies of spray drying's implications for aseptic processing and its impact on particle structure and size. Specifically this talk will highlight the following issues:

- Investment and operating costs
- Drying Kinetics/drying rates
- Degradation during drying
- Particle and powder design
- Aseptic Powder Filling

10:00 *Mid-Morning Break and Exhibit Viewing*

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Formulation Considerations, Part II—Case Studies in Vaccine Scale-Up to Manufacture, and Formulation Selection Using Thermal Methods

10:15 **Vaccine Lyophilization: A Case Study from Lab-Scale to Manufacturing**
Jeffrey T. Blue, Director, Vaccine Drug Product Development, Merck

Successful technology transfer of a lyophilized vaccine product from lab-scale to manufacturing requires significant efforts. Throughout development multiple areas of lyophilization and the formulation need to be explored for a scalable process. This presentation will review the various areas of development investigated during lab-scale efforts to deliver a robust manufacturing window. Following successful transfer of the product, subtle changes to the filling process led to increased issues with product appearance. Discussions around the root cause of the issue and ways to mitigate led to a robust product within the pipeline. This again outlines the importance that no "minor" change can truly be considered minor as scaling occurs and the need to ensure good communication between development and commercialization are achieved.

11:00 **Use of Thermal Methods to Study the Impact of Formulation Selection on the Freeze Drying of Biological Materials**
Paul Matejtschuk, Principal Scientist, Standardisation Science, NIBSC - A Centre of the Medicines & Healthcare Products Regulatory Agency, UK

Understanding the impact of formulation on freeze-drying outcomes is critical to the development of lyophilized biological materials. This presentation will focus on how thermal information, derived from a number of different techniques, including modulated DSC, dynamic mechanical analysis and freeze drying microscopy, can guide the formulation process. Examples will be drawn from the speaker's wide experience of formulating numerous different biological materials as part of NIBSC's program for preparing biological reference standards.

11:45 *Complimentary Lunch and Exhibit Viewing*

Critical Issues: Lyophilized Nucleic Acids and Non-Viral Gene Delivery Systems

1:00 **Stabilization of Lyophilized Nucleic Acid-Based Therapeutics During Storage**
Marion Molina, Associate Director, Pharmaceutics Research and Development, Cureport, Inc.

The recent development of oligo- and polynucleotides as potential therapeutics has generated interest in establishing formulation strategies that provide physical and chemical stability at the pharmaceutical time scale. This presentation reviews the stabilization status of lyophilized naked DNA and DNA-based therapeutics during storage. Presentation highlights include:

- Preservation of "naked" nucleic acids (e.g., pDNA) as dehydrated formulations
- Challenges of lyophilizing non-viral gene delivery systems (e.g., lipid-based)

Quality Assurance & Container Closures for Lyophilized Products

1:45 **Selection of Container Closure Systems for Optimal Lyophilization Product Processing and Stability**
Andrea Straka, Senior Technical Account Specialist, West Pharmaceutical Services

Choosing appropriate closure systems for a new lyophilized drug goes beyond which suppliers to source them from. The material of construction, design, and processing to render closures sterile all have an impact on the success of the stability and shelf life of the

drug. Topics that will be explored will be selecting appropriate containers and materials for lyophilization closures, sterilization cycles and how dry closures need to be, appropriate drug/container compatibility, final sealing of the lyophilized product and container integrity testing.

2:30 *Afternoon Coffee Break*

2:45 **Techniques for the Decontamination of Freeze Dryers**
Mike Geanous, Engineering Manager, Steris Corporation

This presentation will highlight the benefits of low temperature and pressure decontamination of lyophilizers, including techniques for decontamination and validation using Vaporized Hydrogen Peroxide (VHP) for both large and small units. Case studies of existing applications will be presented.

3:30 **LYOPLUS™ - New Technology Implemented in Freeze Drying**
Daniel Steinkellner, Head of Product & Innovation Management GEA Lyophil GmbH

Freeze drying has been used for many years in the production of parenteral dosage forms. During processing of liquid formulation into a more solid dried state and sterilization of the equipment temperatures between -80°C and +125°C and pressures from 50µbar up to 1.2bar are applied. Because of these extreme conditions and additional mechanical stress of movable parts during automated cleaning micro-leaks can occur in the thermal fluid circulation system, typically at flexible hoses. As a consequence small amounts of potentially unsterile silicon oil are released into the sterile lyophilisation chamber and residues have been found in vials as shown in experiments. The implementation of a new technology to detect specific silicon oil patterns within the lyophilisation chamber using mass spectrometry eliminates the current risk of contamination and therefore prevents losing valuable product. In addition the use of such equipment offers new possibilities with regards to PAT and process control besides the silicon oil detection properties.

Over the last three years the technology and also the knowledge about reasons and effects are grown. This presentation will describe the implementation of a system on a lyophilisator for process development and the preparation for the installation on two production freeze dryers. The presentation should give a good overview about function, installation, testing and qualification, and will show success and faults from interesting tests.

4:15 *Close of Program*

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