Lyophilization Forum 2014

Formulation, Cycle Optimization, & Emerging Drying Technologies

October 20-21, Racquet Club of Philadelphia, PA

Featured Speakers:

With Case Studies and Lessons Learned from Industry Experts!

- **Case Studies in Controlled Nucleation**
  - Presentations by Mark Shon, SP Scientific, and Joseph Brower, IMA Life

- **Design Space for Secondary Drying**
  - Presented by Lisa Hardwick, Baxter

- **Clinical and Commercial Tech Transfer: Reducing Risk of Freeze-drying Failure Through Freeze Dryer Characterization and Modeling**
  - Presented by Anthony Gudinas, Pfizer

- **Application of QbD and PAT in Developing a Spray Drying Process**
  - Presented by Sune Klint Andersen, Novo Nordisk, A/S

- **Recent Advances in Understanding Phase Behavior of Ice During Lyophilization**
  - Presented by Dushyant Varshney, Novartis

- **Developing a Lab-scale Model for Life-cycle Management of a Marketed Vaccine**
  - Presented by by Erica Strable, Merck

- **Stabilization and Drying Techniques for Complex Proteins & Biologics**
  - Presented by Jeff Schwegman, AB BioTech

With Special Coverage On:

- **Lyophilized Drug Product Development using QbD Principles**
- **Product Behavior During Lyo when Processed in Dual Chamber Cartridges vs. Tubing Vials**
- **Freeze Drying PAT using Heat Flux Measurement**
- **Spray Drying Challenges—Lab Scale Formulation to Pilot Scale Up**
- **Container Closure Systems for Optimal Lyophilized Product Stability & Processing**
- **Moisture Monitoring, Inspection, & Tracing Methods for Lyophilized Vials**

Featuring Representation From:

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Monday, October 20, 2014

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

Optimizing Formulations for Proteins and Biologics

8:15 **Stabilization and Drying Techniques for Complex Proteins & Biologics**
J. Jeff Schwegman, CEO, AB BioTechnologies

Many of the new active ingredients coming out of discovery these days are biologically based, such as monoclonal antibodies, proteins, vaccines, etc. Unlike small molecules, these types of products can be extremely sensitive to manufacturing stresses such as shear, oxidation, freezing, lyophilizing, etc. This presentation will begin with a discussion on the ways to understand the physical properties of these types of products through the use of specialized analytical techniques. The information obtained from these specialized studies is critical in developing optimized formulations and lyophilization cycles without having to use a "trial and error" approach. Finally, the discussion will turn to developing an optimized, cGMP compliant formulation that is specifically designed for lyophilization. Discussions will be included on pre-formulation assessment, pre-formulation and formulation studies including optimal solution pH and buffer systems, solubility enhancement, controlling oxidation, stabilizers, and bulking agents.

8:55 **Use of Design of Experiment Approaches within Lyophilization Formulation and Process Development**
Paul Matejtschuk, Principal Scientist, Standardization Science, National Institute for Biological Standards & Control, NIBSC - A Centre of the Medicines & Healthcare Products Regulatory Agency, UK

Choosing a formulation for freeze drying that optimizes retention of activity has always been a challenge for those developing lyophilization processes for complex biologicals. We have investigated the use of Design of Experiment approaches and micro scale-down methods in enabling rapid and product-saving approaches to excipient selection. This presentation will review data obtained with a number of model biologicals, including an enzyme, a growth factor and an immunoglobulin preparation. The use and limitations of a DoE approach in freeze-drying cycle optimization will also be discussed.

9:35 **Lyophilized Drug Product Development using QbD Principles**
Sajal Patel, Scientist II, Medimmune

Many biopharmaceuticals are lyophilized in the hopes of improving the shelf life. However, the freeze-drying process itself presents challenges and considerations (both formulation and process) based on protein concentration and drug product presentation, which will be addressed in this talk. Also, the incorporation of QbD elements (design space and PAT) early on during development will be discussed.

10:15 *Mid-Morning Break and Exhibit Viewing*

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Spotlight on Secondary Drying

10:40 **Design Space for Secondary Drying**
Lisa Hardwick, Research Scientist, BioPharma Solutions, Baxter Healthcare Corp

What factors need to be considered when creating a safe set of conditions to secondary dry a lyophilized formulation? Does chamber pressure have an impact? What shelf temperature is safe for the product? Is duration of the transition from primary to secondary drying conditions important? This presentation, detailing a case study using a model formulation, will examine these questions and more.

11:20 **Clinical and Commercial Tech Transfer: Reducing Risk of Freeze-drying Failure Through Freeze Dryer Characterization and Modeling**
Anthony Gudinas, Senior Scientist, Pfizer

Transferring a freeze drying cycle from development scale to clinical or commercial scale is complicated by the inherent functional differences between freeze dryers. Performing freeze dryer characterization to determine vial heat transfer coefficient and minimum controllable pressure as a function of sublimation rate provides key information that can be used in a primary drying model to facilitate cycle design and scale-up. This presentation focuses on the execution of these tests and new methodologies to perform sublimation tests when performing freeze dryer characterization and shows an example of the application of this data. The key points are:

- Defining the purpose of characterization
- Current state of characterization
- New methodology for sublimation tests
- Application of data using a primary drying model

12:00 *Complimentary Lunch Sponsored by Millrock Technology*

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1:20 **Freeze Drying PAT using Heat Flux Measurement**
T.N. Thompson, President, Millrock Technology

A freeze drying recipe will be analyzed and then improved using Heat Flux measurement and control. Heat flux measurements provide critical process information for every step of the freeze-drying process, including: freezing, primary drying and secondary drying. By measuring heat flux in-process, process parameters such as percent of product frozen by nucleation, crystal growth rates post-nucleation (controlled and uncontrolled), end of freezing, thermal conductivity of the vial (Kv), product resistance (Rp), mass-flow, shelf surface temperature and product temperature can be measured. Additionally, a design space can be developed in a single run.

Quality Assurance, Vial Tracing Methods, & Optimal Container Closures for Lyophilized Products

2:00 **Container Closure Systems for Optimal Lyophilization Product Processing and Stability**
Andrea Straka, Senior Technical Account Specialist, West Pharmaceutical Services

Selection of an appropriate container and closure system for a lyophilized drug goes beyond which suppliers to source them from. The material of construction, design, processing to render closures sterile, and how the components are assembled, all have an impact on the success of the stability and shelf life of the drug. In this talk, we will explore criteria for selecting appropriate containers and materials for lyophilization closures, sterilization cycles and how dry closures need to be, drug/container compatibility, final sealing of the lyophilized product, and determining the container's maximum allowable leak.

2:40 **Tracing of Individual Vials—Fad or the Future?**
Daniel Steinkellner, Product & Innovation Management, GEA Lyophil GmbH

While industrial freeze-drying operations have by the consequent use of automatic loading and unloading systems become increasingly independent from human interventions the assurance of line clearance in many cases is the only area requiring direct operator interference. A main reason is that current counting systems are not working precisely enough in order to assure that each vial which entered the chamber has also left it afterwards.

A radical solution to this is to mark every vial with an individual code allowing a seamless tracing for the duration of the freeze-drying operation, or even the entire operation, from washing up to packaging.

In this talk a review on the current status of this exciting technology will be given. Areas discussed will include:

- How to mark the vials?
  Required laser technology
  Are "special vials" required?
  How many individual codes are possible?
- Vial tracing
  Maximum possible line speed
  How much modification of a standard line is required?
  Positions for sensors
- Information obtained
  Example of data obtained during a test run
- Further possibilities
  Anti-counterfeiting
  Trouble shooting

3:20 ***Afternoon Coffee Break and Exhibit Viewing***

Critical Issues: Controlled Nucleation–From Lab to Production

3:40 **Controlled Nucleation in Manufacturing—Current State of Development**
Mark Shon, Vice President, Technology Development, SP Scientific

In 2002, Dr. Michael Pikal in a paper published in American Pharmaceutical Review stated the following: "Control and characterization of the degree of super-cooling can provide a solution to what is perhaps the biggest freeze drying Scale-Up problem." The ability to control nucleation during the freezing step of lyophilization has been considered to be one of the most significant developments in freeze-drying in decades. A number of benefits have been demonstrated at the development scale including: Significant reduction in primary drying times, reduction in protein aggregation, improvement in cosmetic elegance of the cake, reduction in vial breakage, improved vial to vial uniformity and adherence to the FDA's QbD initiative. In order for these advantages to have commercial benefits, controlled nucleation needs to be capable of being implemented in large production dryers. This presentation reviews the current state of commercialization and specifically details two collaborative studies where ControLyo TM Nucleation on Demand Technology was used to control nucleation in two different 28 square-meter production freeze dryers.

- The ability to control nucleation during the freezing step is a relatively new advancement in freeze drying
- Using the ControLyoTM Nucleation On-Demand Technology allows nucleation to occur at warmer temperatures, minimizing super-cooling. This results in larger ice crystals and reduced primary drying times
- Numerous other benefits have been shown in development freeze dryers equipped with ControLyoTM Technology

- Commercialization requires the technology work on production freeze dryers
- This presentation describes how production dryers can be retrofit for ControLyoTM Technology and the results of two collaborative studies showing the feasibility of scale-up

4:20 **Ice Fog Induced Nucleation Case Studies**
Joseph Brower, Technology Manager, IMA Life North America

Control of the process by which parenteral vials are frozen can have a beneficial impact on batch homogeneity, processing time, and finished product attributes. Ice nucleation through the introduction of ice fog provides a simple and safe means of ensuring nucleation of all vials in a batch at warmer temperatures than occur naturally in parenteral products. By inducing ice nucleation at controlled temperatures, it has been possible to demonstrate quality benefits for a number of products, in a number of presentations.

5:00 ***Happy Hour***
Compliments of Lyophilization Services of New England

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Tuesday, October 21, 2014

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

Technology Spotlight—Recent Innovations in Spray Drying

8:30 **Application of Quality-by-Design and Process Analytical Technologies in Developing a Spray Drying Process**
Sune Klint Andersen, Principal Scientist, Novo Nordisk A/S

Spray drying is a continuous and scalable manufacturing process commonly used in the pharmaceutical industry. Due to spray drying's scalable and continuous nature it is possible to apply Quality-by-Design (QbD) and Process Analytical Technologies (PAT) early on in the development of a spray drying process. Knowledge gained from QbD e.g. Design-of-Experiments (DoE) and PAT increases process understanding and the knowledge can be readily applied when scaling up the process and in production scale application of PAT, especially with respect to the control strategy. Highlights of the presentation:

- QbD approach and types of PAT used in spray drying
- Case study QbD and Pat – excipient spray drying
- When do applying QbD and PAT to spray drying pay off?

9:10 **Spray Drying Challenges – Lab Scale Formulation to Pilot Scale Up**
Karl Edelman, President, PSD, Inc.

Spray drying, like lyophilization, is a process that turns unstable liquids into stable powders. The technology has been around for over 100 years and has not changed greatly. What has changed is how it has become a formulation tool for the pharmaceutical industry. Spray drying now is considered a particle engineering tool to make API more stable, soluble, and more bioavailable. We will review spray drying basics, its differences with lyophilization, and discuss how the pharmaceutical industry is moving forward with spray dried dispersions and matrices.

- Spray drying overview
- Spray drying vs Lyo
- Lab scale formulation (aqueous, solvent, particle engineering) Buchi B290-295
- Pilot scale up to GEA Niro Mobile Minor
- Spray dried dispersions – SDD increase of solubility/ bioavailability

9:50 ***Mid-Morning Break and Exhibit Viewing***
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Critical Issues—Life-Cycle Management & Optimization

10:15 **Developing a Lab-scale Model for Life-cycle Management of a Marketed Vaccine**
Erica Strable, Principal Scientist, Vaccine Drug Product Development, Merck & Company

Once a vaccine is marketed, successful life-cycle management is critical to ensuring and expanding access to these life-saving medicines. To facilitate life-cycle management activities without interrupting routine manufacturing, the ability to conduct experiments at the lab-scale is essential. For freeze-dried products, this requires the development of a scaled-down lyophilization cycle that matches the product temperature profile and cycle times experienced in manufacturing. At the lab-scale, changes in the vial type, lyophilization trays or number of vials being lyophilized can impact sublimation rate and heat transfer coefficients. It is important to understand the impact of these changes on the scaled-down lyophilization cycle being developed. The establishment of a representative lab-scale lyophilization cycle is a starting point for cycle optimization. This presentation will provide selected examples of development and utilization of a scaled-down lyophilization cycle and lessons learned along the way.

10:55 **Recent Advances in Understanding Phase Behavior of Ice during Lyophilization**
Dushyant Varshney, Senior Project Manager, Novartis

Phase behavior of water-ice at sub-zero temperatures is fundamentally essential for understanding both the natural phenomena (e.g., freeze-induced de-stabilization in biological systems) and laboratory or industrial operations (e.g., cryopreservation, freeze-drying of biopharmaceuticals or biotechnology products). In most cases, water freezes during either cooling or subsequent warming or annealing as pure ice crystals (mostly hexagonal ice form). When aqueous solutions are cooled, water crystallization is often incomplete if solute(s) does not crystallize. In such cases, a fraction of the water will be a part of the amorphous freeze-concentrated solution. In some systems, water molecules can be either incorporated in the solute's crystalline lattice forming crystalline hydrates, or clathrates and gas hydrates. Understanding the role of ice nucleation, annealing and sublimation is critical for development and optimization of lyophilization cycles, and stabilization of the drug substance or drug product. X-ray diffractometry has been a major tool to investigate phase transitions in aqueous systems at sub-zero temperatures. Especially utilization of high-intensity Synchrotron Radiations for X-ray powder diffraction studies and pairwise distribution function (PDF) analysis of the XRD patterns could provide valuable insights on phase behavior of water-ice (e.g., XRD pattern ice-peak splitting). In this presentation, we will discuss our past and recent results from different model systems including buffered aqueous solutions in presence of excipients and proteins. Specifically, studies using of Synchrotron XRD methods and other supporting analytical techniques will be discussed.

Technology Spotlight – Applying Fluorescence Stokes Shift to Lyophilized Formulations

11:35 **Predicting the Stability of Lyophilized Sugar Glasses by Fluorescence Stokes Shift**
Ken K. Qian, Ph.D., National Institute of Standards and Technology (NIST)

Disaccharides such as trehalose and sucrose are commonly used to preserve therapeutic proteins in lyophilized formulations; however, there is currently no systematic and rational approach to predict the stability of such glassy materials. We have shown firm evidence that protein stability in sugar-based glasses is directly linked to the high-frequency, local mobility of the sugar matrices, occurring on a timescale of nanoseconds. In this talk, we present a new fluorescent instrument to probe the motions of lyophilized formulations. This technique will allow scientist in early development to rapidly screen amorphous formulations, and predict their long-term stability.

12:15 *Complimentary Lunch and Exhibit Viewing*

1:30 **Comparison of Product Behavior During Lyophilization When Processed in Dual Chamber Cartridges and Tubing Vials**
Michael S. Thomas, Research Scientist, Lyophilization Technology, Inc.

Product behavior during lyophilization for material processed in a dual chamber cartridge can be considerably different from the same material processed in a vial. This often warrants unique assignment of the critical independent variables of shelf temperature and chamber pressure to process with success. Evaluated in this study was the influence of the novel container/closure system of a cartridge compared to the more traditional vial and stopper combination. A surrogate mAb solution was filled onto a full tray of both 1 cc cartridges and 3 cc vials and processed simultaneously. The thermal profiles of multiple product containers of each type were assessed during each phase of the lyophilization cycle (loading, freezing, primary and secondary drying). Sublimation rates were assessed for each container in various holding systems. Finished product was evaluated to compare the impact of varied product response during processing. The results demonstrate the importance of understanding product behavior during manufacture of lyophilized drug into these two unique dosage forms.

2:10 **Freeze Dried Tissue Scaffolds**
Mrinal Shah, Senior Engineer, Process Development, LifeCell Corp.

Collagen sponges have been used for various applications ranging from dental plugs, wound healing and as scaffolds for implants. Traditionally, such sponges have been made by dispersing purified soluble collagen derived from various animal sources in suitable aqueous media and freeze drying the same. Favorable biological outcomes from such scaffolds are dependent on multiple parameters such as surface chemistry, biochemical composition, mechanical stiffness/softness, pore size and complex interaction between them.

This work is focused on insoluble fibrous collagen derived from animal or human dermal tissue. The tissue is de-cellularized and processed to form a stable suspension containing varying tissue content [1%, 2% and 4% S (solid)]. The suspensions are cast into molding trays and freeze dried to yield soft, porous collagen scaffolds. While varying the freezing rate and material of construction of the casting mold may modulate the pore size, it did not seem to have a significant role in providing compressive properties to the scaffold. The primary factor that was found to contribute to scaffold stiffness was the amount tissue content of the collagen suspension. The compressive property of the scaffold graded as 4% S > 2% S > 1% S. Freeze drying of the scaffold in a conductive mold yielded smaller pores than an insulator mold. Pore size distribution in the scaffold can be also varied by changing the pH of the collagen suspension.

Residual moisture levels in the suspension post freeze drying were found to be < 5%.

In conclusion, this study shows that pore structure, pore size and mechanical properties of collagen based scaffolds can be targeted by controlling the solid content of the suspension, its pH, freezing rate and material of construction of the casting mold.

2:50 *Afternoon Coffee Break & Exhibit Viewing*

3:10 **Rapid Moisture Monitoring and 100% Container Closure Inspection of Lyophilized Vials**
Derek Duncan, Director & VP of Marketing, LIGHTHOUSE Instruments

Laser-based headspace analysis has proven to be useful in freeze drying activities, from the development of lyo cycles and the validation of freeze dryers to final quality inspection of freeze dried product. Data from industry case studies are presented in this paper, which demonstrates the wide utility of this analytical technique for freeze drying activities.

Quantifying the amount of water vapor in the headspace of freeze-dried vials with an optical method enables rapid non-destructive moisture analysis. Experiments have demonstrated that the amount of headspace water vapor directly correlates to the lyo cake moisture content. Stability studies have shown that the degradation of the active pharmaceutical ingredient correlates to the initial water vapor concentration present in the freeze-dried vial. These results indicate that rapid water vapor determination with an optical method could replace the slow destructive traditional methods for moisture analysis of freeze-dried products. This paper presents data from industry case studies involving lyo chamber moisture mapping, freeze drying cycle optimization, and 100% moisture inspection of commercial freeze-dried products.

3:50 *Close of Program*

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