



Perfecting the Pass: Best Practices in Lyophilization Technology Transfer

September 21, 2006

Baxter RxIQ Webinar

BioPharma Solutions

Baxter

Connect to the resources you need.

Outline – Components of a Smooth Tech Transfer Process

- Identify the critical product quality attributes
- Develop a robust formulation, and characterize both the frozen system and the freeze-dried solid
- Be sure to choose an appropriate container/closure system
- Determine the performance limitations of both laboratory/pilot scale equipment and production equipment
- Account for “edge effects” in scale-up and tech transfer
- Know what the FDA looks for in tech transfer of freeze-dried products

Know the Critical Product Attributes

- Sterility
- Freedom from pyrogens
- Freedom from extraneous particulate Matter
- Complete recovery of activity
- Rapid, complete reconstitution
- Stability
- pH of the reconstituted solution?
- Isotonicity?
- Vial headspace composition?

Smooth Tech Transfer Starts with a Robust Formulation

- The maximum allowable product temperature during primary drying should be $\geq -35^{\circ}\text{C}$
 - Amorphous system: Collapse
 - Crystalline system: Eutectic melt
- The total solids concentration should not be too low, or too high
 - Too low: Inelegant appearance and solids ejection from the vial
 - Too high: prolonged, inefficient drying, and poor process control

Varying Degrees of "Collapse" in a Freeze-Dried Solid



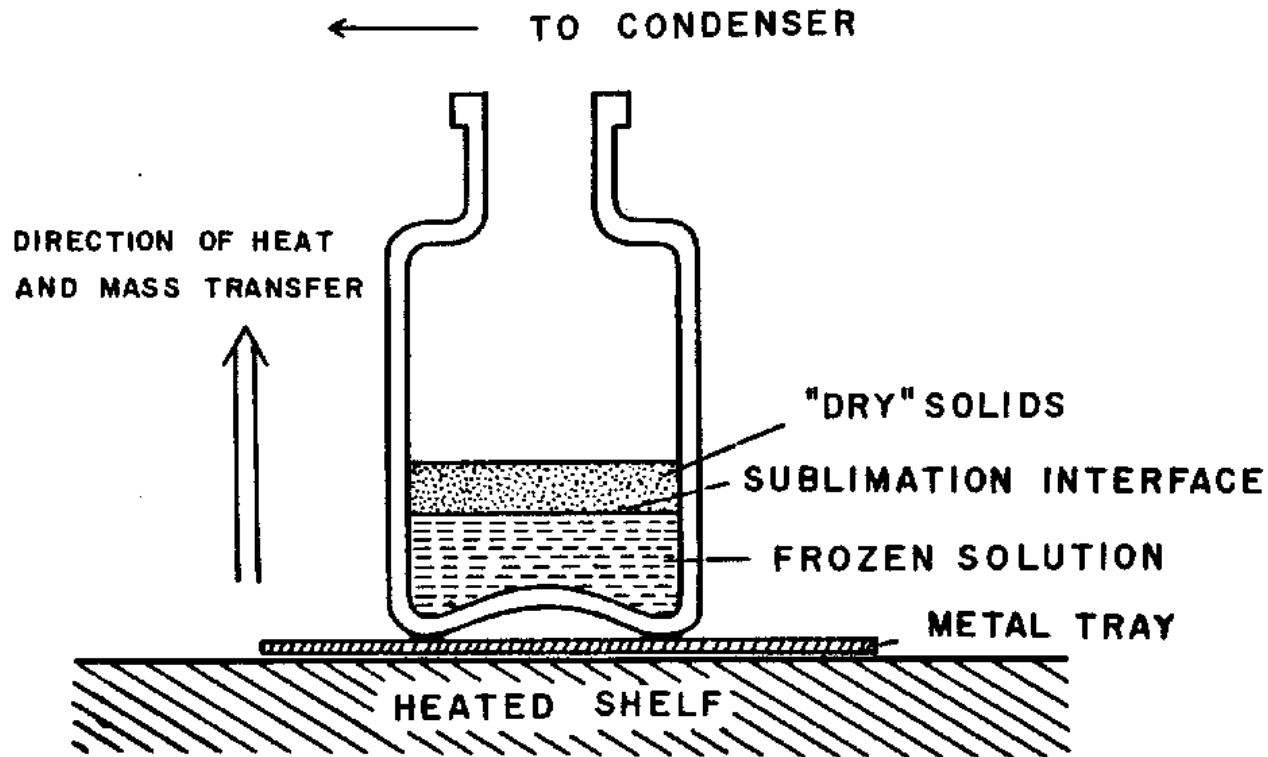
Photo by Steven L. Nail

Result of Eutectic Melting During Freeze-Drying



Photo by Steven L. Nail

Freeze-drying is an example of linked heat and mass transfer



Keep in Mind the Inherent Differences Between Laboratory and Production Settings

- The time scale of manufacture, filtration, filling, and transfer to the freeze-dryer is different between the laboratory and production.
- The production setting is more “particulate-free” than a laboratory setting. This can have subtle effects on the dynamics of freezing.

Characterize the Freeze-Dried Solids

- Determine the physical state of the drug and excipients
 - Thermal analysis
 - X-ray powder diffraction
- Small differences in formulation composition can significantly affect glass transition temperature of amorphous solid
- Beware of changes in physical state during storage

Choose an Appropriate Container/Closure System

- The vial size should be appropriate for the fill volume
 - Generally, fill volume should not exceed about 1/3 of the overflow capacity of the vial. Particularly important for formulations associated with vial breakage.
- Keep mechanical stability of vial in mind – tall, thin vials do not handle as well on filling/traying equipment
- Do machinability trials to determine whether rubber closures handle acceptably on stoppering equipment, and that closure is positioned properly
- Watch for any tendency of stoppers to stick to the bottom of the shelf above after stoppering operation
- Beware of the potential for water vapor transfer from stopper to product

Vial Breakage in Freeze-Drying

- Note: This is of particular concern for oncolytic agents

Shattering



Photo by Steven L. Nail

"Lensing"



Photo by Steven L. Nail

Cycle Development

- Determine what cycle conditions the product will withstand
 - Higher product temperatures and faster drying rates mean more efficient process
- Make sure that the cycle conditions can be supported by the equipment
- Cycle development/scale-up always easier if lab and production dryers are similar in design

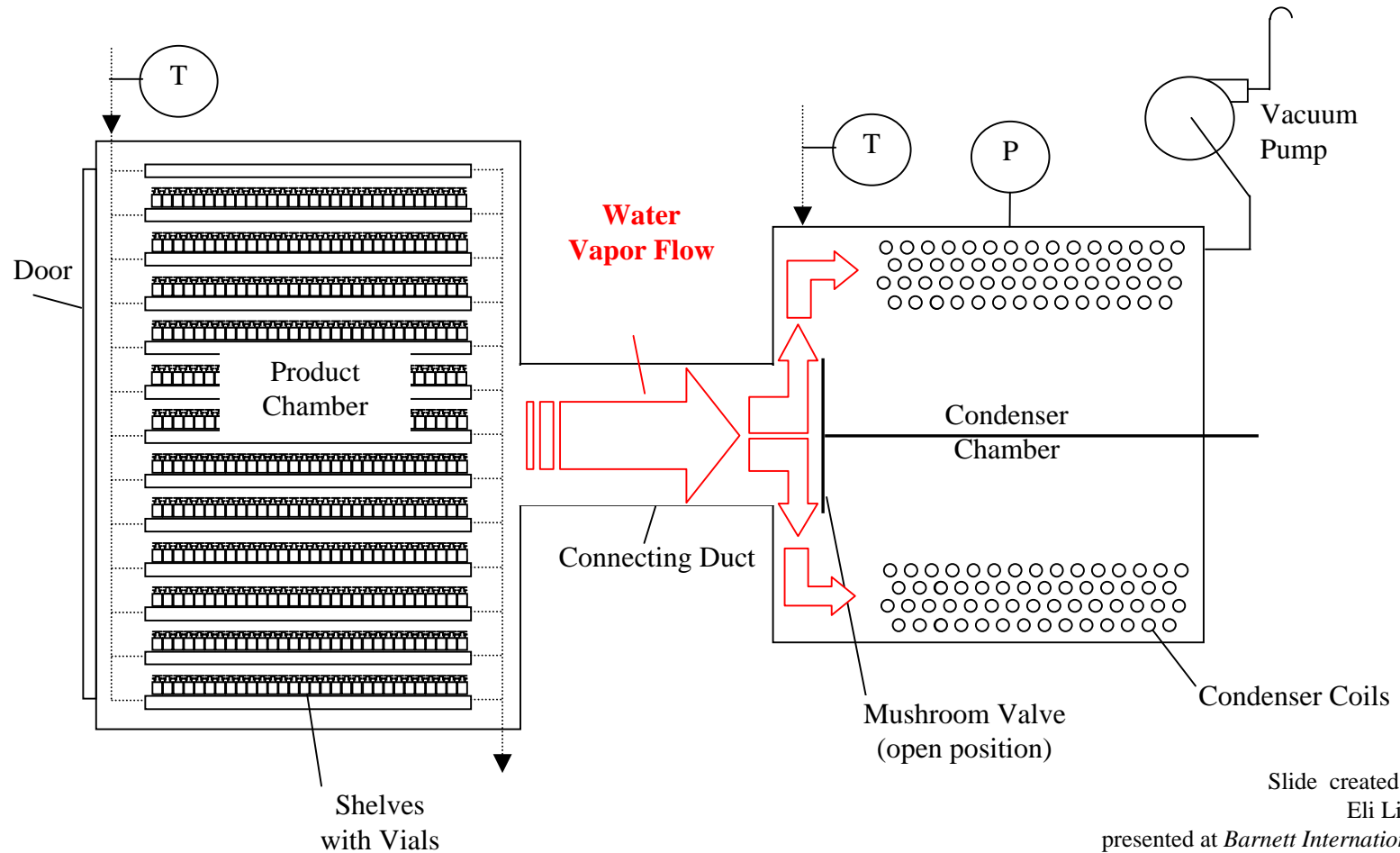
Design Features

- Internal vs. External Condenser
- Door – Stainless Steel vs. Plexiglass
- Surface Finish – can affect heat transfer by thermal radiation

Consider the Following Performance Attributes

- Minimum attainable shelf temperature
- Maximum shelf temperature ramp rate under load, both for heating and cooling
- Minimum controllable chamber pressure during primary drying
- Condenser ice capacity
- Ratio of condenser area to shelf area
- Determine maximum sublimation rate that the freeze-dryer will support
- Note any differences in process instrumentation, particularly for pressure measurement

Flow of Vapor from Chamber to Condenser

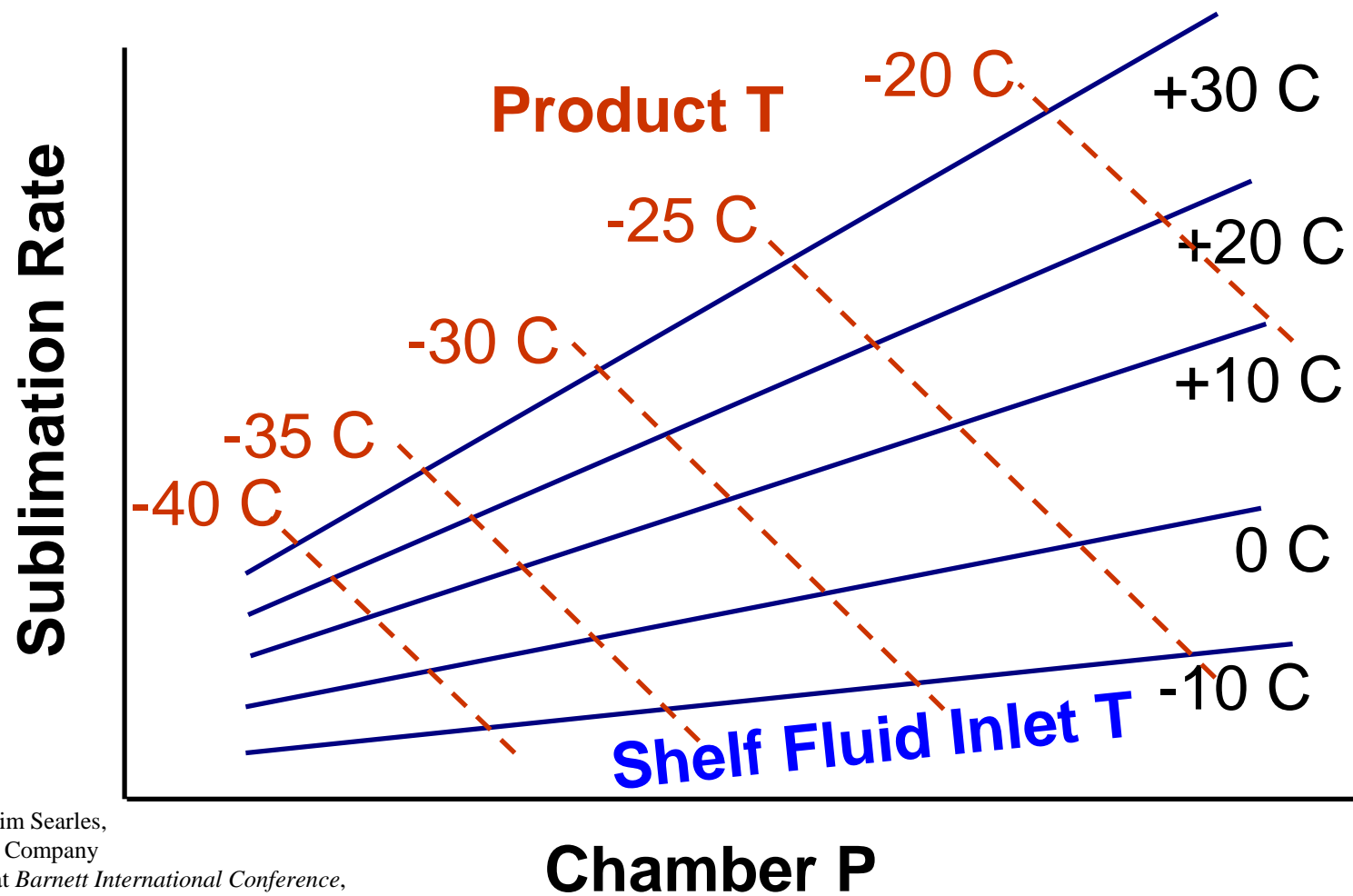


Slide created by Jim Searles,
Eli Lilly & Company
presented at *Barnett International Conference*,
Brussels, Belgium, April 2005

Factors Determining the Maximum Sublimation Rate Supported by Equipment

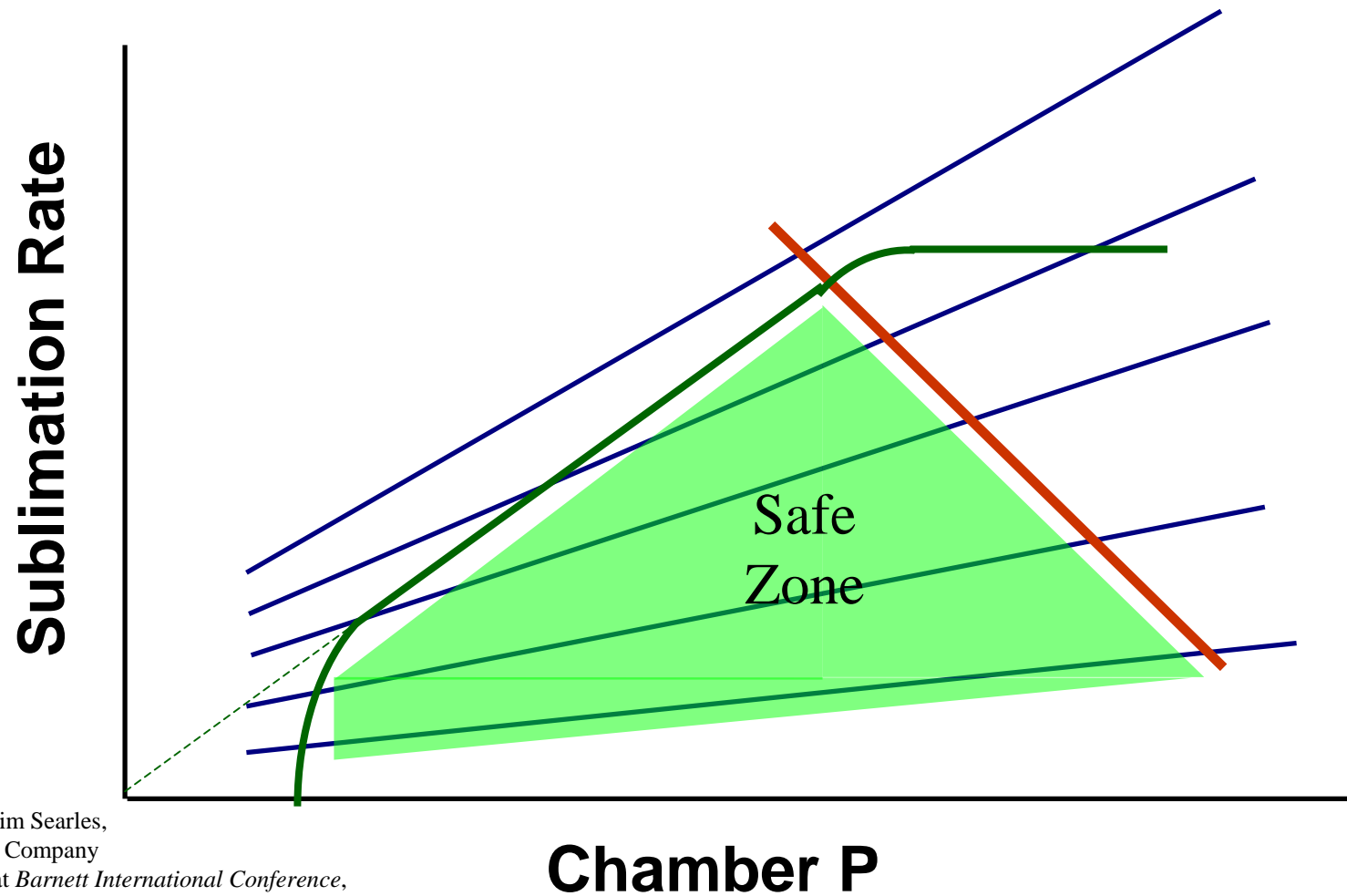
- **Transfer of heat from shelves to the product**
 - Shelf heating power and thermal mass of heat transfer fluid
 - Internal heat transfer from fluid to shelves
 - Vial heat transfer coefficient
- **Transport of water vapor from the product to the condenser**
 - Resistance of the dried product to vapor flow
 - The lyostopper
 - Resistance of the chamber/condenser configuration
 - The significance of “choked flow”
- **Uptake of heat from the vapor by the condenser**

Cycle Design



Graph by Jim Searles,
Eli Lilly & Company
presented at *Barnett International Conference*,
Brussels, Belgium, April 2005

Cycle Design with Dryer Capability



Graph by Jim Searles,
Eli Lilly & Company
presented at *Barnett International Conference*,
Brussels, Belgium, April 2005

Don't impose cycle conditions developed in the laboratory on production freeze-dry cycles without allowing for increased thermal mass and longer dynamic lag in the production environment

Recommendations

- Lyophilizers should be specified, designed, and tested with specific capabilities in mind
- Minimum required drying rate (kg/hr) supportable by the system while maintaining a specific product chamber pressure (>1 kg/hr/m² at 100 mTorr)

Recommendations

- Conduct drying rate tests at a range of operating pressures
- Pay close attention to design of the water vapor flow path, including valves and radiation shields (20 to 50 kg/hr/m² at 100 mT)
- Use capacitance manometers on both the product and condenser chambers

Recommendations

- Pursue Process Analytical Technologies (PAT) that measure the current sublimation rate
- Understand how much of the available drying rate capacity is being used
- Avoid conditions that lead to choking or other equipment limitations

Recommendations

- Trend refrigeration system performance
 - Suction, interstage and discharge pressures
 - Compressor motor amperage draw
 - Expansion valve % open
 - Condenser outlet refrigerant T and P
 - Cooling water temperature and flow rate

FDA Concerns in Freeze-Drying

- In its assessment of the current state of pharmaceutical manufacturing across the industry, FDA has stated that the inability to predict scale-up effects is a major weakness.
- The Quality by Design initiative is predicated on development of a deep understanding of the product and how product quality attributes can be affected by the process.

FDA CDER Compliance Initiatives, Joseph C Famulare, Acting Deputy Director, Office of Compliance CDER (FDA), DIA 42nd Annual Meeting, June 22, 2006, slides 13-22

Freeze Drying and the FDA

Bob Darius

January 20, 2004

Inspection Triggers Related to Technology Transfer

- Inadequate understanding of thermal properties of formulation.
- Inadequate understanding of process and equipment
- "One cycle fits all" lyophilizers without supporting data
- Excessively long lyophilization cycles
- Reconstitution times not based on historical data
- Final product sampling locations in dryer not specified or no rationale for choice
- Evidence of broken or damaged vials during lyophilization
- Unseated or popping stoppers
- Stoppers sticking to shelf bottoms
- Inadequately defined and quantified physical characteristics and appearance

Presentation by Robert Darius, Microbiologist, Center for Biologics Evaluation & Research, Office of Compliance & Biologics Quality, Division of Manufacturing & Product Quality

Freeze Drying and the FDA

Bob Darius

January 20, 2004

483s Related to Lyo Tech Transfer

- No data available for moisture mapping studies performed on actual full scale production runs
- No data available to support acceptability of lyophilization cycle that was transferred directly from the previous lyophilizer to the new lyophilizer.
- No studies on freezing and melting point of formulation
- Batches not uniformly frozen
- No data available to correlate product temperature to shelf temperature
- Shelf temperature mapping studies did not include primary drying
- Specified recon times exceeded during stability testing

Presentation by Robert Darius, Microbiologist, Center for Biologics Evaluation & Research, Office of Compliance & Biologics Quality, Division of Manufacturing & Product Quality

Scope of Baxter Pharmaceutical Solutions Involvement in Cycle Development, Scale-Up, and Tech Transfer

Expertise in formulation and analytical development, including our Lyophilization Center of Excellence.

- Baxter's formulation development scientists are experts in both biomolecule and small molecule parenteral product formulation, as well as processing solution, lyophilized, and dispersed system dosage forms. We have developed dosage forms and manufacturing processes for many commercially available sterile products. Our analytical development scientists are specialists in developing and validating analytical methods that meet regulatory requirements. Our analytical capabilities include KF, DSC, FTIR, freeze-dry microscopy, UV/Vis spectrophotometry, protein assay methods, and high pressure liquid chromatography (HPLC) methods.
- At our Bloomington facility, we have established the "Baxter Lyophilization Center of Excellence," where our focus is to develop and produce high-quality freeze-dried products. We accomplish this by taking an empirical approach to cycle development as opposed to a trial-and-error approach that has traditionally been used in the past. Through the use of thermal analysis techniques and targeted pilot studies, we can provide you with a unique advantage in the development and production of your freeze-dried products, helping to save you both time and money.

Thank You for Attending!

The slide deck will be emailed to you today



Contact Dr. Steven L. Nail
Email: Steven_Nail@Baxter.com



Contact Dr. Michael J. Akers
Email: Michael_Akers@Baxter.com

Meet With Baxter at the following Conferences

CPPR, Center for Pharmaceutical Processing Research- Freeze-Drying of Pharmaceuticals and Biologicals, Garmisch, Germany (Dr. Nail is presenting).....	October 4-6, 2006
ICSE, Paris France- Booth Number 4H22	October 3-6, 2006
AAPS, San Antonio, Texas- Booth Number 606 (Both Dr. Nail & Dr Akers attending).....	October 28-November 1, 2006

For more information on Baxter's formulation, packaging and manufacturing services to support your efforts throughout the development process, visit our website:

www.baxterbiopharmasolutions.com