



Processes Associated with the Transfer of Lyophilized Products

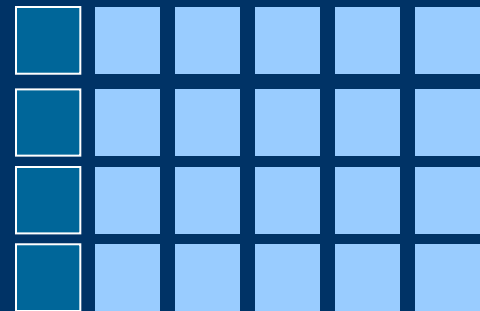
ISLFD Chicago Chapter Meeting

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April 14th, 2011



Objectives of Presentation

- Technology Transfer Overview
- Lyophilization Process Overview
- Technology Transfer Scope
- Lyophilization Technology Transfer Considerations
- Proposed Lyophilizer Technology Transfer Strategy
- Technology Transfer Batches
- Primary Drying Endpoint & Process Improvements

Technology Transfer Overview

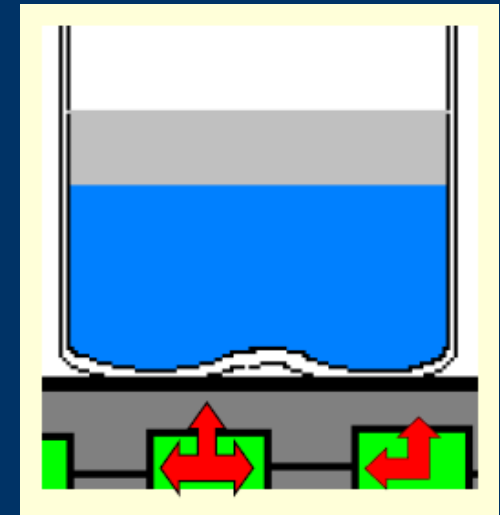
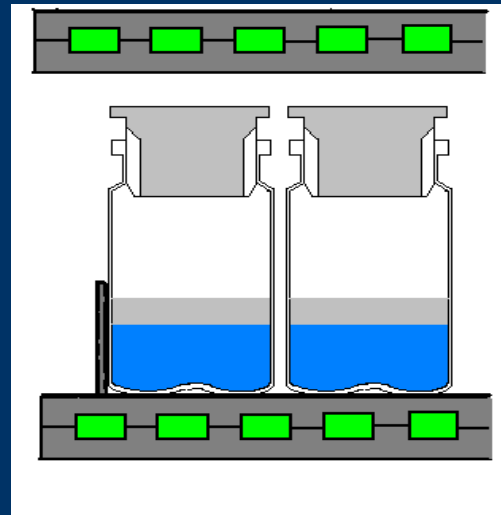
- Why perform Technology Transfer?
 - Introduce a newly developed product or process
 - Product Lifecycle Management
- ICH Q10 Pharmaceutical Quality System¹ – Technology Transfer:
 - New product transfers during development through manufacturing (scale up)
 - Transfers within or between manufacturing and testing sites for marketed products
- Monitoring during scale up and transfer activities can provide an indication of process performance
- Work load associated with technology transfer is dependent on quality of process, equipment and procedural differences between sites

¹ **Guidance for Industry: ICH Q10 Pharmaceutical Quality System. FDA. April 2009**

Lyophilization Process Overview

- The lyophilization step is made up of the following stages:

- Loading
- Freezing
- Primary Drying
- Secondary Drying
- Backfill
- Stoppering
- Unloading



- Lyophilization is directly influenced by heat and mass transfer characteristics of both the system and the formulation
 - Mass transfer a function of container closure, formulation resistance and freeze dryer itself

***Drawings courtesy of S Tchessalov. 2008. Principles of Lyophilization Scale Up. Presented at the Freeze Drying of Pharmaceuticals and Biologicals Conference. Garmish Partenkirchen, Germany**

Technology Transfer Scope

- In Scope:
 - Transfer/ scale up of lyophilization cycle: Modification within filing constraints to 'fit' target system
 - Target applicable analytical characteristics
- Not in Scope:
 - Container closure change – vial & stopper configuration must be identical and processed in the same way
 - Formulation change – a change in excipients and /or concentrations will effect the thermodynamics of the formulation
 - Both changes significantly affect regulatory filing
- Should look for opportunities for process improvements and/ or further optimization within regulatory limits
 - PAT, Robustness studies, optimizing Freezing, Primary & Secondary drying optimization etc.
- Stability studies

Technology Transfer between Manufacturing Sites (Inter or Intra)

- Gather all process and product related information as a **technology transfer package** including analytical methods & process development
 - Retrospective data also very useful in assessing cycle robustness
- Perform a **gap analysis** which will identify areas to focus on, for example:
 - Product Specific Information e.g. Formulation, Thermal Analysis data, stability etc
 - Facilities – Room classifications, cleaning, HVAC etc.
 - Manufacturing e.g. Components, Formulation, Freeze Drying etc.
 - Propose and execute any studies to bridge gaps
 - **Compile document detailing comparability between freeze dryers of interest (Freeze Drying section of gap analysis)**
- **Technology Transfer Protocol** and **Critical Process Parameter** (CPP) assessment must be initiated (CPP assessment to be completed after technology transfer batches)

Technology Transfer from bench to commercial scale (scale up)

- Assumption: good development of lyophilization cycle using QbD methodologies
 - Thermal Analysis
 - Cycle conditions identified
 - Robustness ranges developed
- Comparability studies between bench and commercial freeze dryer should be performed:
 - This will likely identify need to perform heat and mass transfer studies to understand scalability model
- Write Scale Up protocol & execute
- Completion of CPP assessment post technology transfer batch execution

Lyo System Considerations upon Transfer



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- Shelf Cooling and Warming rates:
 - Refrigeration capacity may be different between freeze dryers – may not be able to cool product at the same rate
- Shelf Temperature Control uniformity:
 - Comparable shelf temperature control important to achieve the same conditions during the cycle
- Freeze Dryer Heat Transfer differences:
 - Different primary drying performance as vial heat transfer coefficient (K_v) different
- Radiation (edge) effect :
 - Must consider edge when transferring the cycle
 - Edge effect worse at bench

Lyo System Considerations upon Transfer



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- Condenser Capacity:
 - Condenser must be capable of handling the targeted batch size
- Condenser Operability:
 - LN2; Direct Expansion; Oil e.g. Lexol, Silicone
- Vapor Tube Dimensions:
 - Resistance to rate sublimation if different
- Vacuum Control:
 - Capacitance or thermal resistance
 - Nitrogen Bleed

Lyo Cycle Considerations upon Transfer



- Thermal data availability – mDSC, FDM
 - Critical temperature analysis must be available or thermal analysis must be performed
- Lyophilization development data
 - Has there been any development performed in the past?
 - Retrospective data analysis
 - Target current specifications
- Regulatory Filing – potential limiting factor – can modifications/ improvements be made during transfer?
- Other opportunities could be considered to improve control of the lyophilization cycle step:
 - PAT e.g. TDLAS
 - Potential to optimize the cycle using QbD techniques (within filing changes)
 - Process improvements – control of ice nucleation to improve freezing step

Proposed Technology Transfer Strategy

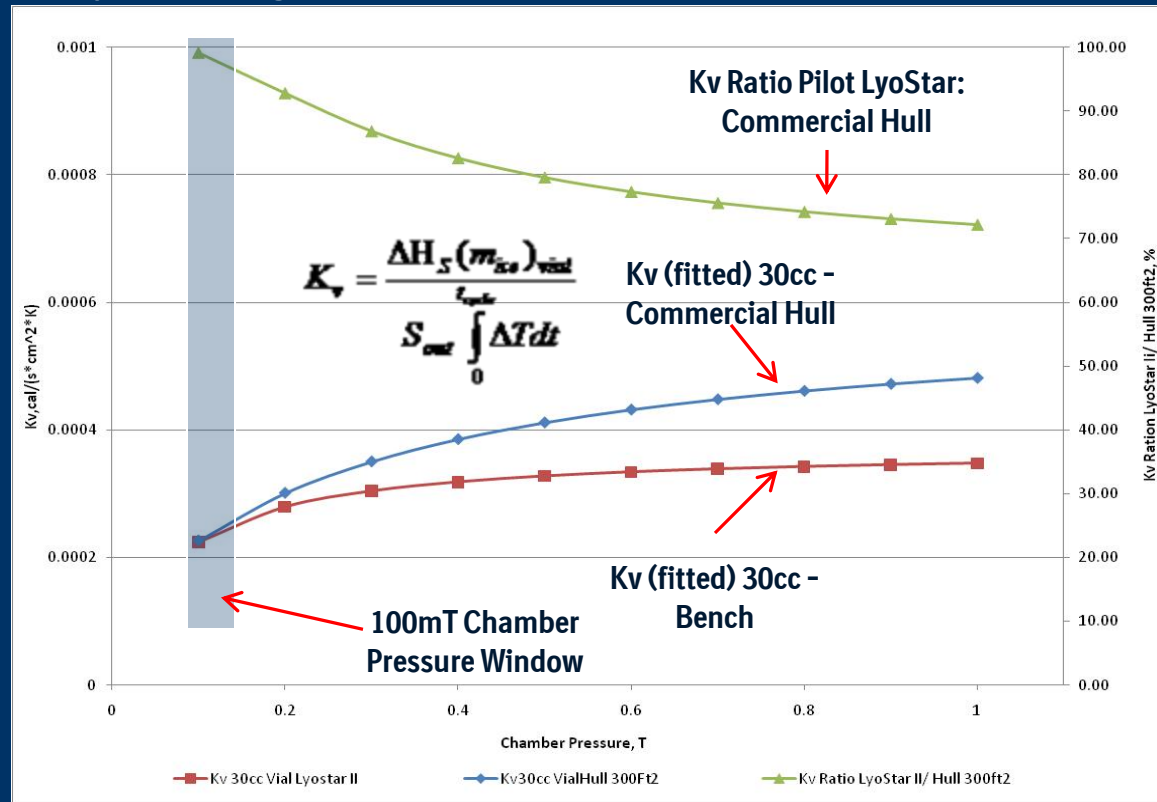


- Gather initial data package
 - Gap analysis
 - Proposed Projects to close any gaps
- Vial Heat Transfer Coefficient (Kv) measurements:
 - A function of chamber pressure (4-5 setpoints)
 - Specific to a given freeze dryer chamber and vial
 - Radiation Effects (edge effect)
- Sublimation/ Mass Transfer Measurements:
 - Pressure control as a function of sublimation rate
 - Min/max cooling and heating
- Propose lyophilization cycle based on cycle data and heat/mass transfer data available
 - Execute technology transfer batch
 - TT Report & CPP analysis

Vial Heat Transfer Coefficient (Kv)

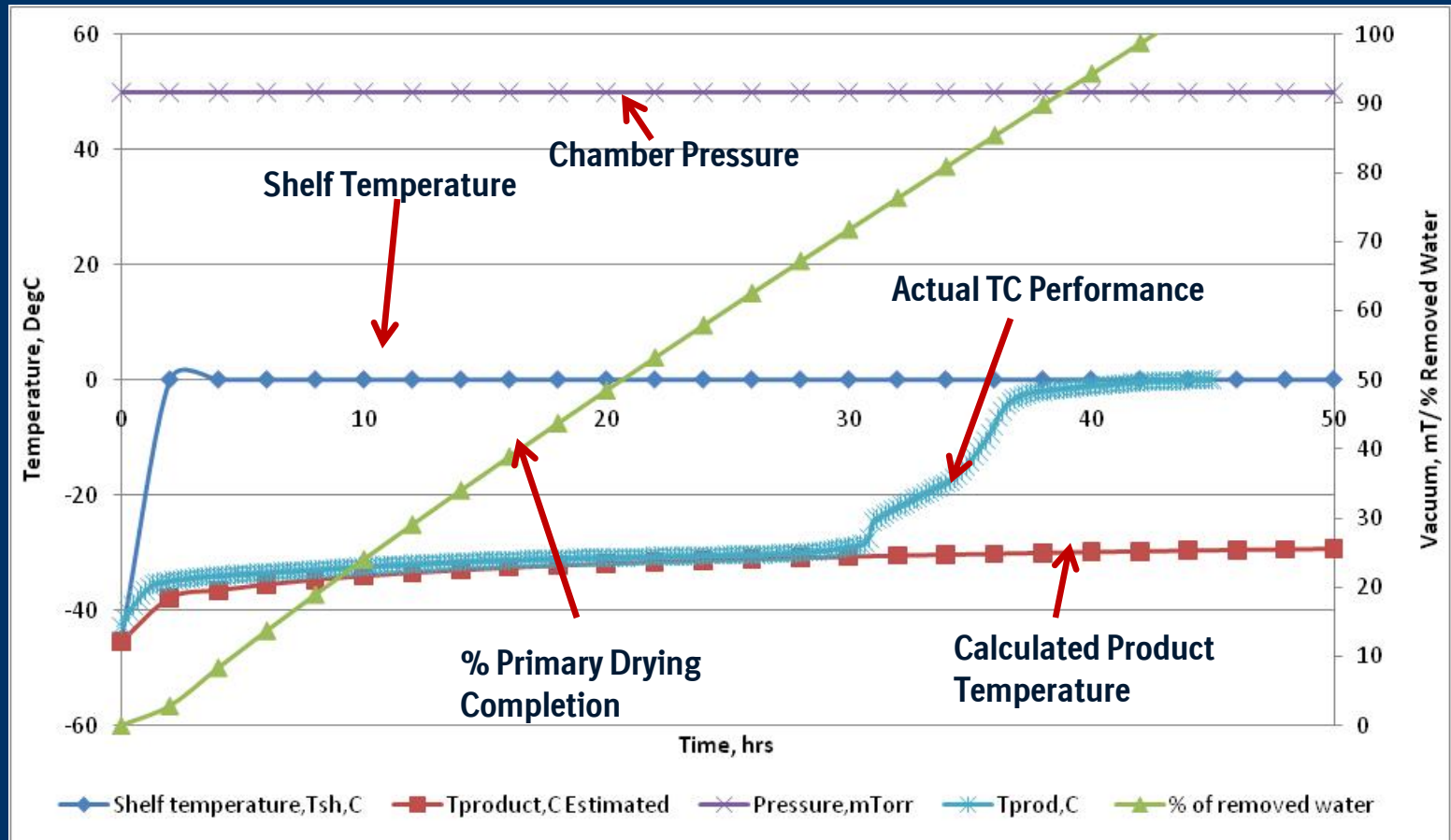
- Ideally, to simplify technology transfer, Kv should be measured as a function of pressure in each freeze dryer for a given vial
- Easy to perform
- Weigh vials filled with water pre and post freeze drying
- Target 20% water loss
- Perform at different chamber pressure setpoints (4-5)
- Clear Scalability link between freeze dryers

$$K_{vial} \left(\frac{Cal}{s * cm^2 * K} \right) 10^4 = a + \frac{b * Pch(mT)}{1 + c * Pch(mT)}$$



S Tchessalov. 2006. Principles of Lyophilization Scale Up. Presented at the Freeze Drying of Pharmaceuticals and Biologicals Conference. Garmish Partenkirchen, Germany

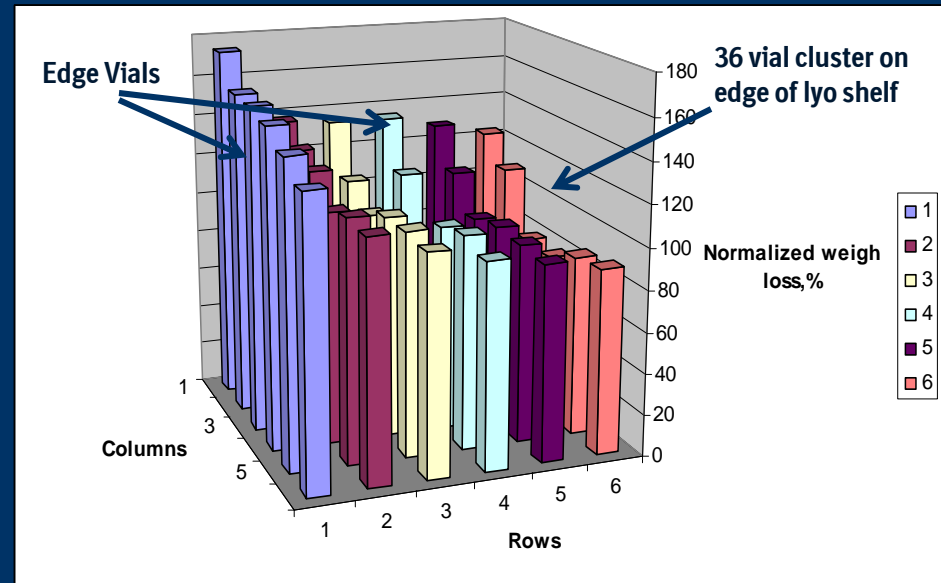
Primary Drying Model Verification Example - Prediction of Product Temperature



Radiation Effects ('edge effect')

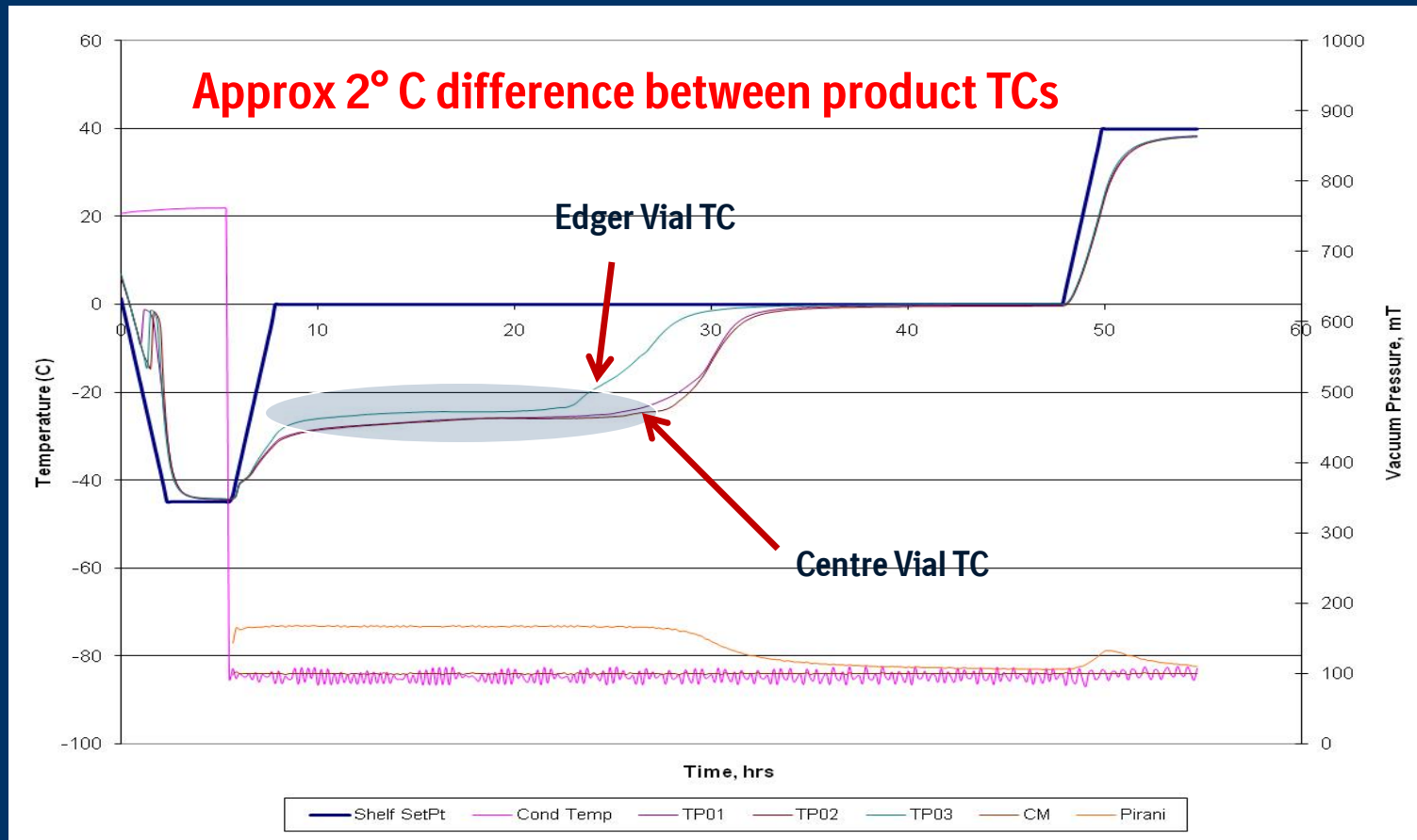
- Examined during the same experiment as the vial heat transfer coefficient measurement

- Edge effect worse at bench
- Chamber set up:
 - Shelf inter distance
 - Material of construction
 - Proximity of walls to product



- Edge vials may display much higher Kv values which results in a higher product temperature under same primary drying conditions
 - If cycle is close to T_c for the centre vials - primary drying may be performed at or above T_c for the edge vials

Radiation Effects ('edge effect')



This may not see significant, but may prove to be if primary drying is aggressive for centre vials!!

Technology Transfer Batches (Lyo specific)

- Purpose:
 - Verify process at scale or in transfer receiving site – Provide lyophilization cycle for validation
 - Generate data to support a validation sample plan by extensively testing across batch and identifying worst case locations e.g. Residual Moisture
- Generally multiple batches to challenge possible load configurations within the lyo
- Knowledge of K_v , R_i and edge effect, the less batch processing work will be required.
 - Therefore, more upfront work, the better
- Note: Supercooling differences between lab and scale or site to site may results in primary drying variability, which is difficult to predict
- Technology transfer protocol, batch record and post run report to feed into process validation (PV)

Primary Drying Endpoint Determination



- Pirani Gauge
 - Pirani identified as the most effective method of primary drying endpoint determination
 - Patel, S.; Doen, T., Pikal, M. 2010. Determination of the End Point of Primary Drying in Freeze-Drying Process Control. AAPS PharmSciTech. 11(1): 73-84.
- Manometric Temperature Measurement (MTM)
 - Barometric Endpoint (Pressure Rise)
 - Gieseler, H.; Kramer, T.; Pikal, M. 2005. Use of manometric temperature measurement (MTM) and SMART freeze dryer technology for development of an optimized freeze drying cycle. PDA Journal of Pharmaceutical Science and Technology. 96(12): 3402-3418.
- Thermocouples
 - Common method: Good product temperature indicator but not fully reliable for primary drying endpoint determination

- Nucleation technology
 - Ice Fog
 - Patel, S.; Bhugra, C.; Pikal, M. 2009. Reduced Pressure Ice Fog Technique for Controlled Ice Nucleation during Freeze drying. AAPS PharmSciTech. 10(4): 1406-1411.
 - ControLyo
 - Sever, R. 2010. Controlling Nucleation in Lyophilization: Effects on Process and Product. Presented at the CPPR Freeze Drying of Pharmaceuticals and Biologicals Conference. Garmish-Partenkirchen, Germany.
- Tunable Diode Laser Adsorption Spectroscopy (TDLAS)
 - Widely studied in the literature – Pikal & Gieseler etc..

- Suggested Lyo Technology Transfer Strategy
- Must perform a gap analysis both on the process and development data
 - Must understand system differences and account for them during transfer
- Considerations around freeze dryer differences with respect to heat and mass transfer dynamics crucial to successful Technology Transfer
 - Vial Heat Transfer Coefficient (Kv)
 - Radiation effects
- Process Improvements – important to look at all options to improve process

Acknowledgements



- Serguei Tchessalov PhD, Principle Research Scientist, Pfizer
- Alex Herbert, MST Ben Venue
- Ben Venue Laboratories MST Pharmaceutical Systems & Pilot Lab departments
- Ben Venue Laboratories Operations Department
- Wyeth Development, Grange Castle, Dublin, Ireland



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Thank you & Questions