Smi Workshop: Lyophilization – Development Through Tech Transfer

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Workshop Topic:
Lyophilization – Development Through Tech Transfer

- Workshop Format
- ICH Q 8: Pharmaceutical Development
- Criticality Analysis as a guide for development of lyophilizates
- Technology Transfer
- Q/A

Agenda

- 9:00 - Introduction
- 9:10 - Development of Lyophilizates – Tarantino
- 9:40 - Roundtable Discussion – All
- 10:30 - Break
- 11:00 - Tech Transfer and Scale-Up – Tarantino
- 11:30 - Roundtable Discussion – All
- 12:20 - Q/A
- 12:30 – End of Workshop

Lyophilization

Lyophilization – why?

- Lyophilization is a drying process which uses sublimation
- Sublimation allows removal of solvents at low temperatures
- Heat and hydrolytically labile solutions therefore benefit by lyophilization
- Generally, for water soluble drugs
- Highest impact in peptide/protein development

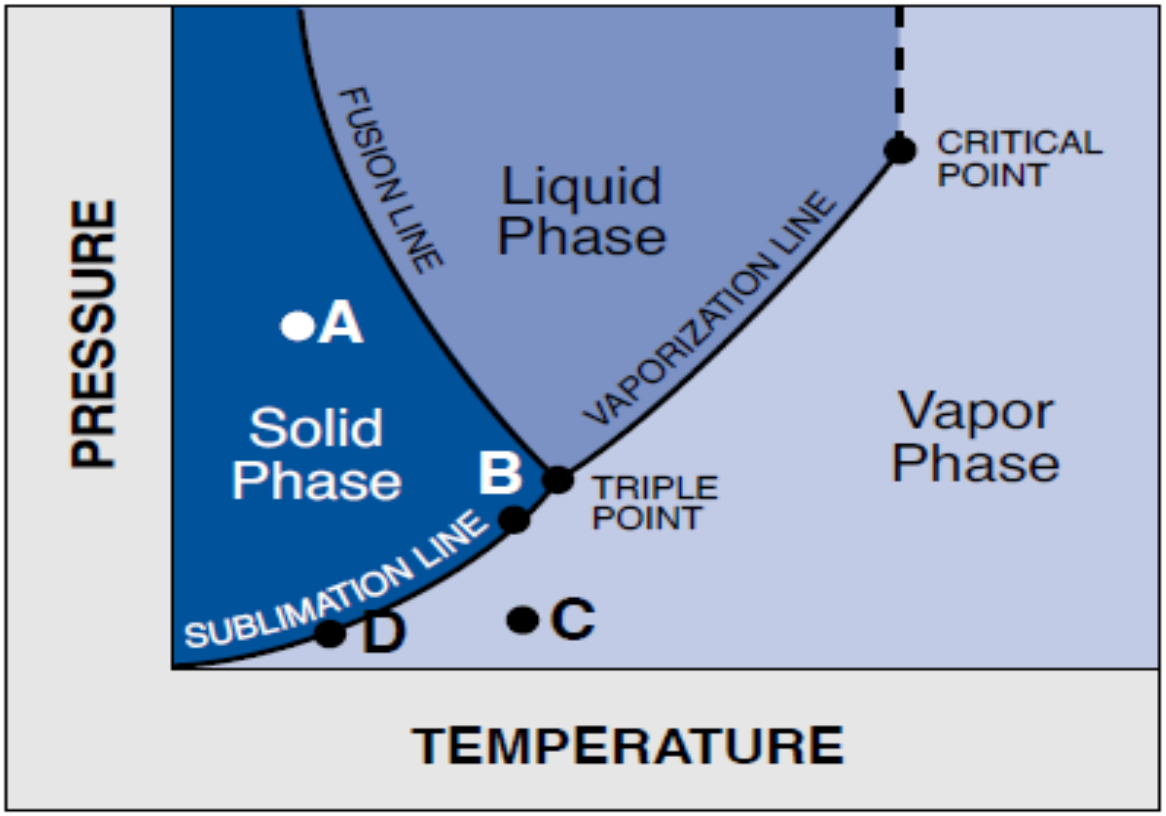
Lyophilization – significant now and in the future?

- Primarily used for peptides/proteins
- Peptide/protein market increasing
- Humira®, Remicade®. Enbrel® Neulasta® etc. all 5 billion + annual sales –Remicade and Enbrel have lyophilized dosage forms
- Biosimilar market increasing
- Solutions preferred but lyophilization likely to remain significant

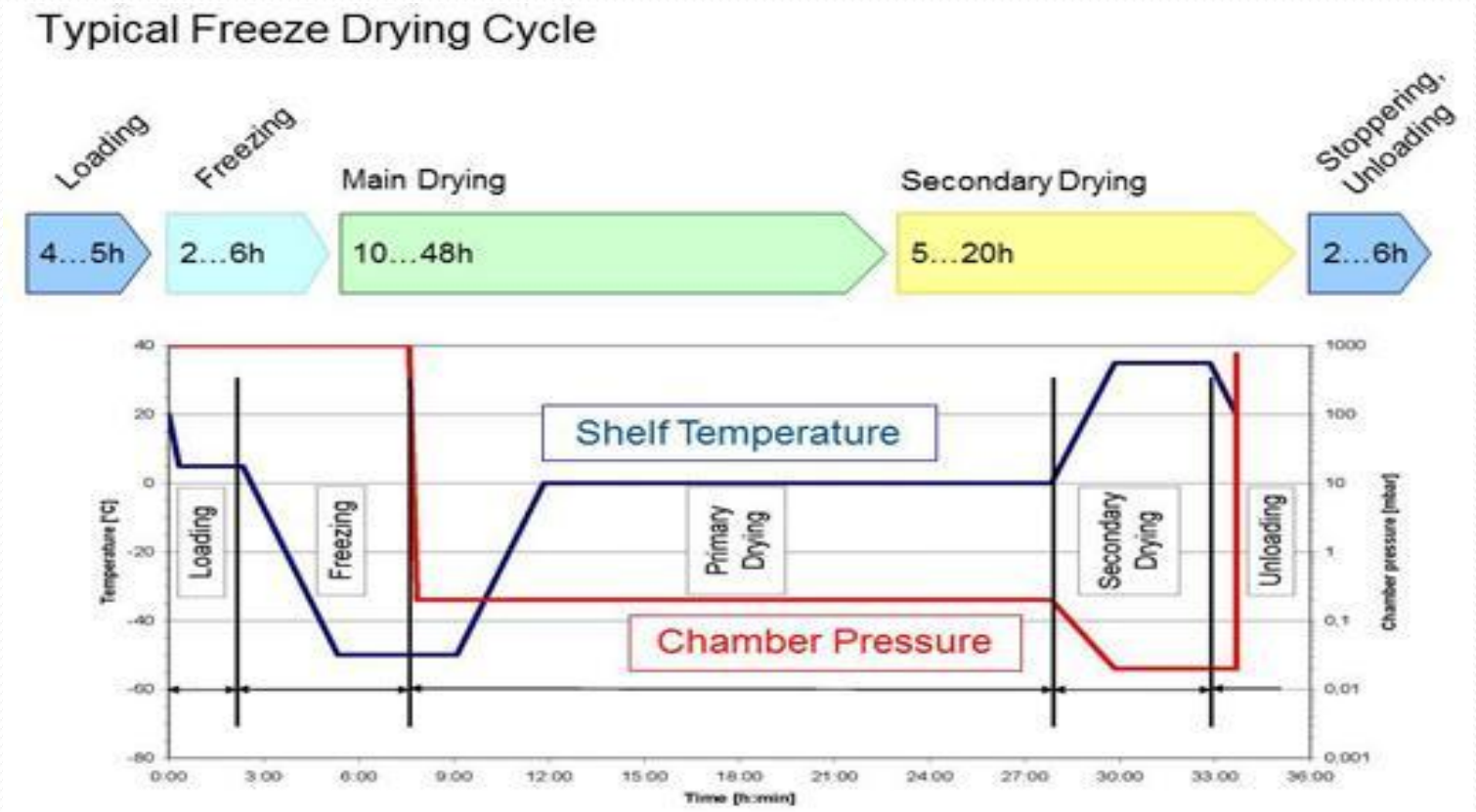
Some Definitions…

- Glass Transition Temperature (T_g) – temperature below which formulations exists in a frozen amorphous sate – formulations tend to soften at their T_g
- Collapse Temperature (T_c) – Temperature at which structure of lyophilized cake softens to a point that it collapses
- Eutectic point (T_{eu}) – Temperature at which lyophilized cake melts

Lyophilization Phase Diagram



Lyophilization Process



Current Pharmaceutical Dosage Form Development

Key Regulatory Input: "Guidance for Industry Q8(R2) Pharmaceutical Development"

– provides outline for Quality by Design (QbD)

ICH Q 8: Pharmaceutical development should include…

- Defining the quality target product profile (QTPP) as it relates to **quality, safety and efficacy**, considering e.g., the route of administration, dosage form, bioavailability, strength, and stability
- **Identifying potential critical quality attributes (CQAs) of the drug product, so that those product characteristics having an impact on product quality can be studied and controlled**
- Determining the critical quality attributes of the drug substance, excipients, etc., and selecting the type and amount of excipients to deliver drug product of the desired quality
- Selecting an appropriate manufacturing process
- **Defining a control strategy**

Quality by Design

- A more systematic approach to development
- Includes:
  - incorporation of prior knowledge
  - results of studies using design of experiments
  - use of quality risk management
  - use of knowledge management
  - enhances achieving the desired quality of the product helps regulators to better understand a company's strategy.

Quality Target Product Profile

- The quality target product profile forms the basis of design for the development of the product. Considerations for the quality target product profile could include:
  - Intended use in clinical setting, route of administration, dosage form, delivery systems
  - Dosage strength(s)
  - Container closure system

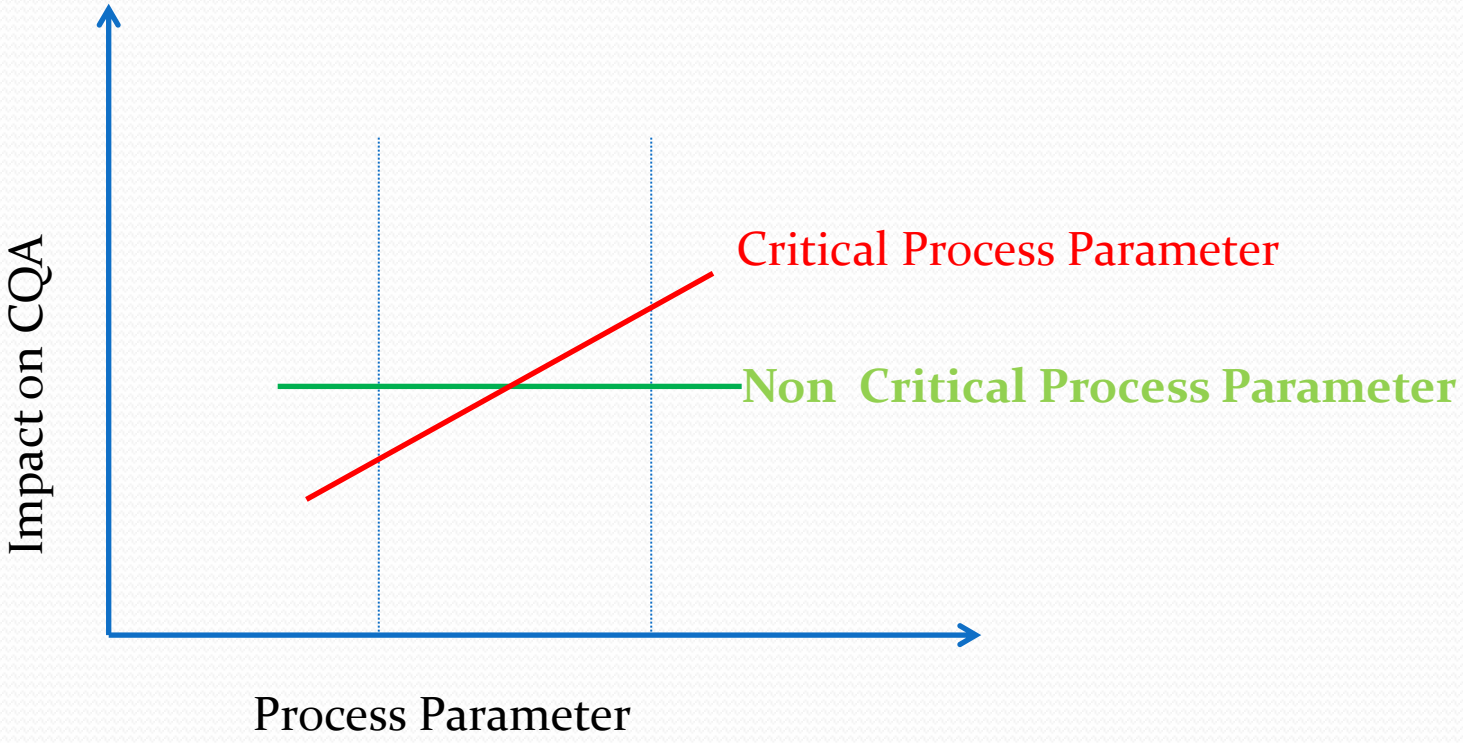
Critical Quality Attribute (CQA)

- A CQA is a physical, chemical, biological, or microbiological property or characteristic **that should be within an appropriate limit, range, or distribution to ensure the desired product quality.**
- CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials), and drug product.

Critical Process Parameter (CPP)

- A process parameter whose **variability** has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality

Critical Process



Risk Assessment

- Risk assessment is a valuable science-based process used in quality risk management that can aid in identifying which material attributes and process parameters potentially have an effect on product CQAs

Design Space

- The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.

  (Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process.)

Control Strategy

- A control strategy is designed to ensure that a product of required quality will be produced consistently.
- The elements of the control strategy describe and justify how in-process controls and the controls of input materials (drug substance and excipients), intermediates (in-process materials), container closure system, and drug products contribute to the final product quality.

Quality by Design – The Process

1. Identify Quality Target Product Profile
2. Identify Critical Quality Attributes (CQAs)
3. Identify Critical Process Parameters (CPPs)
4. Conduct Risk Assessment: Linking Material Attributes and Process Parameters to Drug Product CQAs
5. Develop Control Strategies

Criticality Analysis Exercise

Technology Transfer of Lyophilizates

Bench to Production Scale

Lyophilizer Scale

Scale	Shelf Area	Condenser Capacity
Bench	5 sq ft	4 Kg
Pilot	25 sq ft	40 Kg
Production	500 sq ft	800 Kg

Tech Transfer Process

Demo Batch – R&D Site (R&D "Owner")

↓ R&D and Production Sign-Off

Demo Batch – Production site(R&D "Owner")

↓ R&D and Production Sign-Off

First Scale-Up – Production Site (Production "Owner")

↓ Production Sign-Off

Document Transfer : R&D to Production

↓ Production Acceptance

Tech Transfer Complete

Questions – Other Tech Transfer Models?

“Classical” Tech Transfer: R&D to Production

- Eutectic Point
- Precooling of shelves
- Lyophilization cycles
- Residual Moisture
- Chamber Pressure during closing vials
- Others?

Difficulties in Tech Transfer for Lyophilizates*

- Variations in pressure in the drying chamber depend on freeze-dryer geometry
- The nucleation temperature can vary with environmental conditions in the manufacturing area
- Temperature of the heat transfer fluid can vary with the equipment, although the same set-point value is used
- Rate of heating and cooling for the heat transfer fluid may vary with the equipment used
- Different freeze-dryers may show variations in radiative heat between shelves and chamber walls, because of different values of view factor and surface emissivity
- In laboratory and production freeze-dryers, the condenser may impart a different resistance to mass transfer (e.g., because of a different configuration, internal vs. external condenser), or show a different capability to remove vapor and control pressure inside the drying chamber

*Pisano R, Fissore D, Barresi AA, Rastelli M. Quality by Design: Scale-Up of Freeze-Drying Cycles in Pharmaceutical Industry. AAPS PharmSciTech. 2013;14(3):1137-1149. doi:10.1208/s12249-013-0003-9.

Less empirical process parameters?

- Heat Transfer Coefficient? – heat flux per change in temperature due to different conditions/materials batch sizes?
- Resistance to Vapor Flow? – differences in condenser performance ?
- Others?
- QbD to control these parameters?

Topics for Discussion

- Eliminating product adhering to vial walls and stopper?
- Reducing long cycle times (>24 hours)?
- Developing a lyophilization cycle
- Outsourcing vs. in-house

FDA Inspections of Lyophilized Products

GUIDE TO INSPECTIONS OF LYOPHILIZATION OF PARENTERALS (1993)

- First – An aseptic process
- Low fills not apparent after lyophilization
- Ice on shelves - problematic
- Frozen – well below eutectic point
- Primary drying - at least 4 - 50 below the eutectic point

GUIDE TO INSPECTIONS OF LYOPHILIZATION OF PARENTERALS (1993)

- The scale-up and change of lyophilization cycles have caused problems
- Necessary instrumentation to control and record the key process parameters. These include:
  - shelf temperature
  - product temperature
  - condenser temperature
  - chamber pressure and
  - condenser pressure

GUIDE TO INSPECTIONS OF LYOPHILIZATION OF PARENTERALS (1993)

- The manufacturing directions should provide for time, temperature and pressure limits
- Making continuous changes throughout run results in non-validated process
- Perform a leak test at some time after sterilization, possibly at the beginning of the cycle or prior to stoppering.

GUIDE TO INSPECTIONS OF LYOPHILIZATION OF PARENTERALS (1993)

- Plan of action for equipment failure
- Process with many variables
- As with the scale-up of other drug products, there should be a development report that discusses the process and logic for the cycle.
- **Probably more so than any other product, scale-up of the lyophilization cycle is very difficult**.

GUIDE TO INSPECTIONS OF LYOPHILIZATION OF PARENTERALS (1993)

- A manufacturer that has one cycle for multiple strengths of the same product probably has done a poor job developing the cycle and probably has not adequately validated their process.
- Investigators should review the reports and data that support the filed lyophilization cycle.