Current Lyophilization Initiatives: Integrating Good Science and Regulatory Perspectives

PDA New England Chapter Meeting

January 9, 2013

Current Lyophilization Initiatives

- **Product Design**
- **Development Activities**
- **Finished Product Attributes: CQA**
- **Process Engineering: CPP**
- **Principles of Validation**

Product Design

- **Therapy Regime**
  - *dosage and frequency*
- **Route of Administration**
  - *IV (push/drip), IM, SC, other*
- **Product Delivery**
  - *convenience, compliance and safety*

Product Design Aspects
Unique Design Objectives

- **Product converted and stored as a solid dosage form.**
- **Requires addition of a diluent to reconstitute and administer.**

Product Design Aspects
Unique Design Objectives

Unit dose – patient delivered entire contents
Liquid Stability
– Bulk solution
– Constituted product
Solid State Stability – long term RT storage
Formulation Constructs – unique requirements
Microbiological Considerations – unpreserved
Product Delivery - packaging

Product Design Aspects
Unique Design Objectives

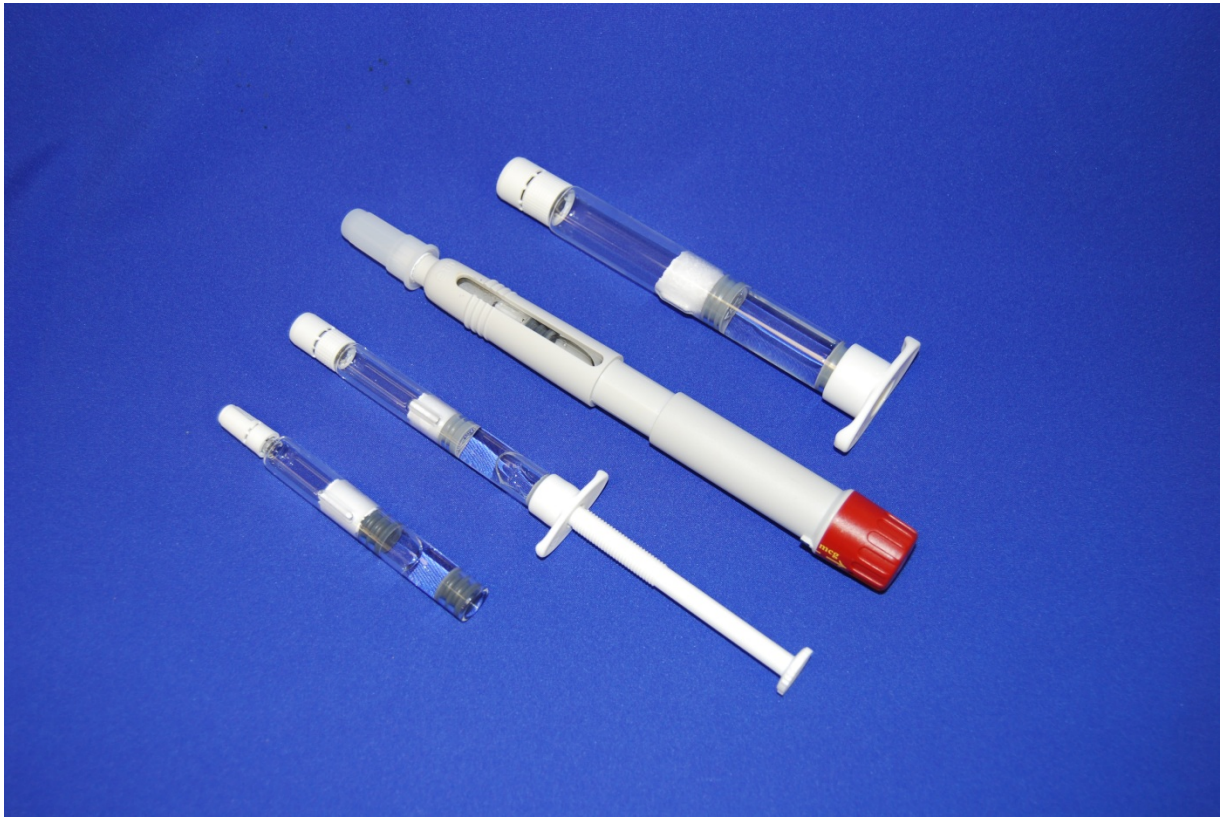
Packaging considerations

- ***Suitable for dosage form***
- ***Processing requirements***
- ***Convenience and compliance***
- ***Cost of product delivery***

Conventional Lyophilized Presentation

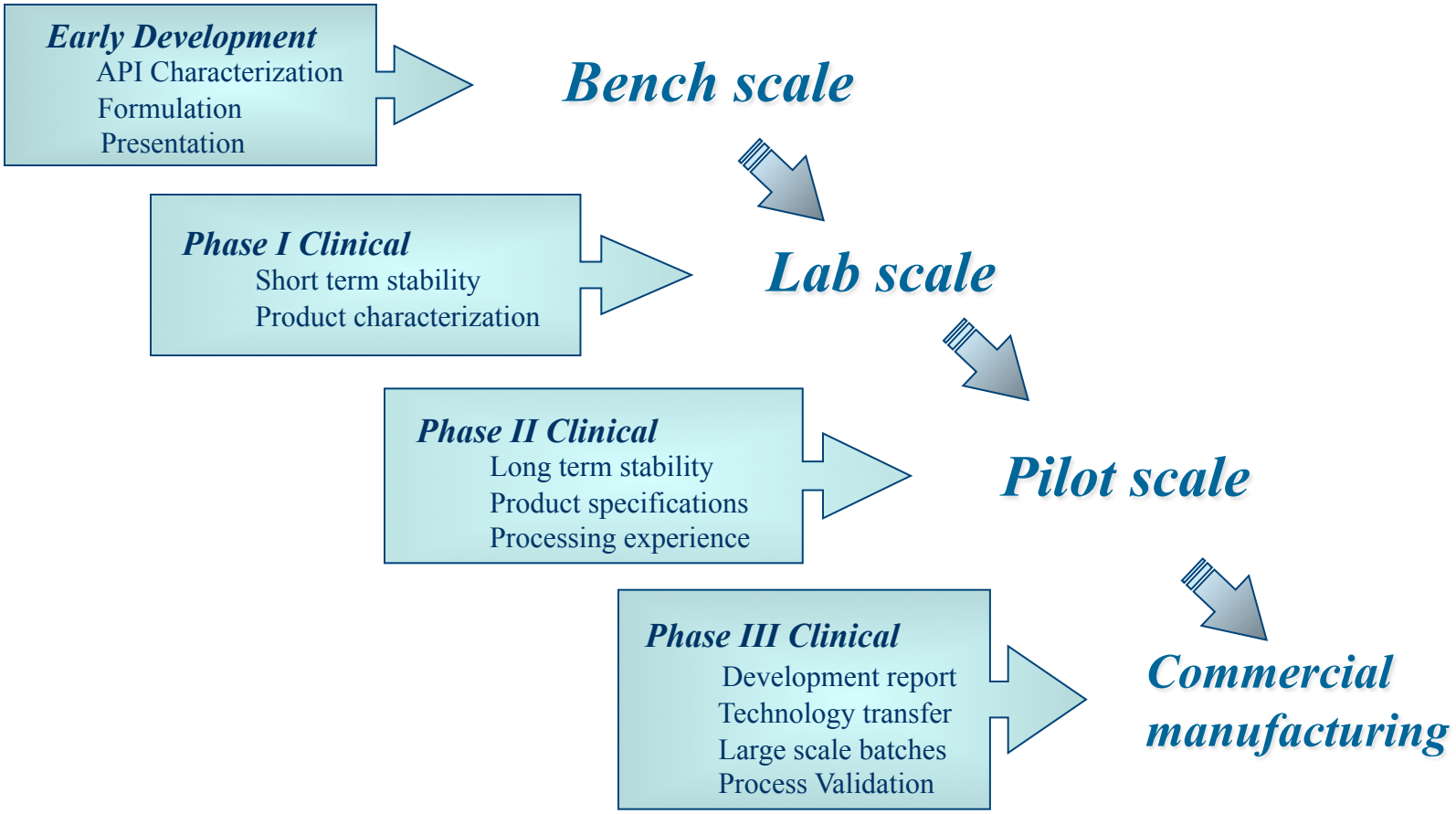
Convenient Reconstitution: Product "Kits"

Convenience for Delivery: Self Administration



from "Practical Aseptic Processing: Fill and Finish"

Development Pathway



Considerations

Development

- **Quality attributes of API**
- **Critical Quality Attributes (CQA)**
- **Critical Process Parameters (CPP)**
- **Stability: liquid and finished product**

Development Story Line

- **Finished product quality attributes (CQA) and process parameters (CPP) are identified during development.**
- **Technology is transferred from development and verified to be suitable for manufacturing.**
- **Reproducible process parameters and consistent product attributes are demonstrated in manufacturing.**

Formulation Constructs
Composition Variables

Character of API

Solubility / concentration

Needs / function of excipients

Suitability for administration

Formulation Constructs

Excipient Functions

- Stabilizers
- Bulking agents
- Isotonicity modifiers
- pH / buffering agents

Formulation Design

Characteristics of compositions

- ***Specific functions for each***
- ***Consequential synergistic effects***
- ***Behaves most like principle constituent***
- ***Dependent upon molar ratio***

Solvents

- ***Aqueous systems preferred***
- ***Organic solvent as additive***
  - ***Solubilize API***
  - ***Enhance dried product attributes***
  - ***Processing aid***

Solvents - Considerations

- ***Organic solvent as additive***
  - ***Limited choices (EtOH, TBA)***
  - ***Minimize concentration***
  - ***Processing challenges***
  - ***Residuals a concern***

Product Attributes

- **Critical Quality Attributes (CQA)**
  - for bulk solution
  - as dried product
  - upon reconstitution
  - at time of administration

Product Attributes – Liquid Parenteral

- **Critical Quality Attributes (CQA)**
  - **Defects, absence of particulate**
  - **Identity, assay and purity**
  - **Sterility and Endotoxin**

Product Attributes – Lyophile Parenteral

- **Critical Quality Attributes (CQA)**
  - **Residual Moisture**
  - **Constituted solution**
  - **Content Uniformity**
  - **Physical Appearance**

Finished Product Attributes

- **Acceptable Residual Moisture**
  - ***Correlated to solid state stability***
  - ***Individual values indicated***
  - ***Stated as average with high and low***
  - ***Reported as a range***

Finished Product Attributes

Reconstitution

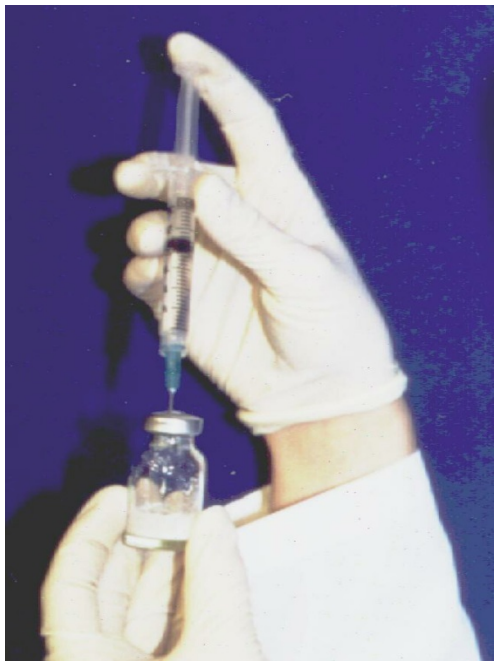
- Time

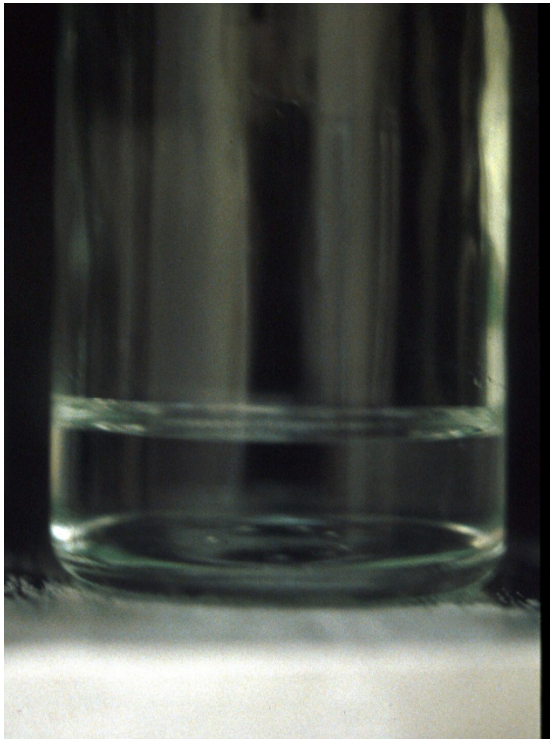
Solution appearance:

completeness,

clarity,

color.





Finished Product Attributes

Reconstitution

- *Solution appearance: completeness,*

  clarity,

  color.

Finished Product Attributes

Dried cake appearance

- **Expected appearance:**

  Color, density, uniformity, shrinkage

Finished Product Attributes

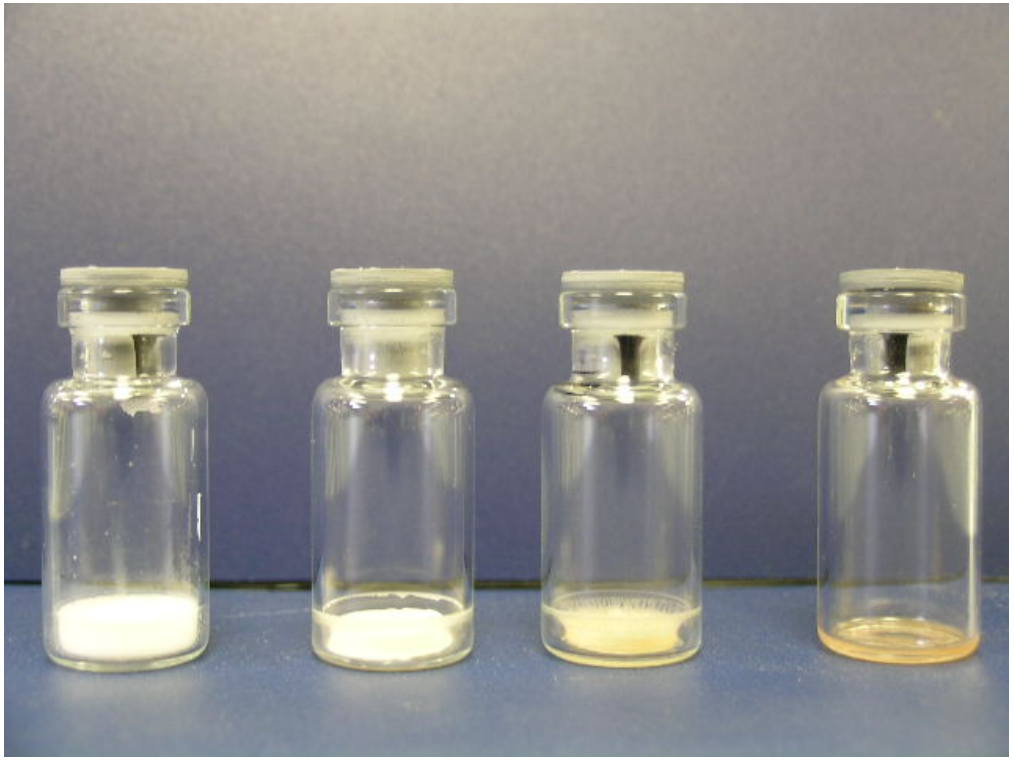
Dried cake appearance

- *Expected appearance:*
  - *Color, density,*
  - *uniformity,*
  - *shrinkage*

Finished Product Attributes

Dried cake appearance

- **Expected appearance:**
  - **Absence of collapse**



Finished Product Attributes

Dried cake appearance

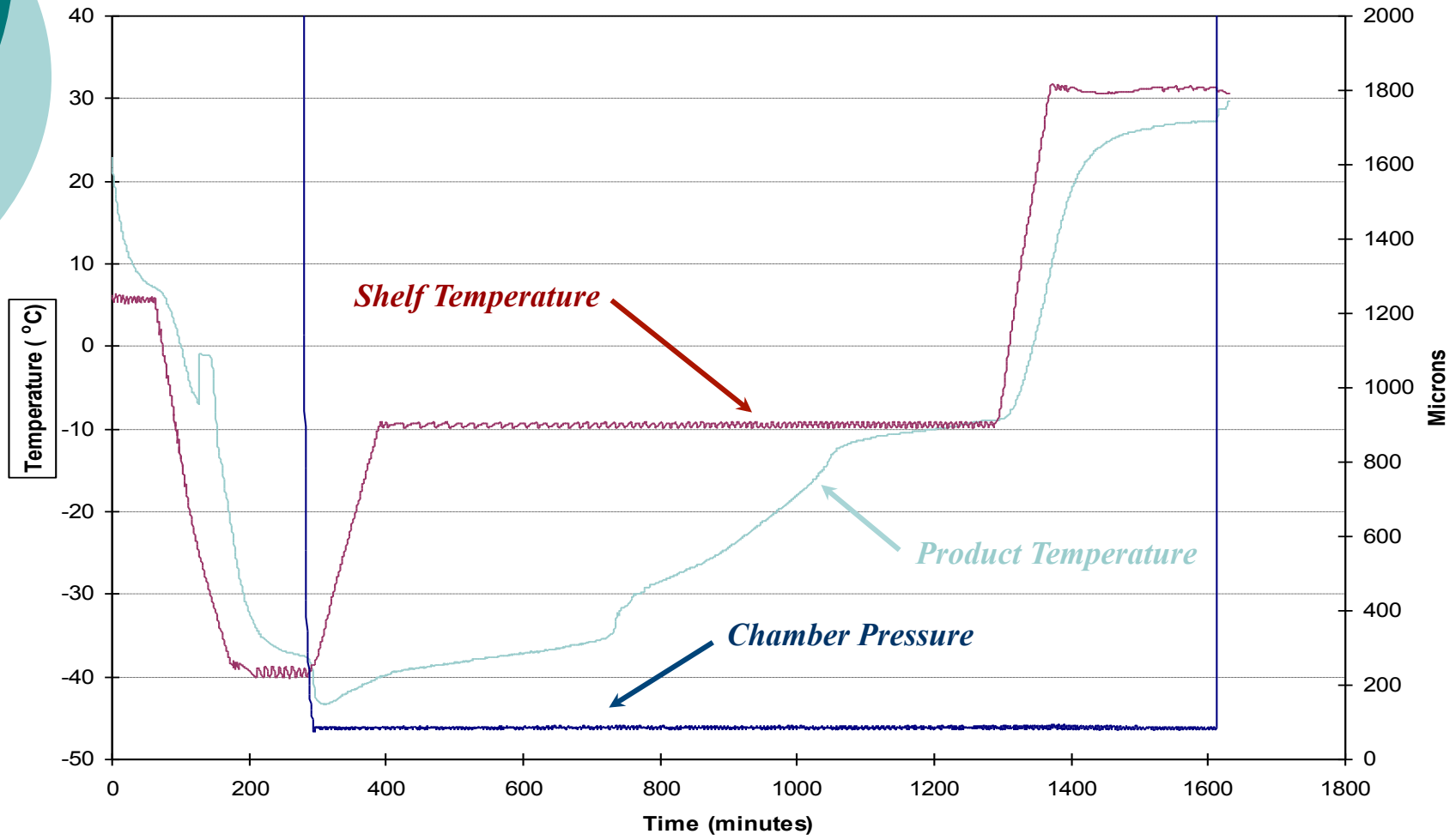
- **Expected appearance:**

  Absence of meltback

Process Parameters

- **Critical Process Parameters (CPP)**
  - Shelf temperature
  - Chamber pressure
  - Time
- **Key Process Parameters (KPP)**
  - Product temperature
  - Condenser temperature

Process Engineering



Project Steps: Flow of Events

SHOULD BE:

BIO-BATCHES
(***Product Specifications***)

SCALE UP BATCHES
(Process Parameters)

DEVELOPMENT REPORT

VALIDATION PROTOCOL

VALIDATION BATCHES

VALIDATION REPORT

Project Steps: Flow of Events

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DEVELOPMENT REPORT

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OFTEN IS:

BIO-BATCHES

SCALE UP BATCHES

DEVELOPMENT BATCHES

DEVELOPMENT BATCHES

DEVELOPMENT BATCHES

VALIDATION REPORT

Heather Pederson, former Pre-Approval Inspection Program Manager, USFDA (Newark District)

Validation Objectives

- ***Address and Document***
  - Intended outcome of process
  - Critical processing parameters
  - Key processing parameters
  - Critical quality attributes
  - In-process and finished product testing
  - Stability data

Validation for Compliance
Example of an Objective

The objective of validation for XYZ is to show that (product) manufactured and tested in accordance with Master Batch Record ABC and Validation Protocol 123 will consistently meet its predetermined specifications and quality attributes. This will be done using 3 consecutively manufactured batches of product.

Heather Pederson, former Pre-Approval Inspection Program Manager, USFDA, ORA (Newark District)

Development for Quality
Example of an Objective

Design Excellence (DEX) / Design for Six Sigma (DFSS)

Achieving Design Excellence using a set of design tools and methodologies for improving product and process development to consistently provide reliable and manufacturable products that consistently meet customer requirements.

Denise Hudson, VP Worldwide Process Excellence, J&J Pharmaceutical Group

Validation for Quality

Design for Six Sigma

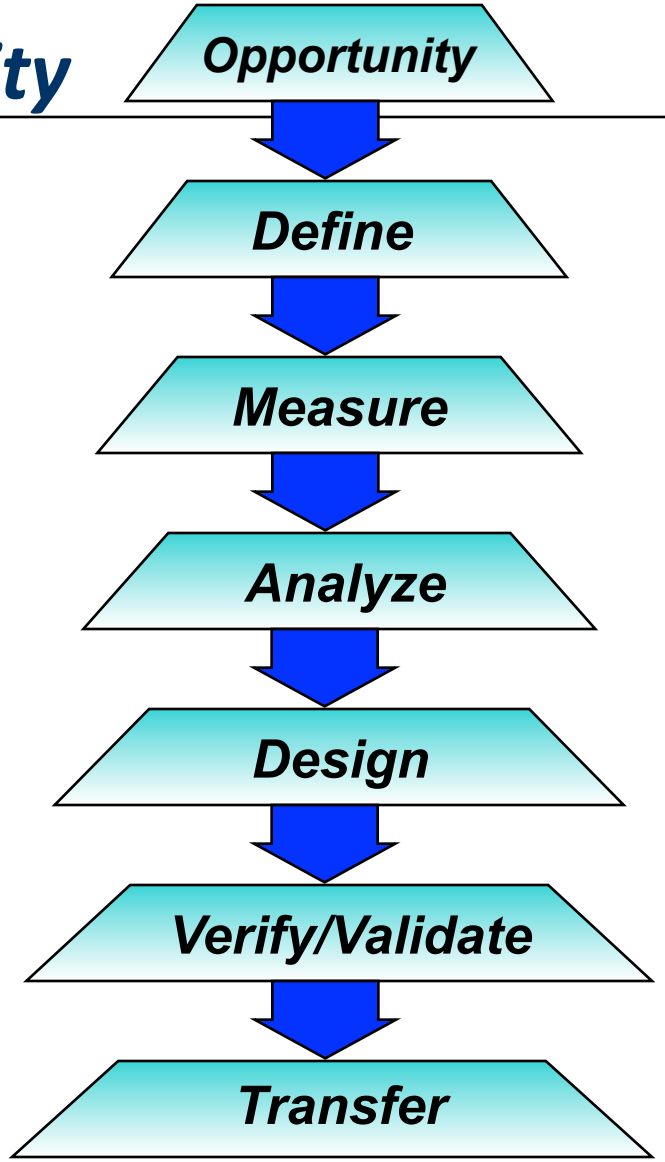
Define
Develop Scope and Charter the Project

Measure
Gather & Quantify Design Inputs

Analyze
Develop and Investigate Conceptual Designs

Design
Develop Detailed Product Design & Production Process

Verify/Validate
Confirm design outputs meet design input requirements and ensure specifications conform with Intended Uses and Users



Achieving Design Excellence

- **Product design (CQA) and processing conditions (CPP) are identified during development.**
- **Reproducible CPP and CQA are verified during scale-up and technology transfer.**
- **Control and reproducibility of the process to consistently yield product of acceptable quality, purity, and efficacy is verified during manufacturing.**

FDA Validation Guidance
Life Cycle Approach

Collection and evaluation of data, from the process design through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products.

Paradigm Shift

1987 - 2011: "…documented evidence…"

(Run 3 X's in Manufacturing)

2011 - current: "…collection and evaluation…"

(Development - Scale-up – Routine Manufacturing)

Process Parameters

- **Process capability**
  - ***Process knowledge, understanding***
  - ***process parameter relationships to quality attributes***
- **Causes of variability**
  - ***Sources***
  - ***Impact***

Process Capability

- ***Definition of Critical Process Parameters***
- ***Identified Independent vs. Dependent***
- ***Targeted Processing Parameters***
- ***Proven Acceptable Range***

Proven Acceptable Range
Boundary Studies

Three batches at target conditions

- ✓Process conducted at “ideal” parameters

Four batches at boundary conditions

- ✓ High and low shelf temperatures
- ✓ High and low chamber pressures

Proven Acceptable Range
Boundary Studies

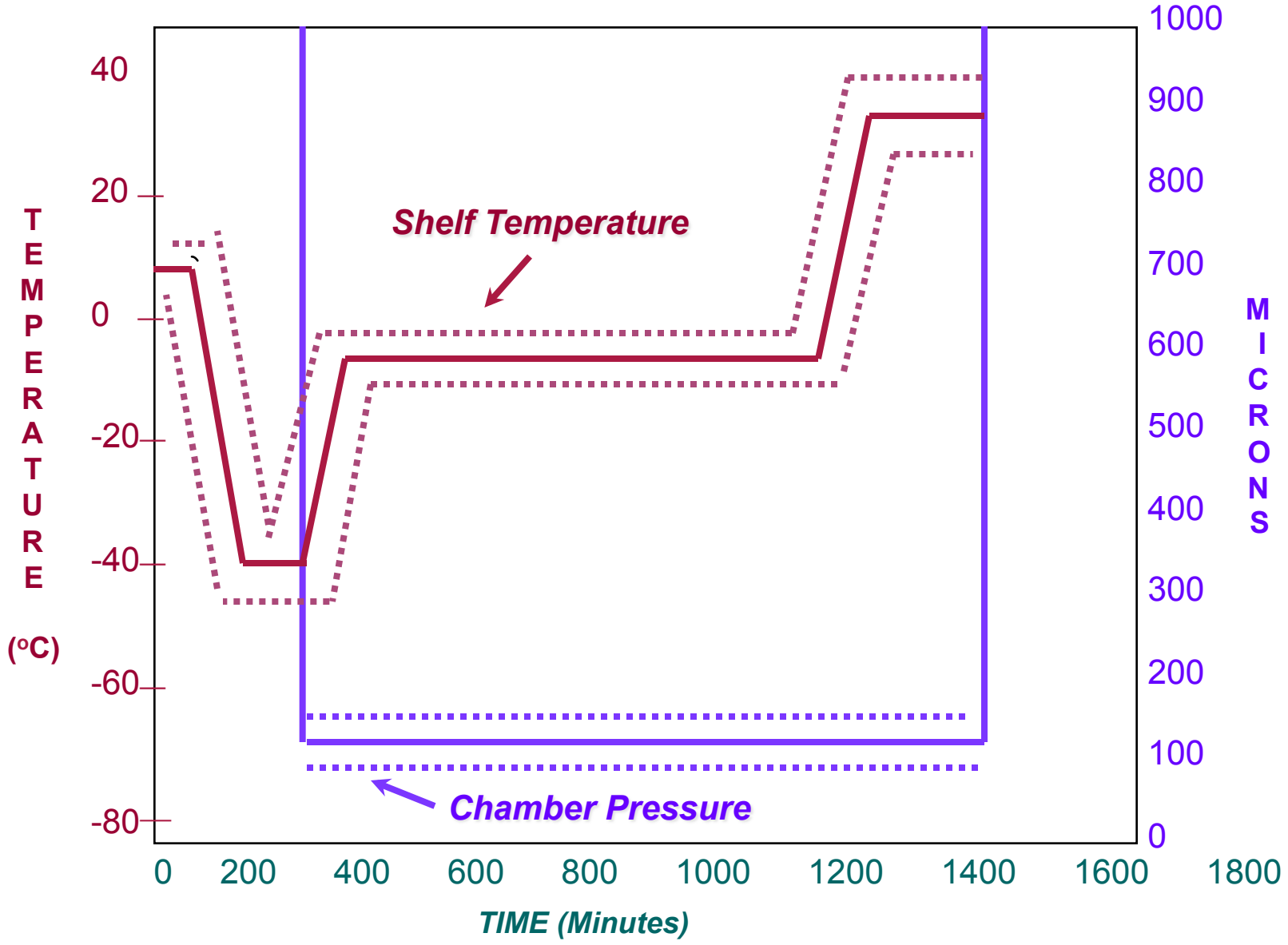
Three batches at target conditions

- ✓ Demonstrates reproducibility
- ✓ Confirms consistent product qualities

Four batches at boundary conditions

- ✓ Envelopes processing conditions
- ✓ Establishes proven acceptable range

Acceptable Boundary Conditions



Proven Acceptable Range
Boundary Studies

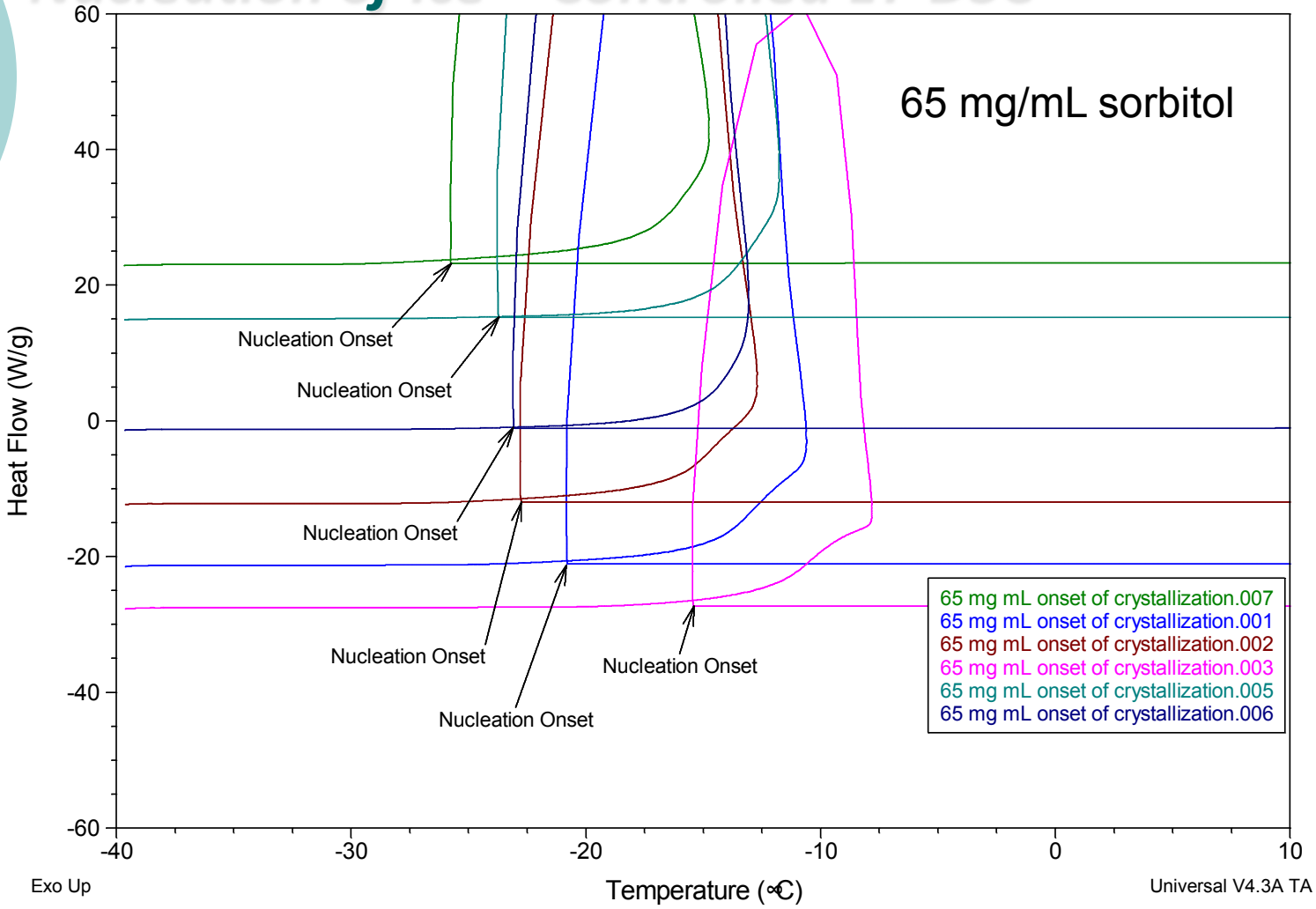
- ✓ ***Define acceptable critical parameter range***
- ✓ **Verify with product analysis and stability**

Process Parameters

- **Process capability**
  - ***Process knowledge, understanding process parameter relationships to quality attributes***
- **Causes of variability**
  - ***Sources***
  - ***Impact***

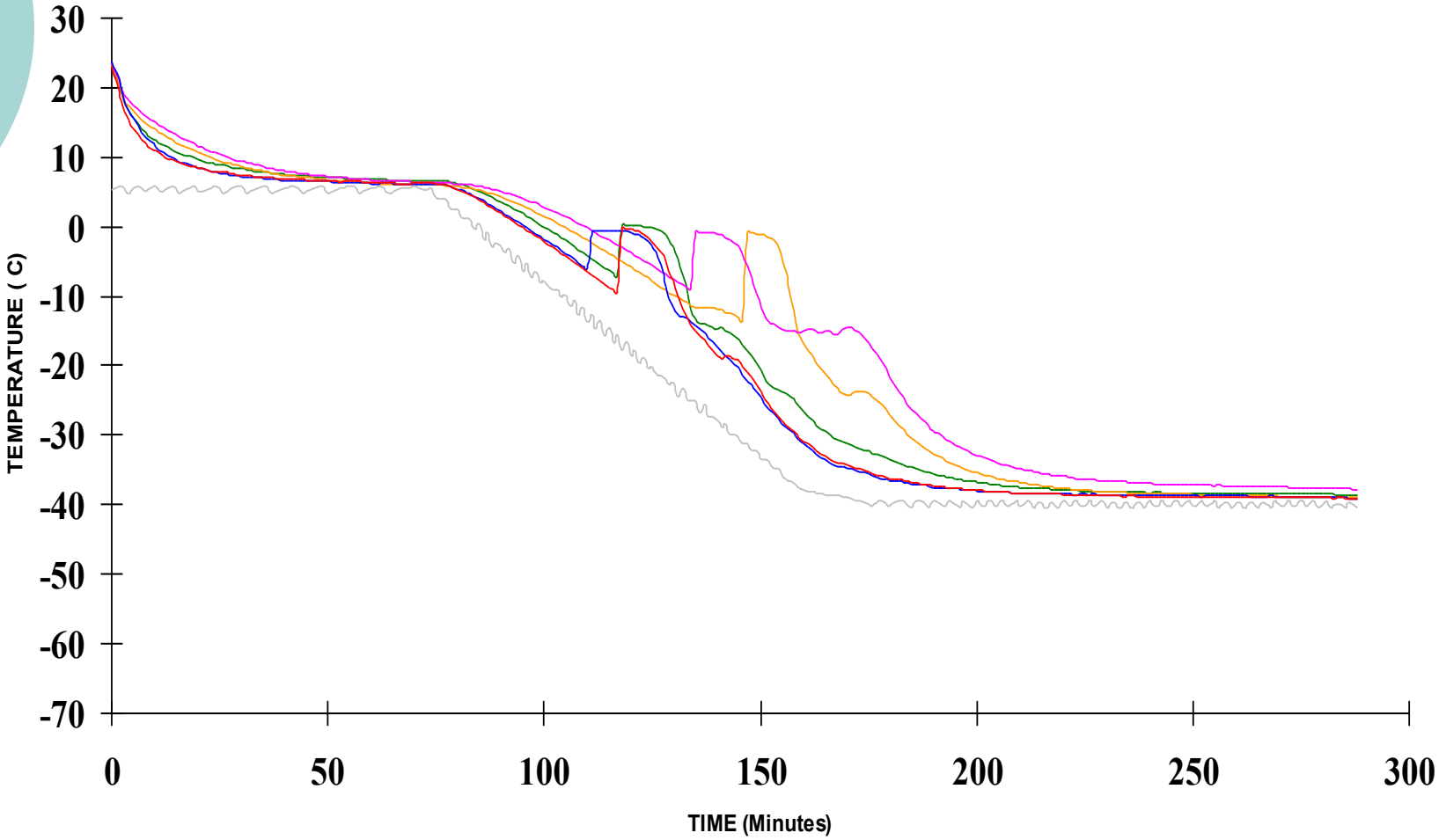
Causes of Variability

Nucleation of Ice – Controlled LT-DSC



Causes of Variability

Nucleation of Ice – Product monitoring



Causes of Variability

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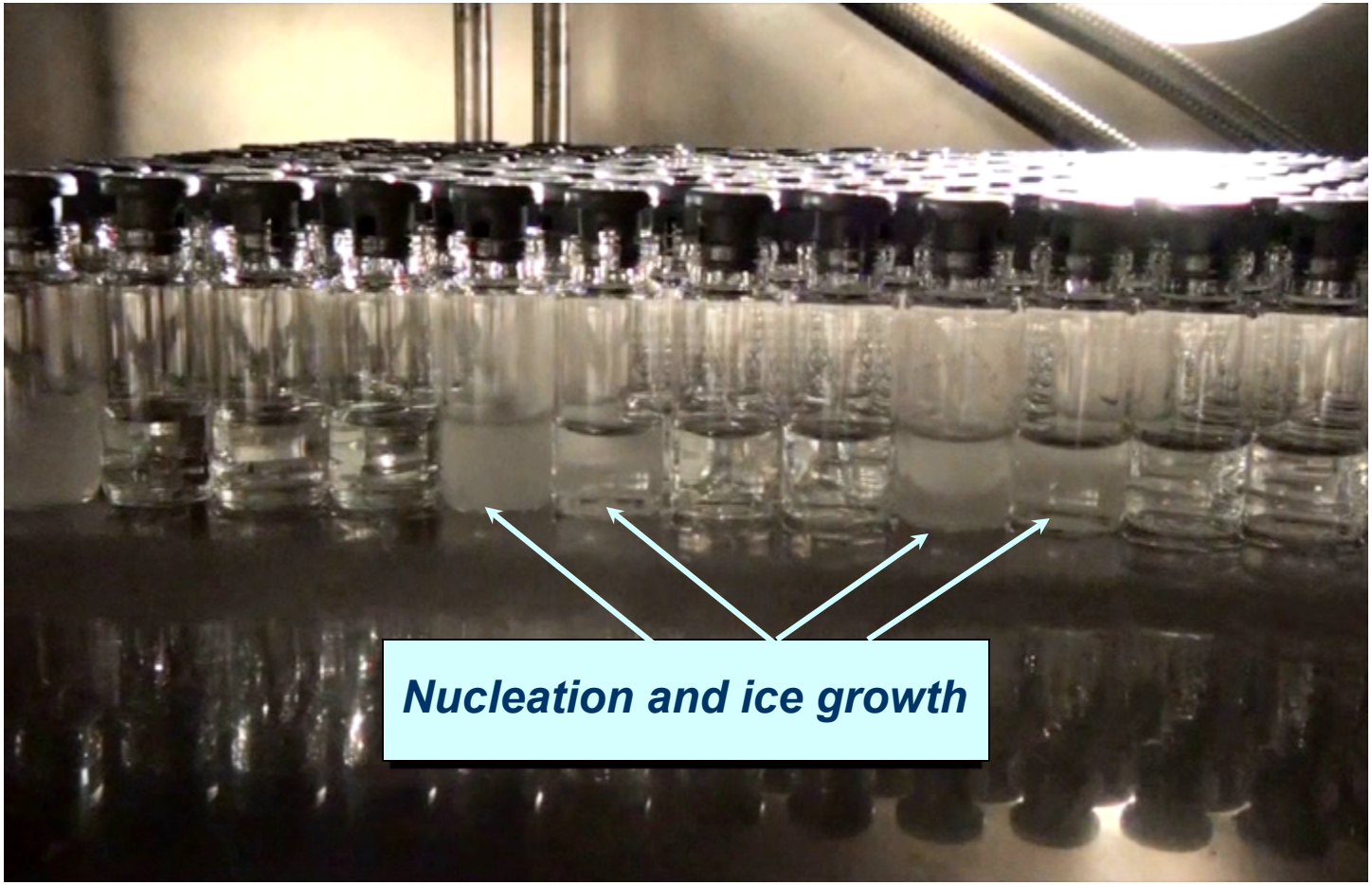
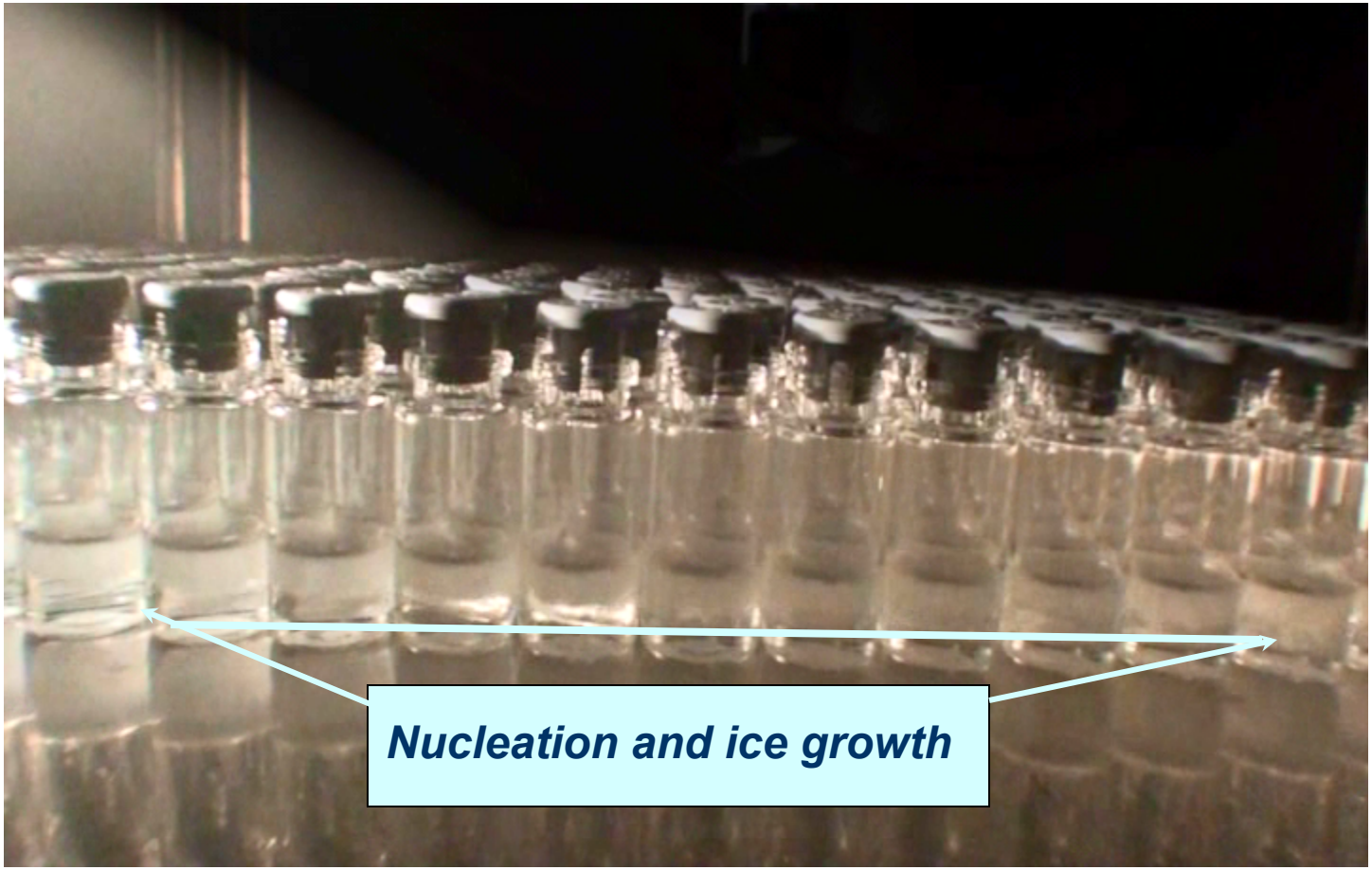


Finished Product Attributes

- ***Effect on appearance:***
  Color, density, uniformity, shrinkage

Causes of Variability

Nucleation of Ice



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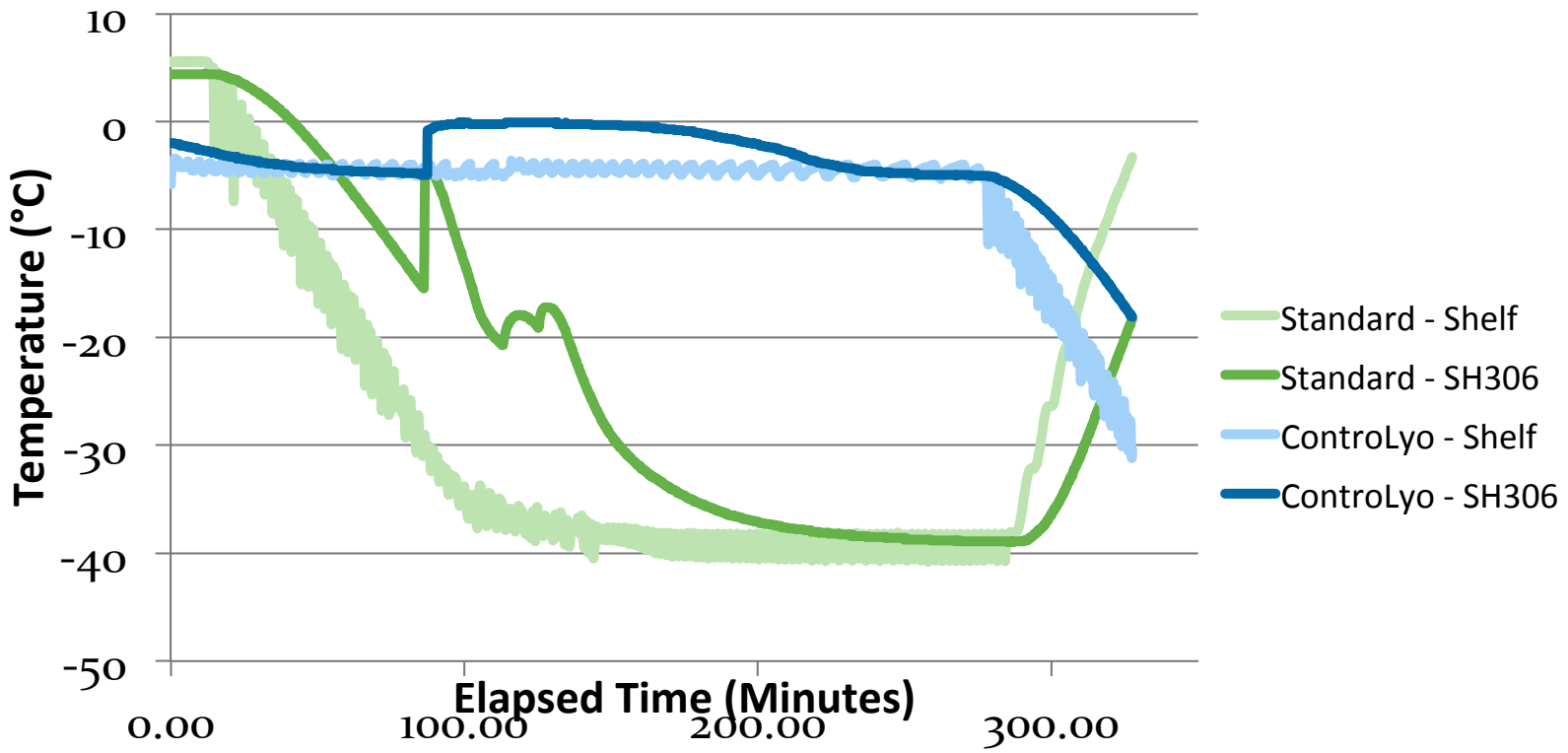

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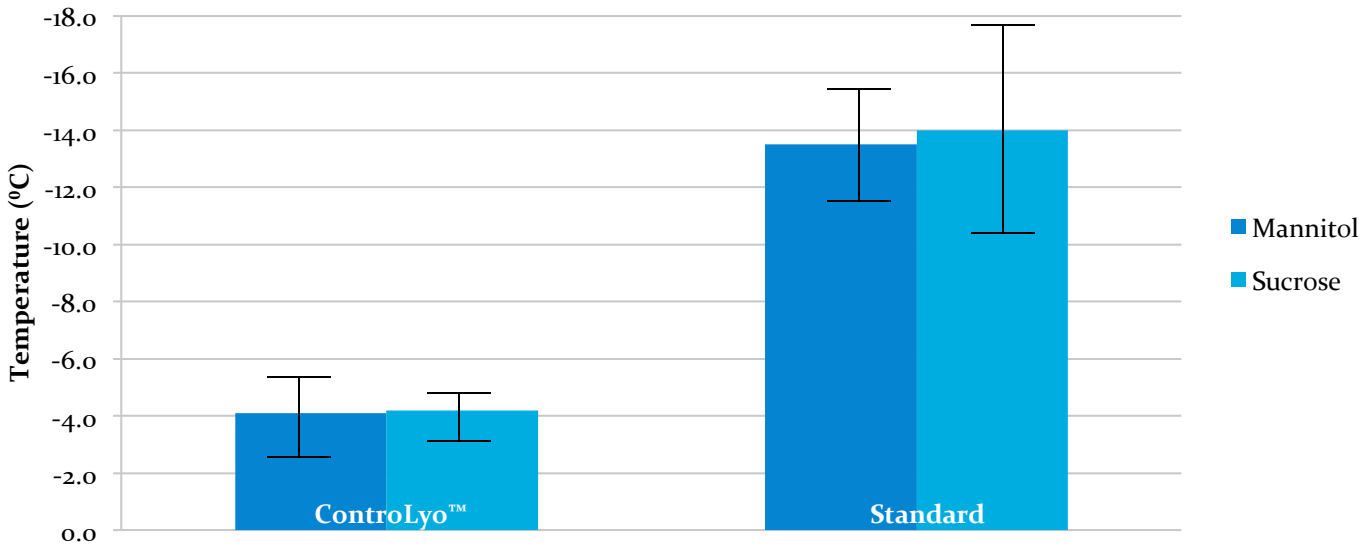

	Product Temperature (°C)			
	Mannitol		Sucrose	
	Average	Std. Dev.	Average	Std. Dev.
ControLyo™	-4.1	1.0	-4.2	0.7
Standard	-13.5	2.0	-14.0	3.4

Considerations: Development

- ***Critical process parameters (CPP) and Critical Quality Attributes (CQA) are identified during development.***
- ***Reproducible process parameters and consistent product quality are quantified during validation (Process Performance Qualification, PPQ).***
- ***Quality attributes of Active Ingredient and stability of finished product are verified.***

Considerations: Scale-up / Transfer

- ***Processing equipment is qualified for processing requirements.***
- ***Technology is transferred from development to manufacturing.***
- ***Reproducible process parameters, batch uniformity and consistent product characteristics are verified in manufacturing.***

Considerations: Routine Manufacturing

- ***Critical Process Parameters and controlled and monitored.***
- ***Critical Quality Attributes are assessed.***
- ***CPPs and CQAs are trended to demonstrate reproducible process parameters and consistent product quality to assure a continuing level of control.***