ASHRAE Technical Symposium Series May 2018
Refrigeration in the Biotech industry

learn.

The project delivery specialists
Introduction
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M.I.E.I

Background:
Commenced Career as Design / Project Engineer at Brian A. Flynn Ltd. Industrial Refrigeration. Moved to PM Group in 1998 acting as Refrigeration Specialist and Building Services Engineer. While maintaining role as refrigeration specialist has occupied various roles including process mechanical engineer, utilities project engineer and Project Definition Lead for a Vaccines Production Client.
2003 – 2005 - 3 Year Period at Pfizer Ringaskiddy as Site Utilities Lead when site won 3 SEI energy awards.
Topics Covered

- Introduction to Biopharmaceuticals
- Mean Kinetic Temperature and Cold Chain
- Research, Product Development & Commercialisation Facilities
- Bulk Drug Substance Cooling Applications
- Product Freezing and Storage
- Logistics and Transportation
- Formulation Fill and Packaging Cooling Applications
- Miscellaneous Applications – Laboratories, Waste Water Treatment
- Commissioning and Qualification
- Questions
Refrigeration Conditions the Product
Introduction to Biopharmaceuticals
Understand Business Fundamentals

- Refrigeration Systems Follow Production
- Prompts Questions To Ask
- What Is Important to Client
- Regulatory Framework
- Client Customer Requirements
- Product Values / Insurance Requirements
- Similar Questions to Architect – Different Purpose
Biopharmaceuticals Overview

R&D

Utilities

Laboratory

Utilities

Waste

Logistics

Cell Growth (Upstream)

Logistics

Purification (Downstream)

Logistics

Waste

Packaging

Utilities

Final Packaging

Utilities

Waste

Logistics

Shipping

Utilities

Formulation

Utilities

Logistics

Waste

Formulation

Fill

Utilities

Logistics

Waste

Logistics

Filling

Logistics
Mean Kinetic Temperature and Cold Chain
Mean Kinetic Temperature (MKT)

A single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period.

\[
TK [K] = \frac{-\Delta H / R}{\sum_{i=1}^{n} \exp \left( \frac{-\Delta H}{R \cdot T_i} \right)} \cdot \ln \left( \frac{\sum_{i=1}^{n} \exp \left( \frac{-\Delta H}{R \cdot T_i} \right)}{n} \right)
\]

\(\Delta H\) is the activation energy
R is the universal gas constant
= 83.14472 KJ/Mol
T is the temperature in degrees K
n is the total number of (equal) time period over which data are collected
MKT – Practical Effect

Ideal Time/ Temp Profile

Lower Consistent Production Temp = Longer Shelf Life in uncontrolled condition
Planned Time/ Temp Profile

Temp °C

End User

Production

Time Period

Planned MKT Limit

Planned Time/ Temp Profile

Temp °C

End User

Production

Time Period

Planned MKT Limit

Planned

MKT

Limit
MKT – Practical Effect

Excursion Time/ Temp Profile

- **Unplanned Event**
- **MKT Within Limit**
• Risk of Contamination of Biopharmaceutical Products is reduced if they are kept outside of the temperature range where cells can grow i.e. below 10ºC.
• R&D sections of pharmaceutical companies work out a maximum MKT allowed over an expected lifecycle of the product.
• An overall timeline is calculated to maintain MKT within product stability limits.
• Stay Within Parameters – No need for real time calculation of MKT.
• Each Step Fully Validated.
• Design of Refrigeration systems must be fully documented.
• Temperature conditions recorded and validated throughout cycle.
• Calculation of MKT only necessary in event of excursion.
Research, Product Development & Commercialisation Facilities
Research, Product Development & Commercialisation Facilities

Water Treatment

- Cooling Tower
- Process Water
- WFI / PSG

Electrical

- Boiler house
- Comp Air
- Electrical

Chillers

- (HVAC & Process)
- 

Sprinkler

Generator

Fuel Tank

CO₂ N₂ O₂

+ CIP Tanks

Utilities

- Laboratory
- Cell Growth (Upstream)
- Purification (Down Stream)
- Formulation
- Filling

Waste

- Bio Waste Collection
- Process Waste

- Biokill

- Waste Tanks
- WWTP
- PH

- Ambient Warehouse
- Cell Bank -70°C
- 2 – 8°C Store
- HAZ Store 2 – 8°C

- Finished Goods -40°C
- Stability Chambers 2 – 8°C 25°C, 35°C
Bulk Drug Substance Cooling Applications
Bulk Drug Substance Complexity

Level 2 Plant Space

Level 1 Plant Space

Level 0 Plant Space

High Level Metrics

- Building Size 100m X 60m X 25m (h)
- Process Cooling Users: 110
- HVAC Cooling Users: 100
- 7 Grade C 2-8º HVAC Systems

<table>
<thead>
<tr>
<th>Connected Load</th>
<th>Peak Load</th>
<th>Minimum Load</th>
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<tr>
<td>7000 kW</td>
<td>3300 kW</td>
<td>700 kW</td>
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Biotech Processing
Main Process Cooling Demands

- WFI – Water For Injection – lifeblood of facilities. Used for all sterile processing. Distributed at 80°C. Usually cooled to ambient (20°C) before point of use.

- Media/ Buffer Staging and BDS downstream vessels/equipment cooled to 2-8 ºC when in production. Cooling medium must cool vessel contents to below +4ºC or lower without risk of freezing.

- All plant must be cleaned and sanitised. For sanitisation ambient WFI Loops or PW loops heated to 80ºC. Must be cooled post sanitisation.

- Equipment including vessels sterilised using pure steam (SIP – Steam in Place). All points on vessels reach over 100ºC for sterilisation. Vessels are cooled before re filling.

- Solvents are used in Chromatography Columns. Columns are stored and packed at 2 – 8 ºC. All items internal to rooms are Zone 1 or 2 ATEX rated.
Sample BDS Production Suite
Typical Refrigeration Requirements

Application Key

- Process Cooling
- 2 – 8 ° Cold Room / Staging
- LN2 Cryogenic Cell Store
- 2 – 8 ° Grade C Air Handling System
Product Freezing and Storage
Product Freezing

- BDS typically leaves process in liquid form at either ambient or 2 – 8 ºC.
- For stability and transportation it is usually frozen.
- Freezing can happen either in production building or warehouse/logistics centre.
- Production System and Batch Size determines Freezer Type.

Modular Product Freezer / Storage by Specialist Supplier
Individual Units / Sections Built and Validated Off Site

Sartorious Production System Plate Freezer

Traditional Build Final Product Blast Freezer and Staging
Sample Details

- -40 °C Coldroom
- 1,000 kgs Product
Sample Details

- -40 °C Coldroom
- 1,000 kgs Product
- 4 Weeks Production
- Insured Value €100 Million
- 3 hr Fire Rating of Enclosure
- Control +/- 1 °C incl. Defrost
- Variance +2 / -1 °C incl. Door Opening
- Over 100 Documents to be supplied with Package
- Payment on Completion of Documentation / Validation
Logistics and Transportation
Logistics and Transportation

Features

- Proprietary Shippers
- Validated System with Loggers in place during transport.
- Shippers packed with Gel Packs or Dry Ice.
- Gel Pack Freezers required.
Formulation Fill and Packaging Cooling Applications
Fill Finish And Packaging
Typical Refrigeration Requirements

Formulation
Fill

- Cooling Tower
- Chillers (HVAC & Process)
- LN2 Storage
- Utilities
- Waste

Packaging
Shipping

- Cooling Tower
- Chillers (HVAC)
- Final Packaging
- Utilities
- Logistics
- Waste

- Formulation
- Filling
- Process Cooling
- Staging Room 2-8 °C
- 2 - 8 °C BDS Store
- -40 °C Store
- WWTP Cooling Tower

- Finished Goods 2-8 °C
- Stability Chambers 2 – 8°C
- LYO Freeze Drying
- -20°C Gel Freezer / Storage
- 2 – 8 °C AMB

- Finished Goods 2-8 °C
- Staging Rooms 2-8 °C
- Finished Goods 2-8 °C & Gel Freezer
- 2 – 8 °C AMB
Miscellaneous Applications
QA/QC Laboratories
• Walk In 2-8 °C and -40° C Coldrooms and Freezers.
• Environmental Chambers
• Multiple Upright and Chest Coolers/Freezers

Service Conditioning
• Some Liquids are heated for transportation in pipe distribution systems and then cooled before addition to vessels.
• Where cooled liquid is standing in pipework for long periods, sometimes pipework it is trace cooled to avoid raising vessel temperature when liquid is added.

Waste Water
• End of line cooling towers and heat exchangers due to hot waste characteristics.
Commissioning and Qualification
Commissioning and Qualification

**Common Perception**

- **Design Specification**
  - By Engineering Office

- **Installation Commissioning**
  - By Contractor / Supplier

- **Qualification**
  - By C&Q
Commissioning and Qualification

User Requirement Specification
By Client

Performance Specification
Bid Documents
By Engineering Office

Design Qualification
Detailed Design
Installation Qualification (IQ) Preparation
Operation Qualification (OQ) Preparation
Installation
IQ Execution
Commissioning
OQ Execution
Handover Package
By Contractor / Supplier
By Engineering Office

Production Qualification (PQ)
By Client

Qualification & Management of Qualification Process
By C&Q

Compliance Review
By Engineering Office
Questions
Thank You

If you have any questions or like further information please do not hesitate to contact

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