



ICH Q9: Application of a Risk-Based Approach to Freeze-Drying Process

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09.00-10.30 Theoretical Part

- Part I: Description of freeze-drying technology
 1. The equipment
 2. The process
 3. The product and the primary packaging items
 4. The ancillary function (SIP, CIP)
 5. Aseptic level (automatic loading, people presence)

- Part II: Brief review of ICH Q9

- Part III: Tools presentation
 1. CQA and CPP
 2. Dependant / Independent parameters
 3. CQA: critical quality attributes
 4. FMEA approach
 5. Examples



10.30-11.00 Break

11.00-12.30 Practical part

- Team rule's and organization
- Part I: Product
 1. independent parameters linked to formulation
 2. independent parameters linked to freeze-dryer load
- Part II: Process
 1. independent parameters linked to the freeze-dryer

12.30-14.00 Lunch



15.30-16.30 Practical part

- Part IV (con't): ancillary function
 1. CIP
 2. SIP
- Part V : aseptic level

16.30-17.00 Conclusions

- Q&A
- Conclusion and feedback



Theoretical part: I

I-Description of freeze-drying technology



1. What is freeze-drying
2. Why freeze-drying
3. Evolution in freeze-drying
 - a. Equipment side
 - b. Process side
 - c. Formulation
 - d. Primary packaging items
4. Alternatives technologies
5. Conclusions

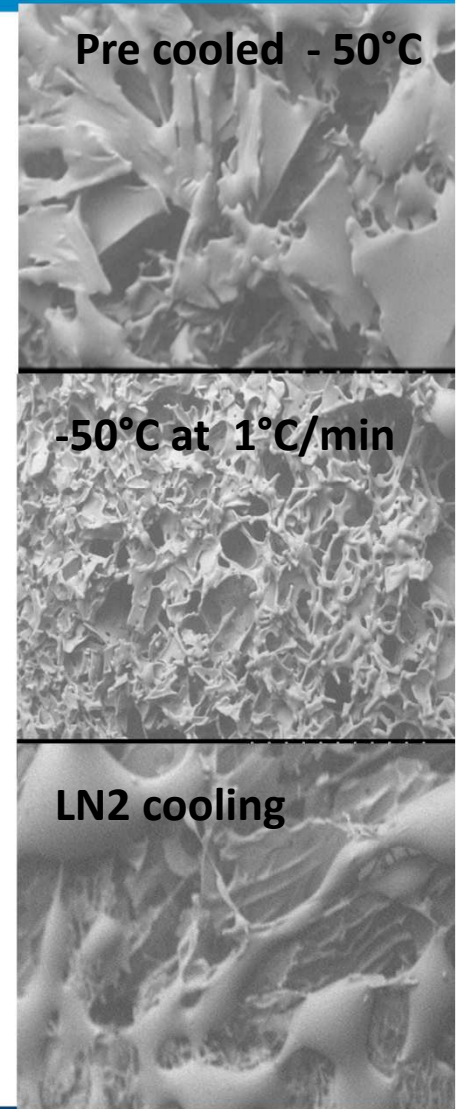


What is Freeze-Drying

- The process of freeze-drying is constituted of 3 steps:
 1. Freezing
 2. Primary drying
 3. Secondary drying



- Freezing is the most critical part of the process, the geometrical structure will be determined at that step
- Nature and structure of the plug will allow a good protection or not



- During the primary drying the product temperature should remain below the T_g' of the product to obtain cake elegance
- During that step the free water is removed by sublimation

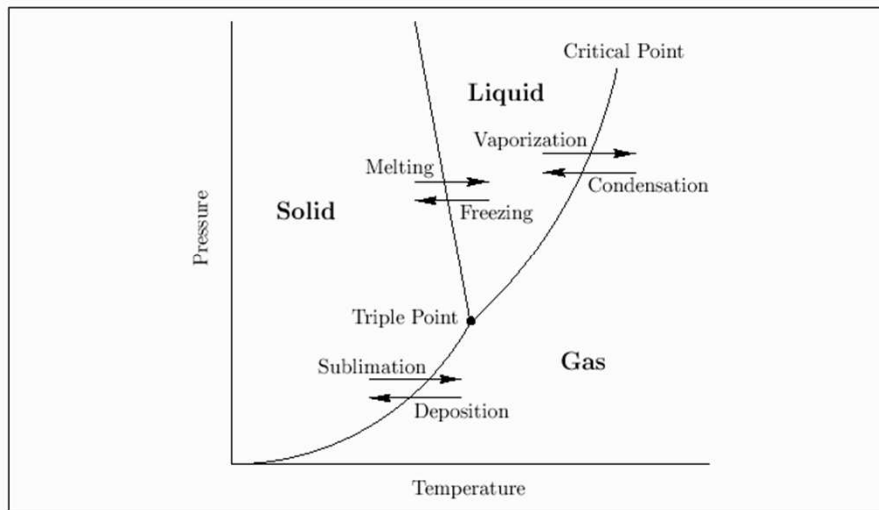
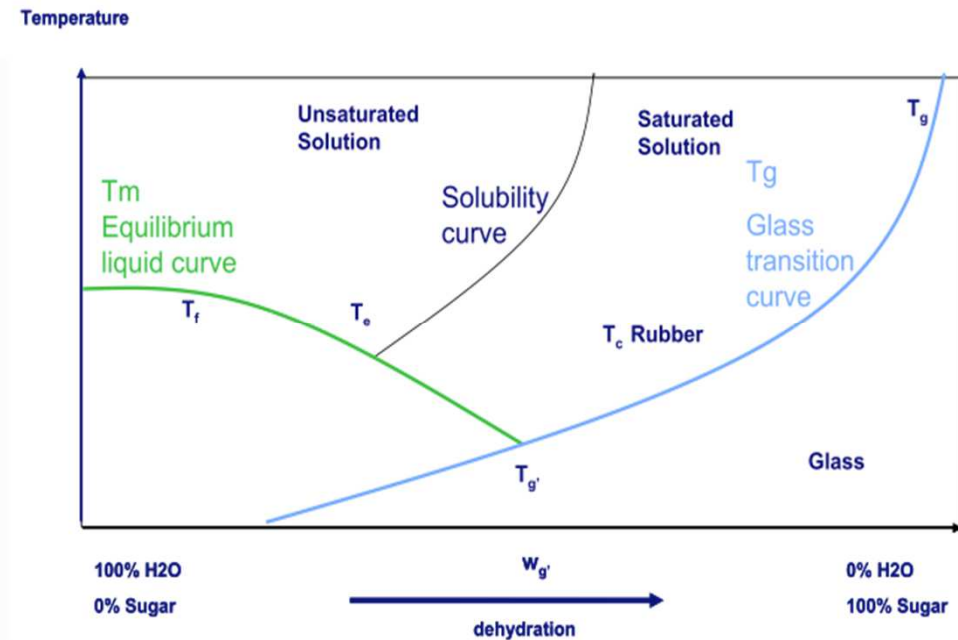


Figure 3.1 Pressure-temperature diagram for a substance that expands upon freezing.



1. During that step the bound water is removed up to a certain level
2. The removal speed should be controlled to avoid collapse by overcoming the capacity of the plug to release water
3. Over-drying of the product should equally be taken into account





➤ **Pro's:**

1. It's a well accepted form for injectable product
2. The new molecules become more and more complex , meaning that they are difficult to stabilize.
 - Freeze-drying allow a better stabilization than liquid formulation
 - More than 50 % of new molecules are freeze-dried
3. Time to market

➤ **Con's:**

1. Batch process
2. Higher price due to the need of a diluent

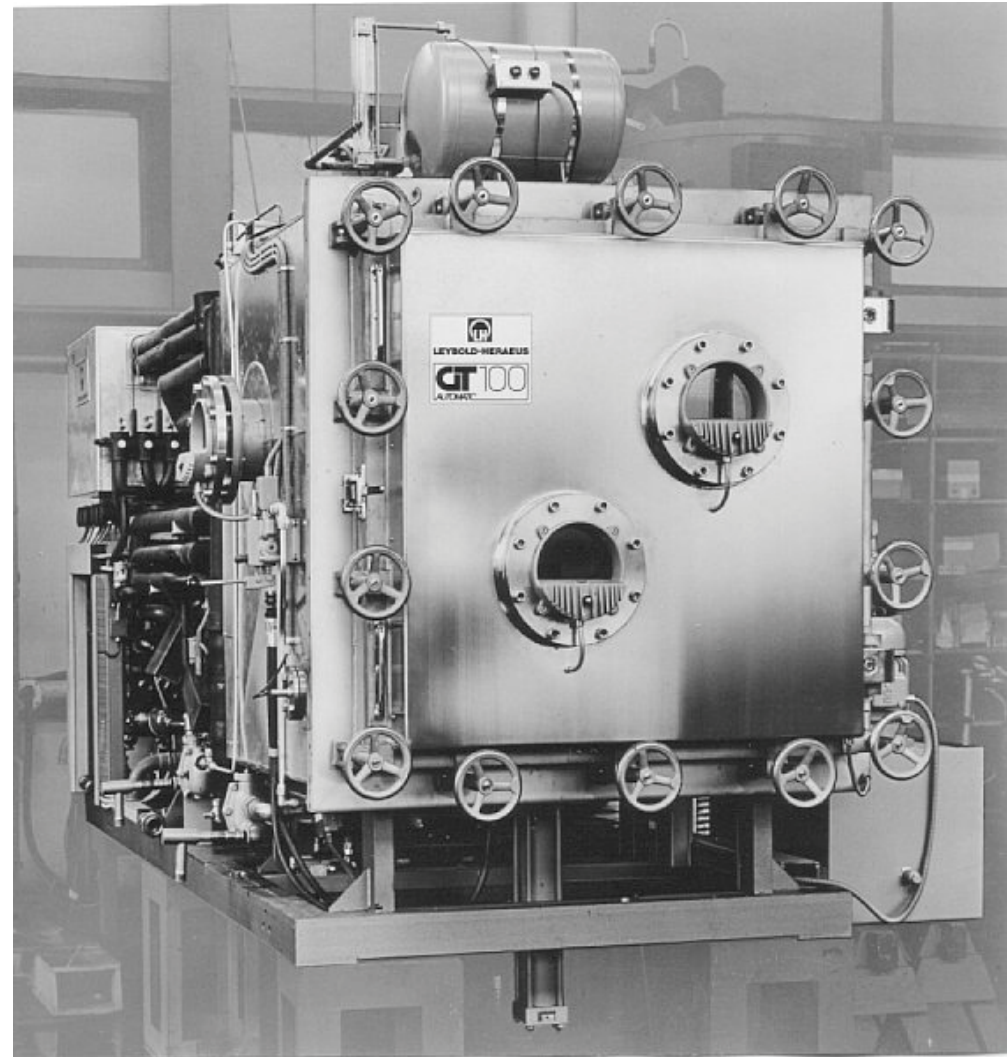
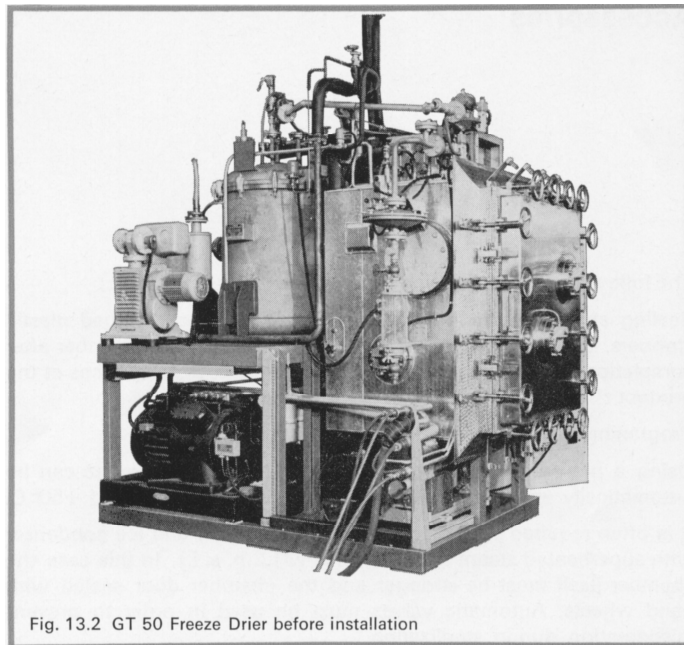


Evolution in Freeze-Drying

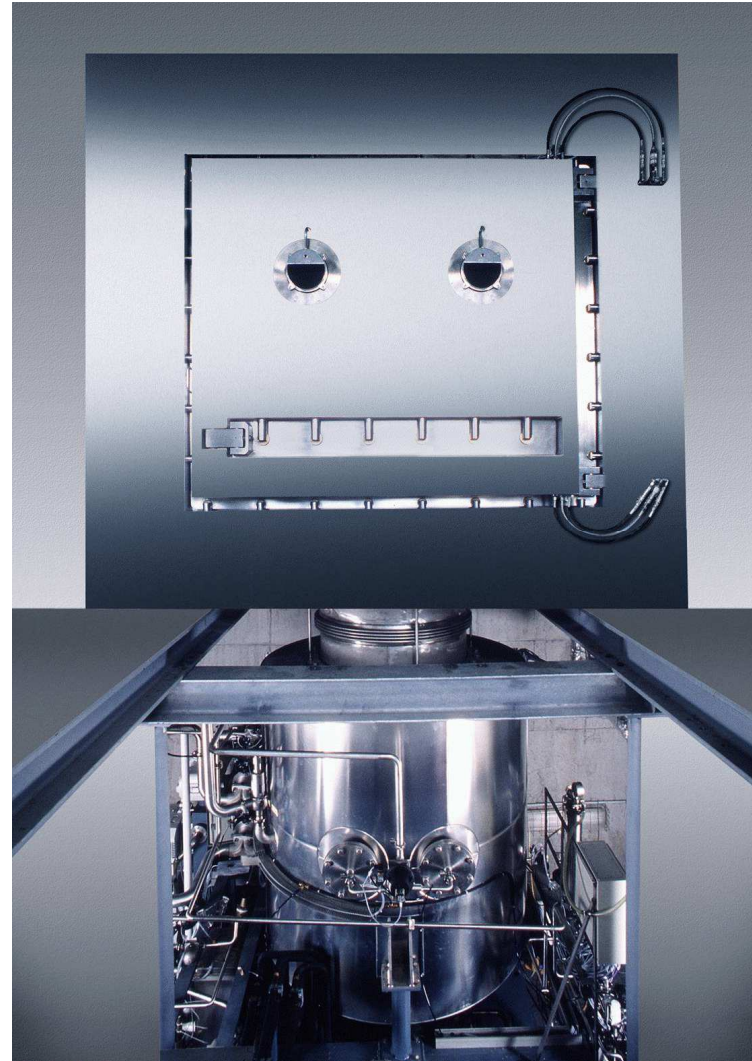
- Freeze-drying exist since world war II
- The science and technology has evolved during the last 70 years
- There's no revolution, but a steady evolution in term of :
 - Equipment
 - Process
 - Formulation
 - Primary packaging
 - Surrounding environment

- The industrial freeze-dryer with a chamber for product and a separate condenser had become the standard in the 70 's
- Since that time :
 - Computer has been added
 - Sterilization in place
 - Cleaning in Place
 - Automatic loading and unloading system
 - PAT tools

Formerly:



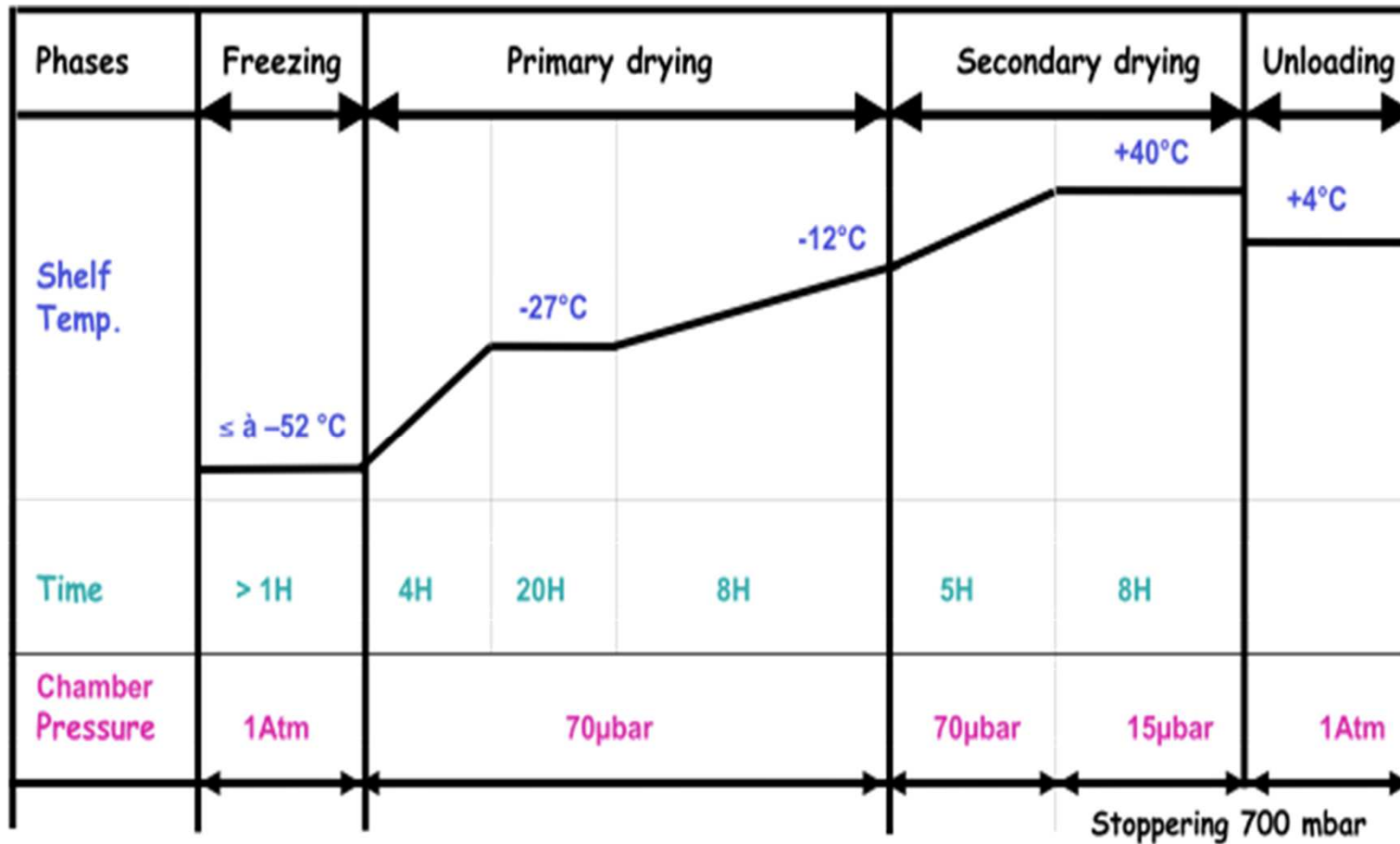
Nowadays:



- In term of brand, the market is very stable:
 - The majority of current supplier exist since the 50 's even if brand name change regularly
 - Some have been bought by filling equipment supplier in order to propose a complete offer
 - Newcomers from Asia appear on the market

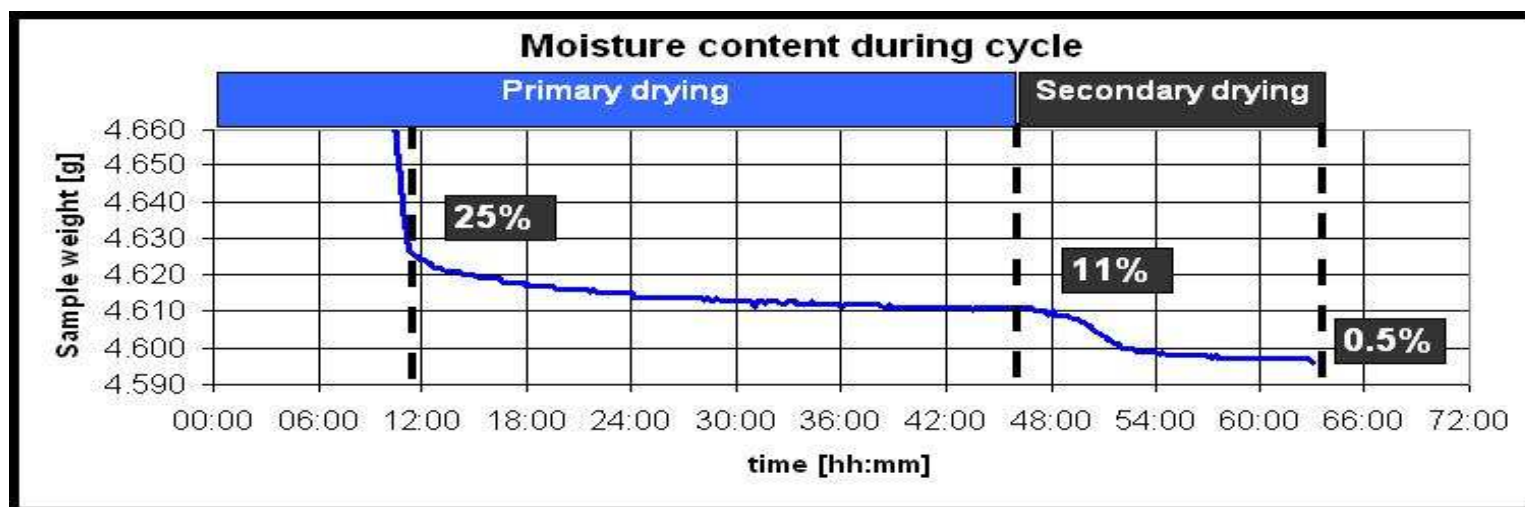
- The design of freeze-drying cycle is not any more empirical
- New tools allow to characterize the formulation
- Some models exist to better predict the output of the process
- A scale-up is done on each freeze-drying cycle before going to industrial freeze-dryer

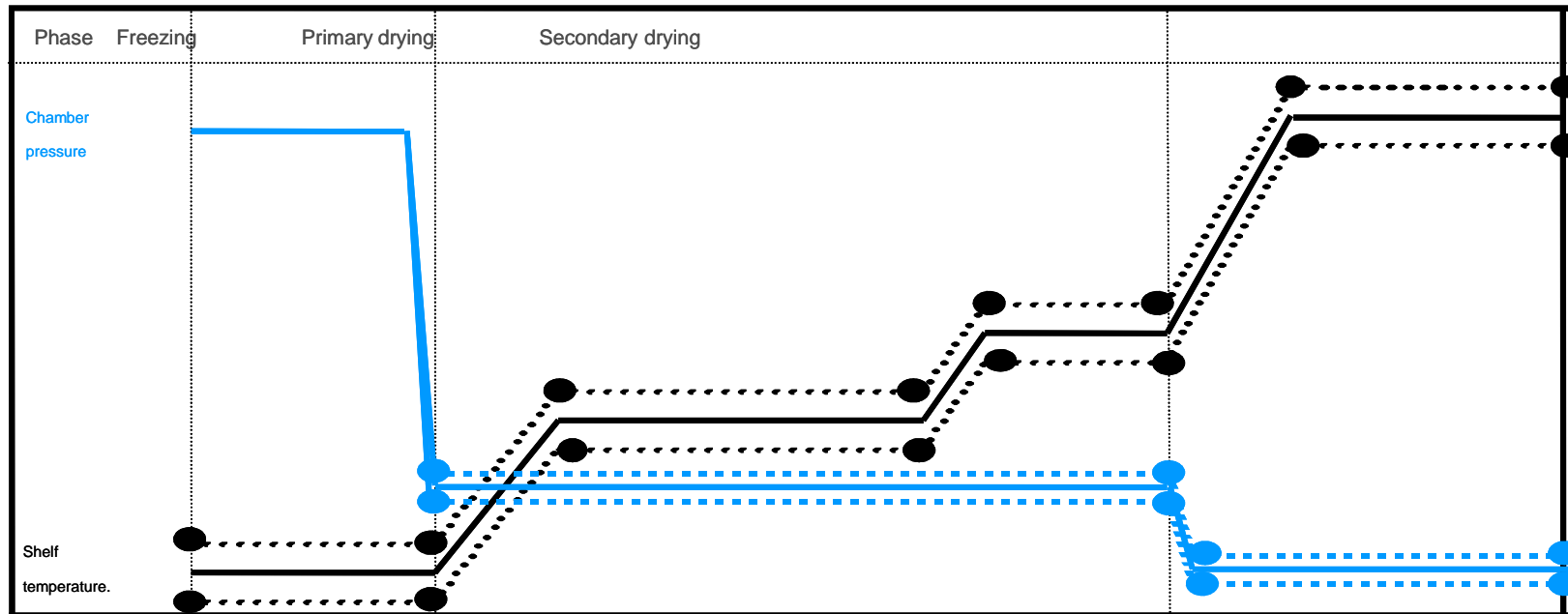
The cycle:



PAT tool and others

- Cryomicroscope
- Microbalance





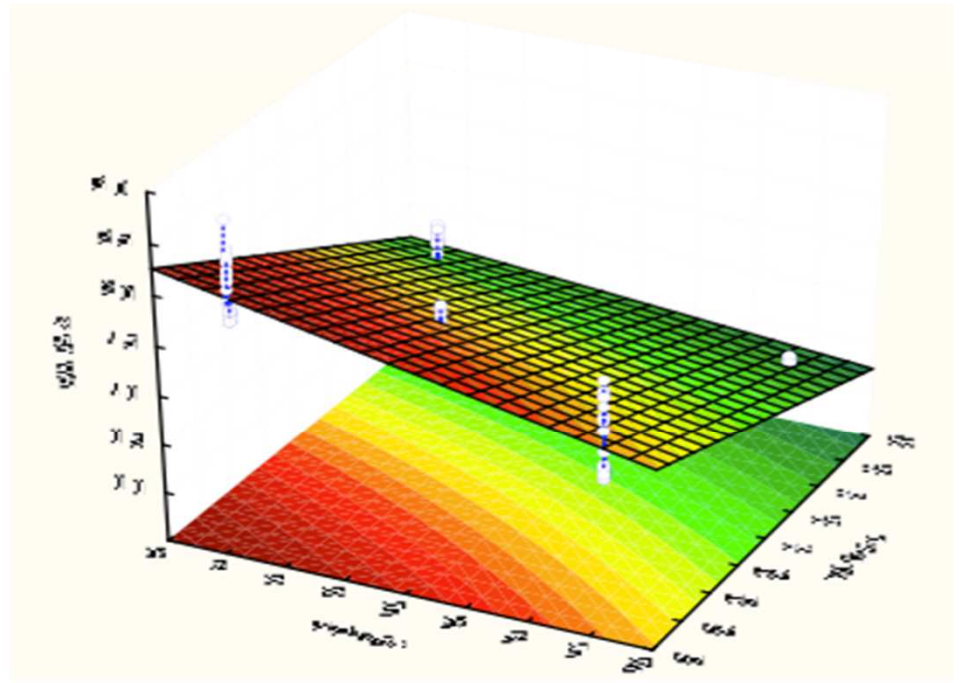
Typical critical process parameters :

- time
- shelf temperature
- chamber pressure

Typical critical quality attribute :

- moisture content
- visual appearance
- Potency
- Stability
- Reconstitution time
- Sterility

- Trend in process development are :
 - Availability of new PAT tools
 - Models development become more easy
 - Pure mathematical models
 - Statistical models (DOE) with design space determination



- The protective effect of sugar that are now widely used have been recognized during the 70's
- The protective effect of different excipients are far better understood :
 - physical part :
 - Tg' and Tg
 - Amorphous versus crystalline
 - The capability of bonding between active molecules and cryoprotective agent

- Up to now there's no unified theory that explain the capacity of excipients to protect active molecules
- There's different theory that explain partially the effect of the excipients
- The number of available cryoprotective molecules decrease regularly
 - Avoid human origin
 - Purity request increase
 - Potential side effect
- But effort are done to find new one
- The trend is toward well defined formulation with only a few cryoprotectives molecules for which the role is well understood



- The aseptic level increase regularly around the freeze-dryer
- Some adaptation of the process are needed to comply with the new rules

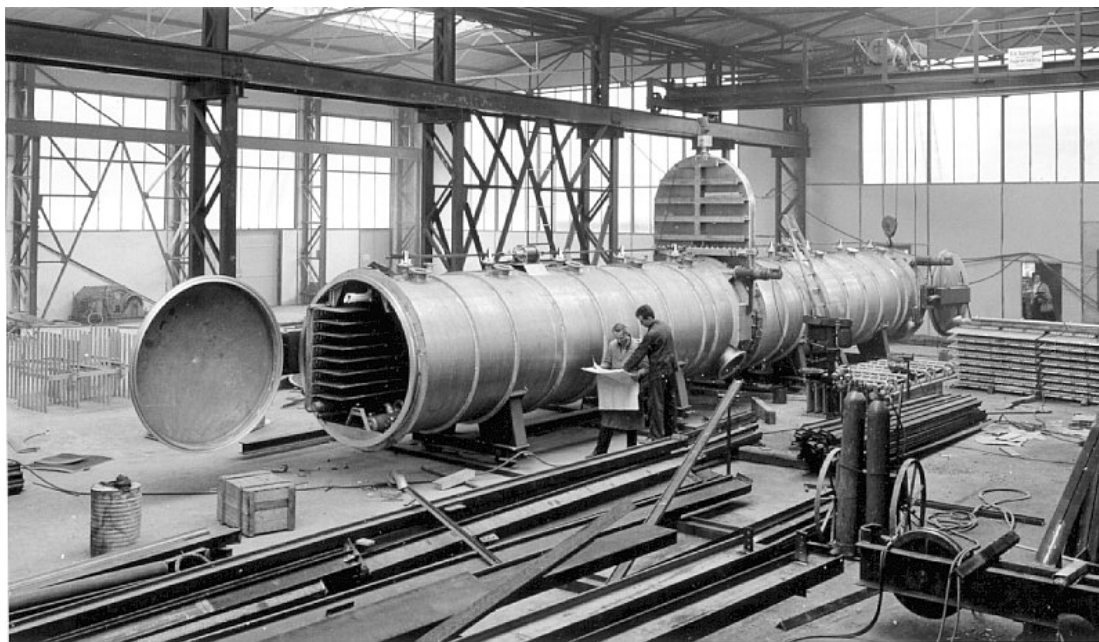
- Loading in Class A
 - Change in the undercooling effect
- Automatic loading under isolator
 - No more possibility to place product probes with wires, now wireless probes are reliable and available can become again a PAT tool



- Classically most of the product are freeze-dried in vials
- Nowadays appear :
 - Plastic vials
 - Dual chamber syringes
 - Direct sealing inside the freeze-dryer
 - New generation of stoppers release less humidity, leachable and extractible
 - Teflon coated stoppers



- There's always alternative technology that has been evaluated to replace freeze-drying in order to decrease the cost and complexity
- Continuous freeze-drying
- Direct LN2 freezing
- Spray drying technology
- High viscosity liquid drying
- Microwave freeze-drying





- There's a constant evolution in freeze-drying in term of
 - Equipment : reliability, efficiency
 - Process : better understanding and better control with new PAT tools
 - Formulation : new cryoprotective search and better understanding of the theory
 - Quality : aseptic level increase and better understanding of the technology



II & III- Review of ICH Q9 and Tools Description



- ICH Q9 quality risk management was adopted beginning of 2006 by EMEA
- The objective of the guideline is to promote the use of risk management that is a valuable component of an effective quality system
- Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle



Principles of quality risk management:

→ The two primary principles of risk management are :

1. The valuation of the risk to quality should be based on scientific knowledge and ultimately linked to the protection of the patient
2. The level of effort, formality and documentation of the quality risk management should be commensurate with the level of risk

There is different aspects in the freeze-drying science:

- The equipment where we can evaluate a risk of failure
- The process where we can evaluate the cycle development in regard to the potential product impact:

↳ wrong secondary drying design

↳ too high humidity

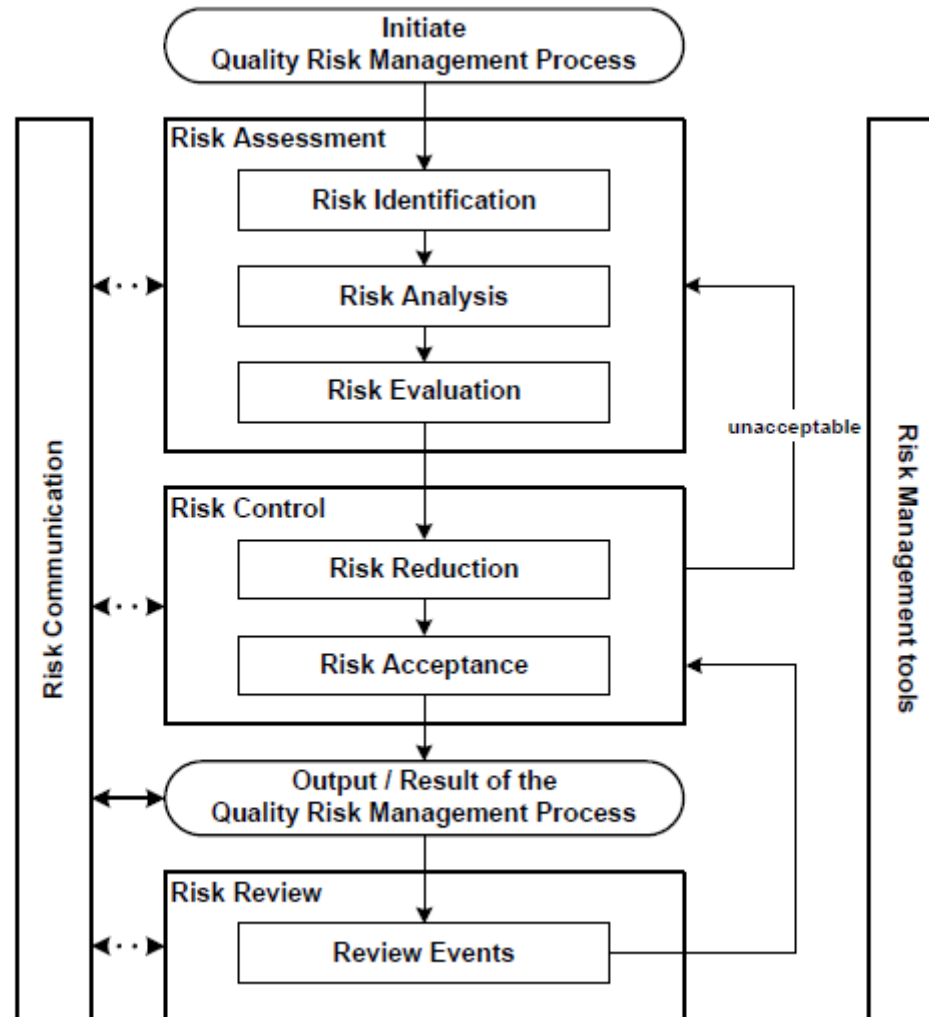
↳ product degradation increase compared normal batches

- The formulation and products:
 - known sensitivity to aggregation, oxidation of the active ingredients
 - use of polymorphic stabilizer (mannitol) that can end up to various formulations



Presentation objectives

- Demystify risk management approach for freeze-drying
- Show benefit of risk management approach
 - Use of common tools
 - Increase freeze-drying knowledge
 - End up with a robust process (no more unknown risks)
 - Improve the potential or scale-up and transfer of the process



Graph from ICH Q9



- The first difficulty is to decide how to divide the process in order to perform the risk analyze and evaluation
- The best approach is to start from a mapping of the process:
 - Input and output parameters will be defined:
 - the input will be the dependent and independent parameters of the process
 - the output will be the CQA (critical quality attribute) in regard to witch the process will be analyzed



Input and output parameters:

- CPP - Input parameters
 - Shelf temperature
 - Chamber pressure
 - Time
- CQA - Output parameters
 - Visual aspect
 - residual moisture
 - Potency
 - Some specific tests for the product function of known weakness :
 - oxidation
 - aggregation



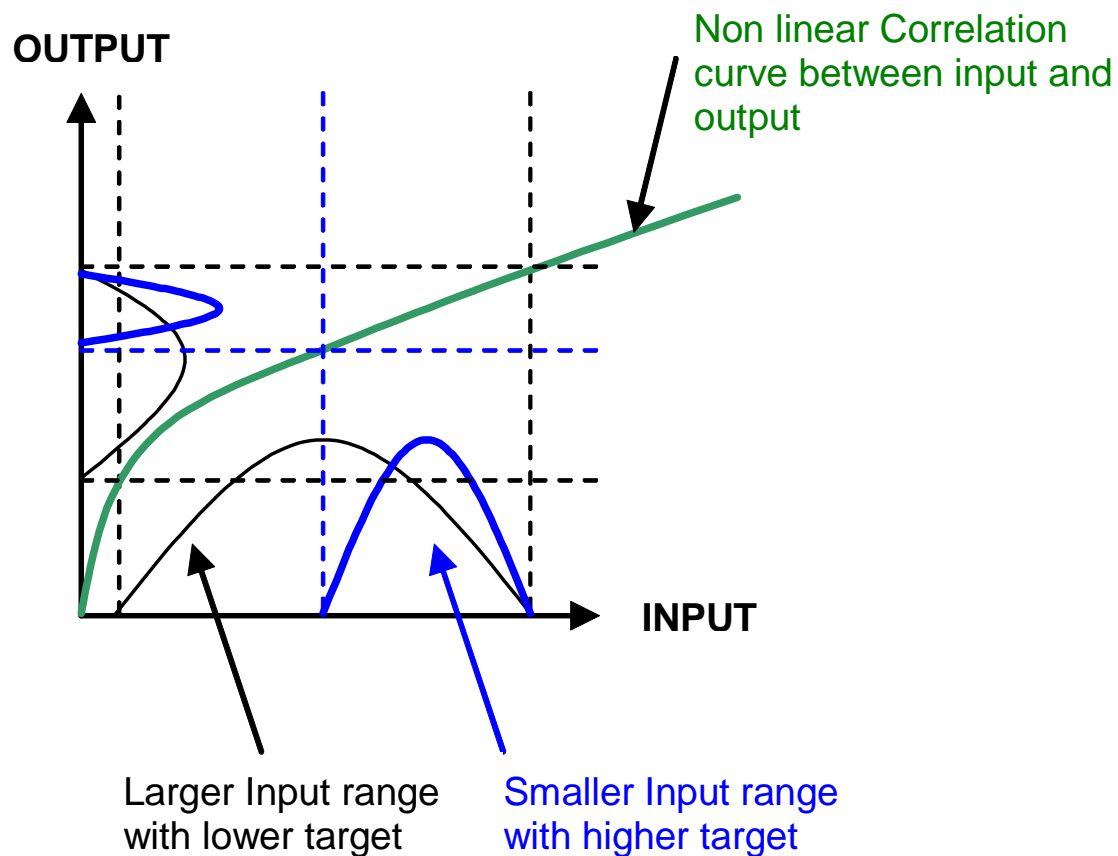
Dependent and independent parameters:

- Independent parameters:
 - we can act on them
 - i.e.: shelf temperature

- Dependent parameters:
 - we can monitor them but cannot directly control them
 - i.e. : product temperature
 - this is the conjunction of a lot of variables

Smaller Output range
= robust process

Larger output range
= sensitive process





Available tools:

- It's not mandatory to use a formal risk management approach
- The chosen tool should be determined in function of the knowledge and complexity of the analyzed process
- Commonly , FMEA (Failure Mode and effect Analysis)
- There is far more sophisticated tools such as Hazop (hazard operability analysis) or simple one as FTA (Fault tree analysis)if process knowledge is low



FMEA Risk Analysis according to PDA Technical Report n°44, Quality Risk Management for Aseptic Processes, 2008 based on ICH Q9

The objective of this analysis is to determine rationally which parameter is key. Therefore, all key parameters will be subject to further evaluation.



DETECTION

LOW

MEDIUM

HIGH

OCCURENCE

HIGH

This cause is likely to occur, but when it does, it will be detected. If we are certain it will be detected, it is **LOW RISK**, but if we are not certain then it could be a **MEDIUM RISK**

This cause is likely to occur, and the detection is not certain. It is a **HIGH RISK**

This cause is likely to occur, and is not likely to be detected. It has a **HIGH RISK**

MEDIUM

This cause could occur, but if it does, it would be detected. Depending on the frequency of occurrence and the confidence in the detection, it is a **LOW** or a **MEDIUM RISK**

This cause could occur, and it could be detected. Depending on our confidence in the detection, its risk would be **MEDIUM** or **HIGH**

This cause may occur, and it will not be detected. The **RISK IS HIGH**

LOW

This cause is not likely to occur, and if it does it will be detected. This is a **LOW RISK**

The cause is not likely to occur, and if it does occur, it may be detected. Depending on the frequency of occurrence and the confidence in detection methods, it would be a **LOW** or **MEDIUM RISK**

The cause is not likely to occur, but if it does occur, it probably would not be detected. The **RISK IS MEDIUM**



RISK Category Ranking/ Definition	LOW=1	MEDIUM=2	HIGH=3
SEVERITY	N/A	N/A	Direct and severe impact to patient health; life threatening.
OCCURENCE	The possibility that the cause rarely occurs; unusual event.	The possibility that the cause may occur and may result in loss of product quality.	High possibility that the cause will occur and result in loss of product quality; a common and known event.
DETECTION	There is a high likelihood that existing controls will detect the cause or the defective product and prevent its release.	The cause if it occurs may be detected by existing controls.	If the cause happens it will probably not be detected by existing controls, and defective product could be released



A Risk Priority Number is defined as following:

•RPN = Severity X Occurrence X Detection

➤ **RPN [1;27]**

•Ranking:

➤ **If RPN [0;3] acceptable risk**

➤ **If RPN [4;8] medium risk**

➤ **If RPN [9;27] high risk**



- The freeze-drying process is the association of 3 elements
 - A product in a formulation
 - This is the basis of the system
 - It has characteristics such as :
 - Collapse temperature
 - Moisture desorption
 - A freeze-dryer
 - This equipment has specific characteristics such as :
 - Shape (i.e. : internal or external condenser)
 - performance



- The third element is the freeze-drying cycle :
 - The freeze-drying cycle is the link between the product and the equipment
 - The good development of the cycle will assure a constant quality for the product even if some equipment and formulation parameters are fluctuating



- Definition : 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. (PDA TR 60)
- Examples of product quality attributes
 - Efficacy
 - Purity or potency
 - Residual humidity
 - Visual aspect
 - Sterility
 - Endotoxins level
 - Safety
 - Particles



Critical process parameters for freeze-drying process

- Definition: CPP is a process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produce the desired quality (PDA TR 60)
- Typical critical (input) parameters
 - Shelf inlet (outlet ?) temperature
 - Pressure in the chamber
 - Process duration
- Typical (output) quality attributes
 - Purity/ potency
 - Residual humidity
 - Aspect
- Examples
 - A modification of 2°C shelf temperature lead to a product lost of 10%
 - A lot of others parameters can have an influence on the final product
 - i.e. vials bottom curvature --> aspect



Workshop - Agenda

- Condenser temperature vary of 5 °C
 - Severity: 1
 - Occurrence: 2
 - Detection: 1
 - =>RPN: 2 --> acceptable risk
- Shelf temperature vary of 5°C
 - Severity: 3
 - Occurrence: 2
 - Detection: 1
 - =>RPN: 6 --> medium risk





Risk type analysis

1. We will realize risk analysis for a dummy product
2. A risk analysis on an equipment can equally be performed
3. Or a risk analysis can even be performed on ancillary function
 - SIP
 - CIP

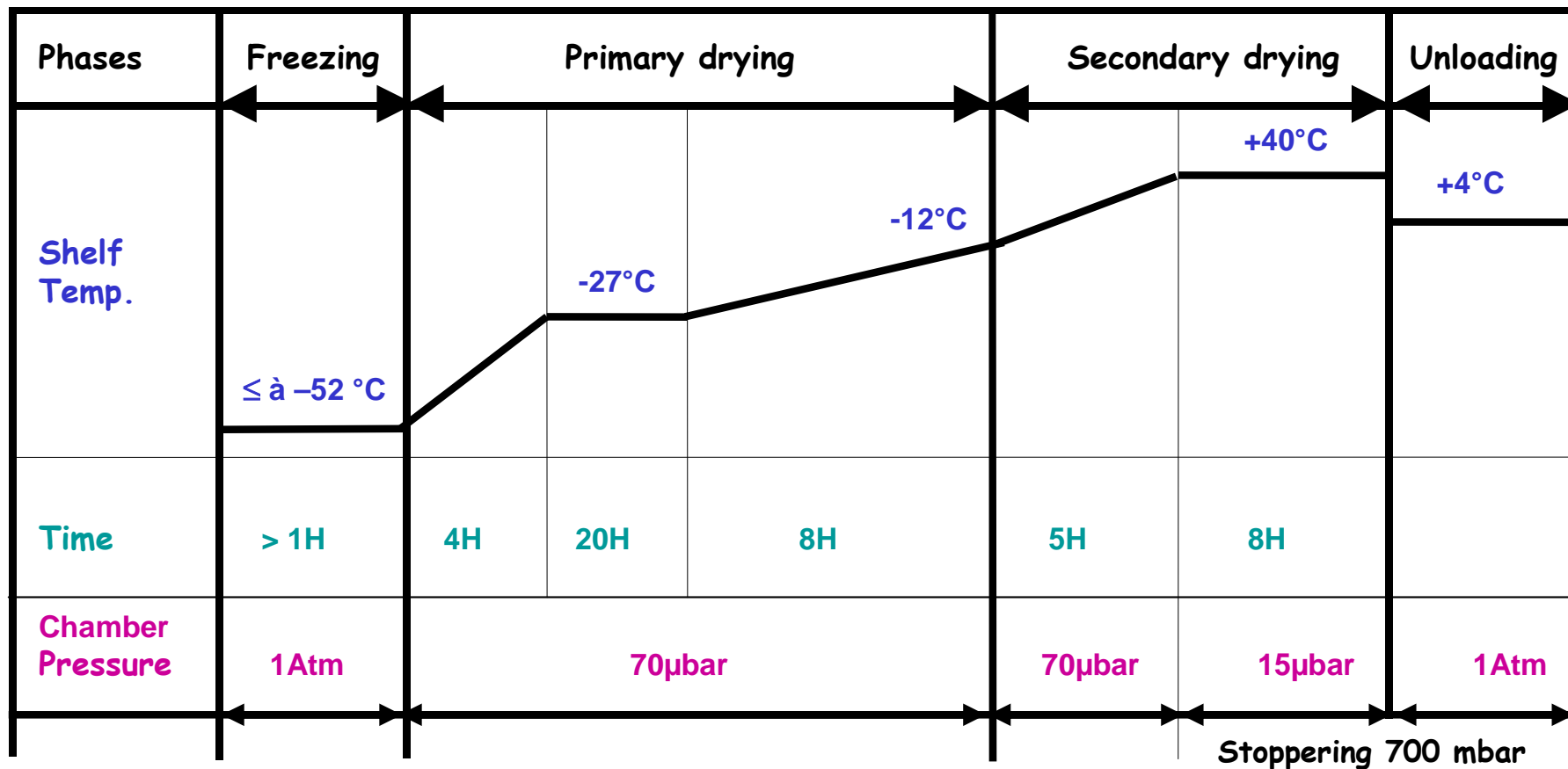


Dummy product

- A Mab formulated in a sugar mixture
- Formulation :
 - Maltose 5 %
 - Mannitol 2 %
 - Buffer : phosphate
- Vials 3 ml white, type I
- Fill volume : 0.6 ml



The freeze-drying cycle

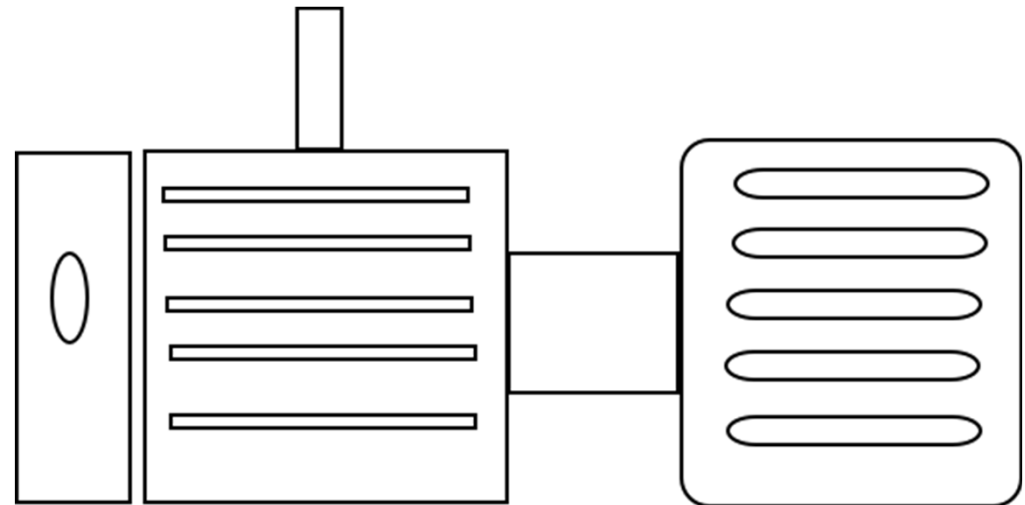


- Product independent parameters linked to formulation
 - Appropriate Cryo & lyoprotectant
 - Phase separation
 - Controlled Particle content
 - Sterility & endotoxins
 - Potency before FD
 - Reconstitution time
 - Liquid instability before FD

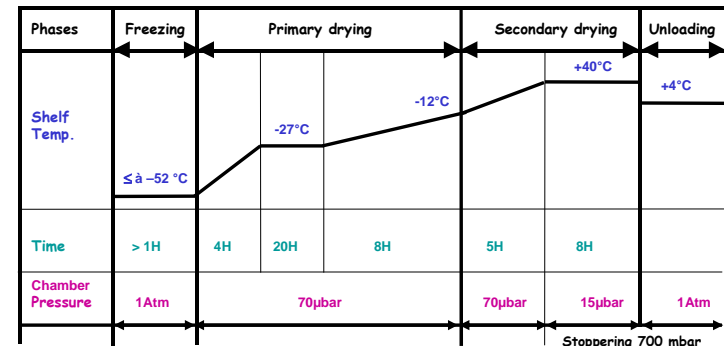


- Product independent parameters linked to freeze-dryer load

- Batch size
- Vial stopper integrity
- Bottom vial flatness
- Siliconization of stoppers
- Geometry of stopper neck
- Stopper residual moisture
- Vial sterility & endotoxins
- Vial particle content
- Stopper sterility & endotoxins
- Stopper particle content
- Volume per vial



- **Process independent parameters that are controlled and measured during the cycle**
 - Freezing slope shelf temperature
 - Shelf freezing time
 - Shelf primary drying temperature ramp
 - Shelf primary drying temperature
 - Shelf primary drying temperature holding time
 - Chamber gas injection regulation
 - Shelf secondary drying temperature ramp
 - Shelf secondary drying temperature
 - Shelf secondary drying holding time
 - Stoppering gas content
 - Stoppering pressure
 - Stoppering force
 - Stoppering and unloading shelf temperature



- Process independent parameters linked to the freeze-dryer
 - Freeze-dryer brand ☺
 - Freeze dryer size
 - Number of vial per shelf
 - Space between shelves
 - pumping vacuum flow
 - Condenser maximal capacity
 - Condenser nominal capacity

- Process independent parameters linked to the freeze-dryer
 - Various Wall and door heat transfer rate
 - Homogeneity of shelf
 - Nominal capacity of cooling system
 - nominal capacity of heating system
 - Equipment clean & aseptic
 - Equipment leak rate

- Process dependent parameters linked to the freeze-drying cycle
 - Product freezing rate
 - Undercooling / homogeneity
 - Product final freezing temperature
 - Frozen matrix microstructure
 - Shelf heat flow transfer rate
 - Vial heat flow transfer rate
 - Product mass flow transfer rate
 - Product temperature profile

- **Process dependent parameters linked to the freeze-drying cycle**
 - Product drying rate
 - Heterogeneity of drying
 - Product sublimation endpoint
 - Product sublimation front pressure
 - Chamber pressure
 - Condenser ice surface temperature
 - Secondary drying product temperature profile
 - Product desorption rate



Interactive workshop rules

1. Choose which kind of parameters to be evaluated in the excell table
2. Discuss in group the parameters
3. Obtain a concensus quotation for the parameter with a rational
4. Start a new one

All the parameters will not becovered during the training

The excel file will be supplied through e-mail afterwards



Examples

Process steps	Unwanted event	Severity	Occurrence	detectability	RPN	Recommended action	Risk mitig	CQA
•Product independent parameters linked to freeze-dryer load								
-Batch size	None		1	3	1			
-Vial stopper integrity								
-Bottom vial flatness								
Siliconization of stoppers	Particles - > contamination							
-Siliconization of stoppers	Process		2	2	3	Implement leak 12 detection		4 Sterility
-Geometry of stopper neck								
-Stopper residual moisture	Meltback during stability and stability loss		3	2	3	18		
-Vial sterility & endotoxins								



Pictures good and bad cake





- What do you think about the ICHQ9 ?
 - Strength
 - Weakness
- Do you see alternative approach ?
- Do you believe it is useful ?



ICH Q9 : Quality risk management – Nov 2005

PDA Technical Report n°44, Quality Risk Management for Aseptic Processes, 2008

PDA Technical Report n°60, Process Validation : A life cycle approach, 2013

Thank you