# CHALLENGES OF APPLYING A QbD APPROACH TO BIOPHARMACEUTICAL FREEZE DRYING

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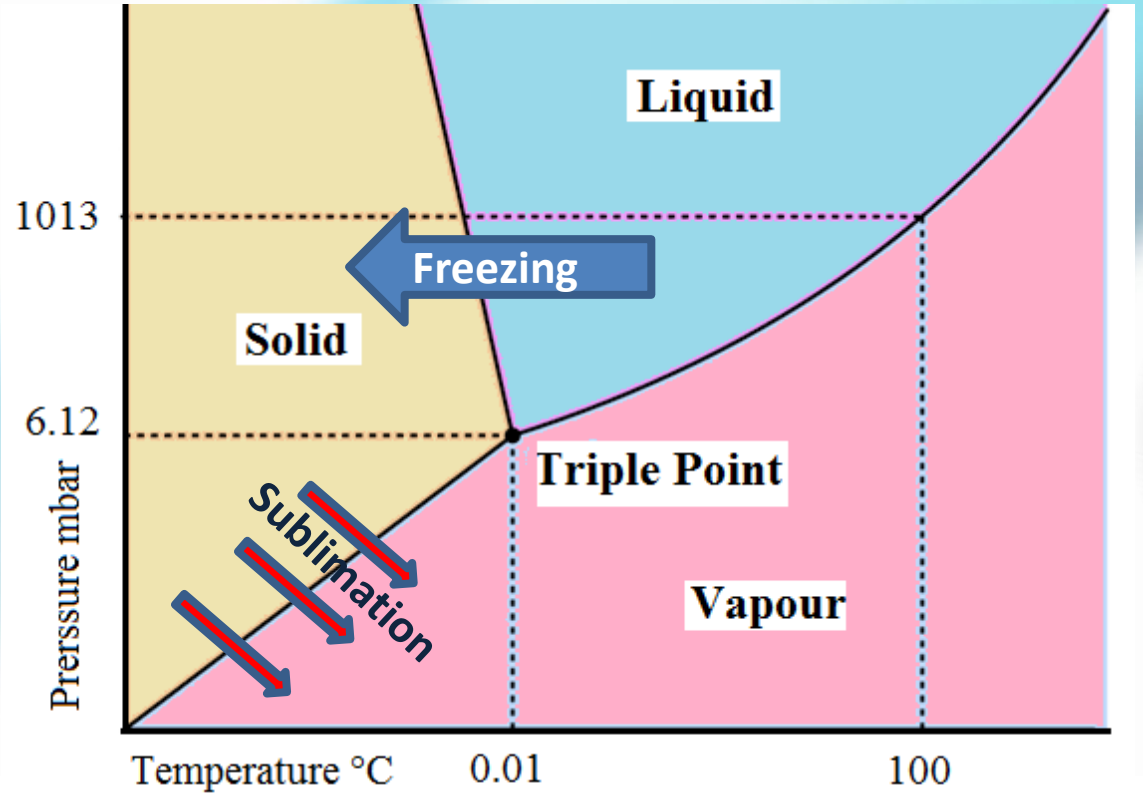
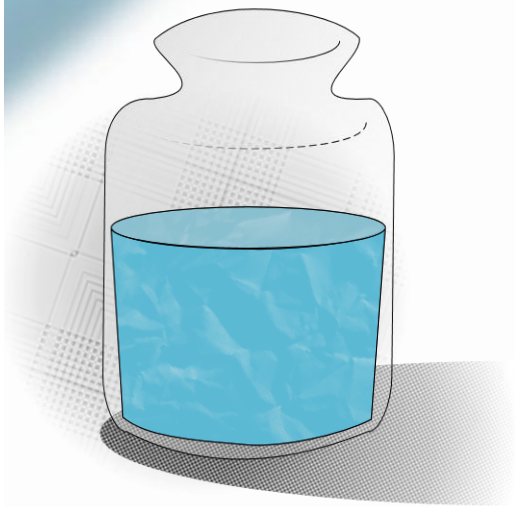
# Challenges of Applying A QbD Approach to Biopharmaceutical Freeze Drying

- What is Freeze Drying & Why is QbD Relevant?
- The QbD Family: CQA, QTPP, CPPs for Freeze Drying
- Risk mitigation
- Constructing the Space – Theory and Practice
- Assembling the Train
- Overview

# What is Freeze Drying?

- Freeze-Drying (*Lyophilization*) is the removal of solvent (usually water) from the frozen state under reduced pressure (sublimation)



# Why is QbD Relevant to Freeze Drying?

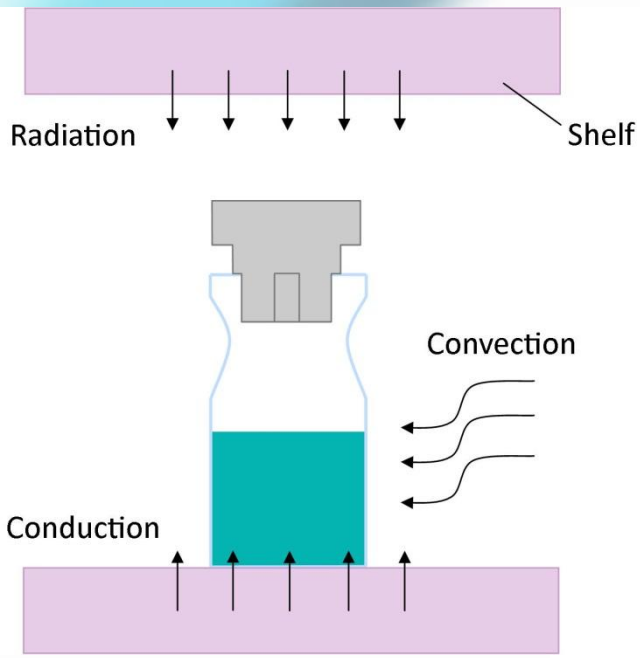
- Good Practice: *[ICH guidelines – Q8, Q9, Q10…]*
- Regulation – FDA / MHRA Product Registration
  - Empirically derived cycles no longer good enough
  - Mandatory robustness – How close are you to the edge?
  - Pre-empt the policeman!
- Production Benefit:
  - Know strength of cycle
  - Balance robustness with efficiency
- Economic Benefit: Relate your box to production economics
- Customer Benefit: Integrate your QbD with customer QbD

# The QbD Family for Freeze Drying

| CQAs | QTPPs | Issues |
|---|---|---|
| Appearance | • Type of Cake / Uniformity<br>• Shrinkage / Cohesiveness | |
| Residual Moisture | • % moisture by Karl Fisher | Strength & duration of drying |
| Reconstitution Speed | • Porosity<br>• Pre connectivity<br>• Crusting<br>• Crystallinity / Amorphous | Primary drying, type of structure<br>Viscosity, freezing rate, thermal profile<br>Drying time, wetability, containment Choice of excipient |
| Preservation of Activity | • Customer assay & toleranace | Formulation (protectant compatibility?)<br>Freezing (pH change / concentration damage?)<br>Drying (denaturing esp. in secondary drying) |
| Dried Product Stability | • Stability length<br>• Storage conditions<br>• Sales stock cycles | Excipient choice<br>Glass transition testing |
| Mechanical Properties | • How will product be transported / used | Stress / strain resistance<br>Intermediate or final |
| Sterility | • Product application | Production conditions<br>Component controls |

# The QbD Family for Freeze Drying

- Product temperature should be maintained below formulation critical temp during sublimation.
- Freeze drying has abnormally low CPP numbers
- Product temperature cannot be controlled but is influenced by
  - Shelf temperature
  - Chamber pressure
  - Condenser temperature (LN2 only)
- Influence level increased by proxy CPPs
  - Vial size & proportions
  - Fill depth
  - Fine tuning formulation esp. concentration

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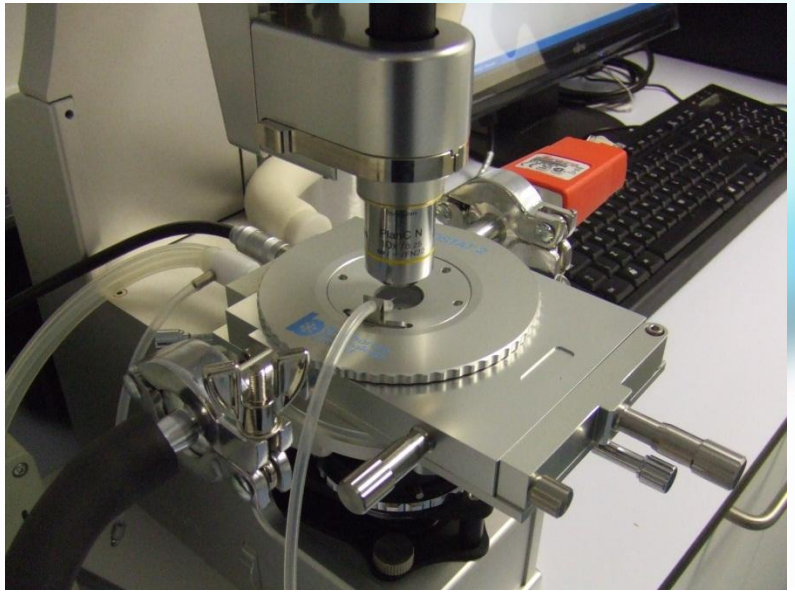
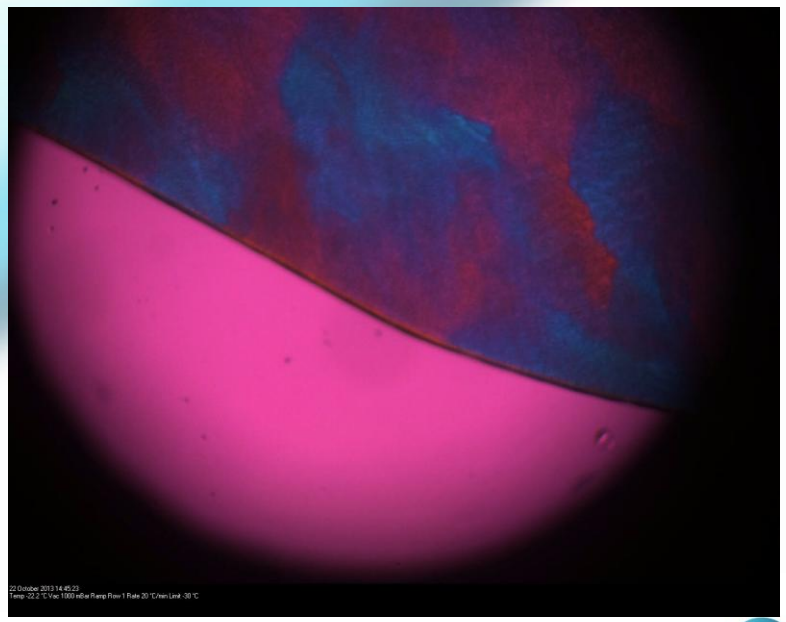
# Risk Mitigation

- Understand your freeze dryer:
  - Read manufacturing spec!
  - Ice slab test / choked flows
  - IQ / OQ – is your machine qualified?
  - Shelf mapping
- Assess robustness
- Understand product critical temps before drying
  - Freeze drying microscopy
  - Differential thermal analysis / impedance
- Understand risk transfer & change of risk types during process

# Risk Mitigation: Critical Temperatures

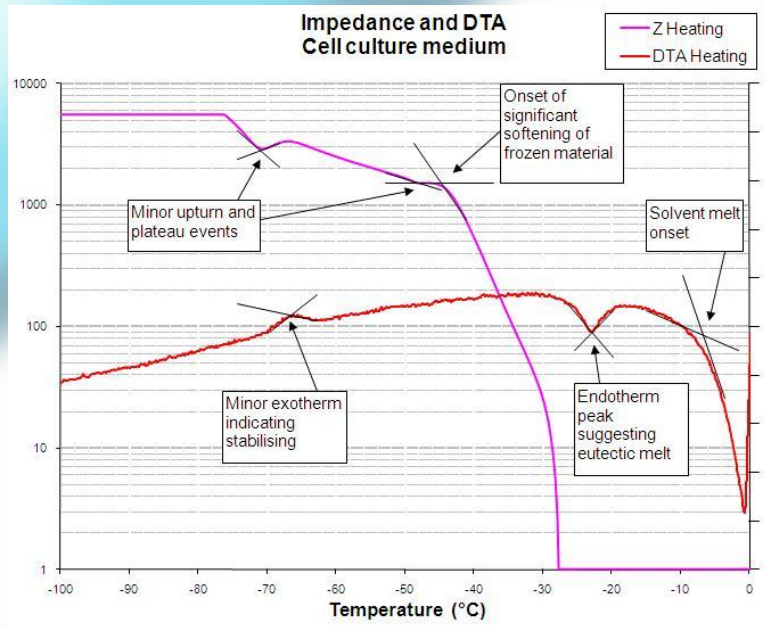
- Freeze drying microscopy:
  - define eutectic melt temperature
  - collapse temperature





# Risk Mitigation: Critical Temperatures

- DTA: Allows determination of significant endothermic / exothermic events, e.g crystallisation, eutectic melt, glass transition
- Impedance: Detects changes in molecular mobility that thermal techniques may not pick up. This allows determination of events such as glass transition in more complex amorphous products

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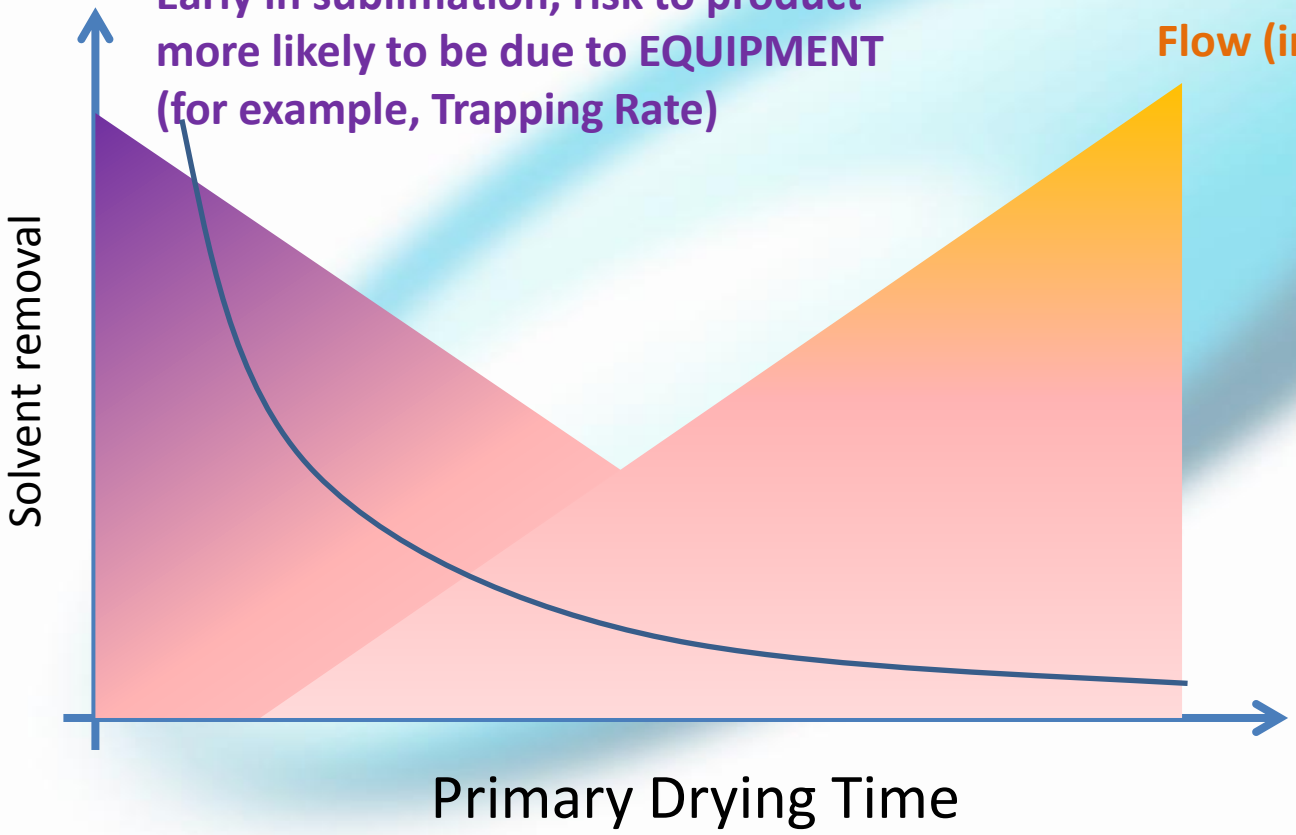
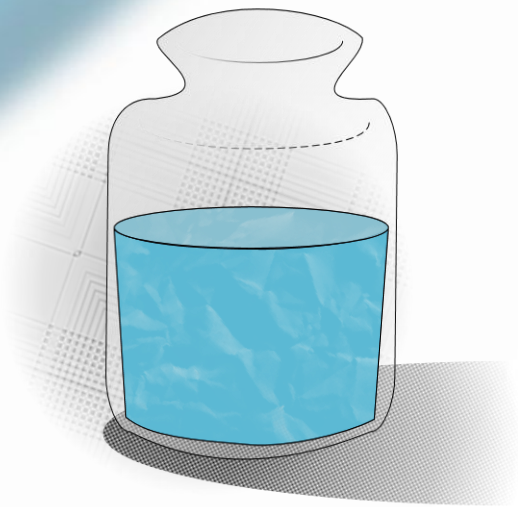
# Risk Mitigation:
## *Understanding Risk Change*

Early in sublimation, risk to product more likely to be due to EQUIPMENT (for example, Trapping Rate)

Later in sublimation, risk to product more likely to be due to PRODUCT resistance to Vapour Flow (increasing dry layer)

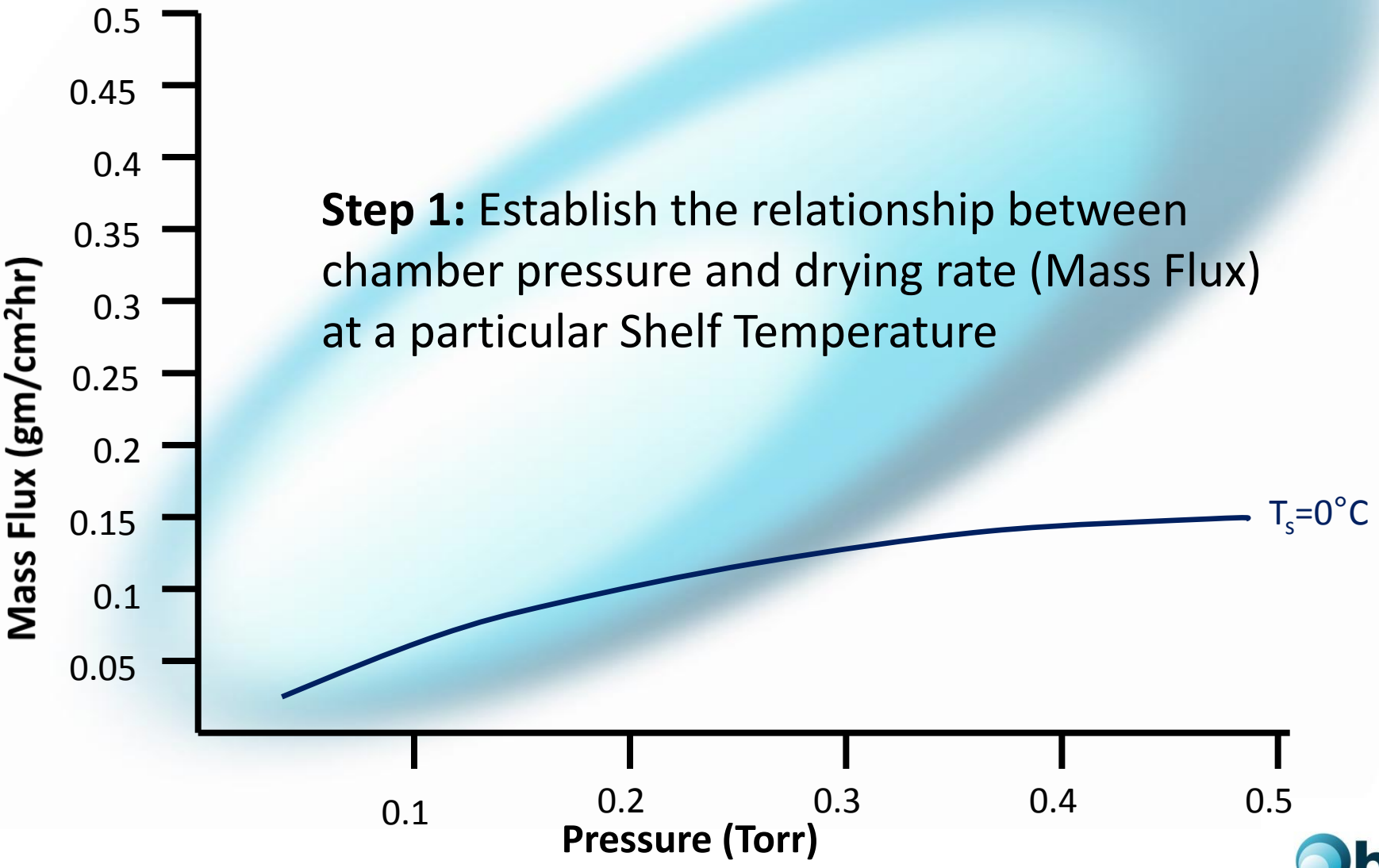


# Building Design Space: Creation of "The Box"

| | | |
|---|---|---|
| Box Proportions | Thermal Characteristics of Product | Critical Temps |
| | Machine specification | Trapping rate<br>Minimum shelf temp<br>Processing limits<br>Degree of control<br>Ability to monitor |
| | Economic performance / process cost | |
| Box Size | Relate design space to product brief tolerances<br>Change in risk type during process<br>Customer appetite for risk – compromise between efficiency & safety<br>What degree of robustness is required?<br>Regulation<br>Usage pattern<br>Shelf Life | Defined by agreement of Process Brief |
| Conclusion: | Prove box edges by empirical work | High Pressure / Low Temp<br>Low Pressure / Low Temp<br>High Pressure / High Temp<br>Low Pressure / High Temp |

# Building a Design Space




**Step 1:** Establish the relationship between chamber pressure and drying rate (Mass Flux) at a particular Shelf Temperature

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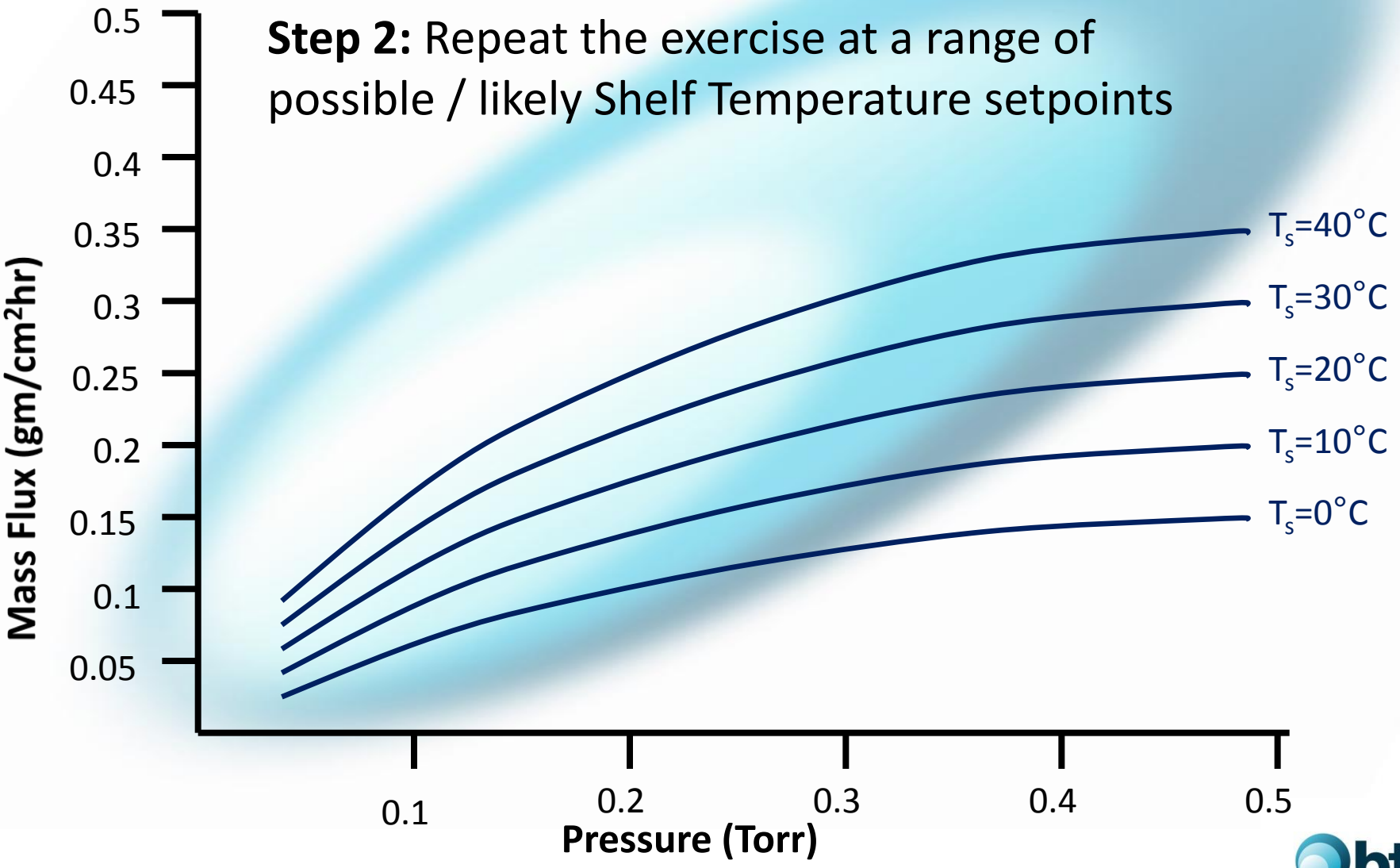
# Building a Design Space

**Step 2:** Repeat the exercise at a range of possible / likely Shelf Temperature setpoints

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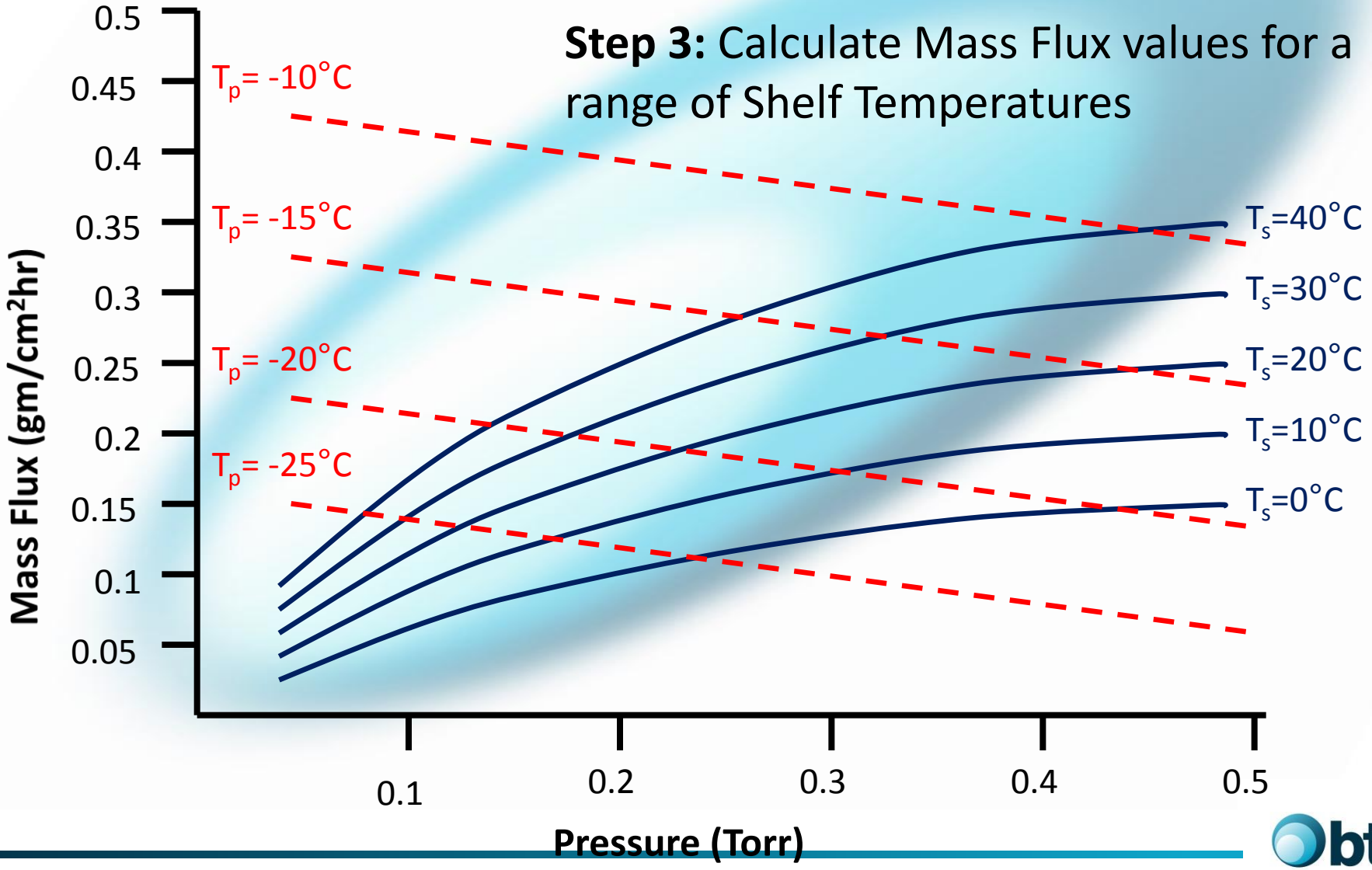
# Building a Design Space

**Step 3:** Calculate Mass Flux values for a range of Shelf Temperatures

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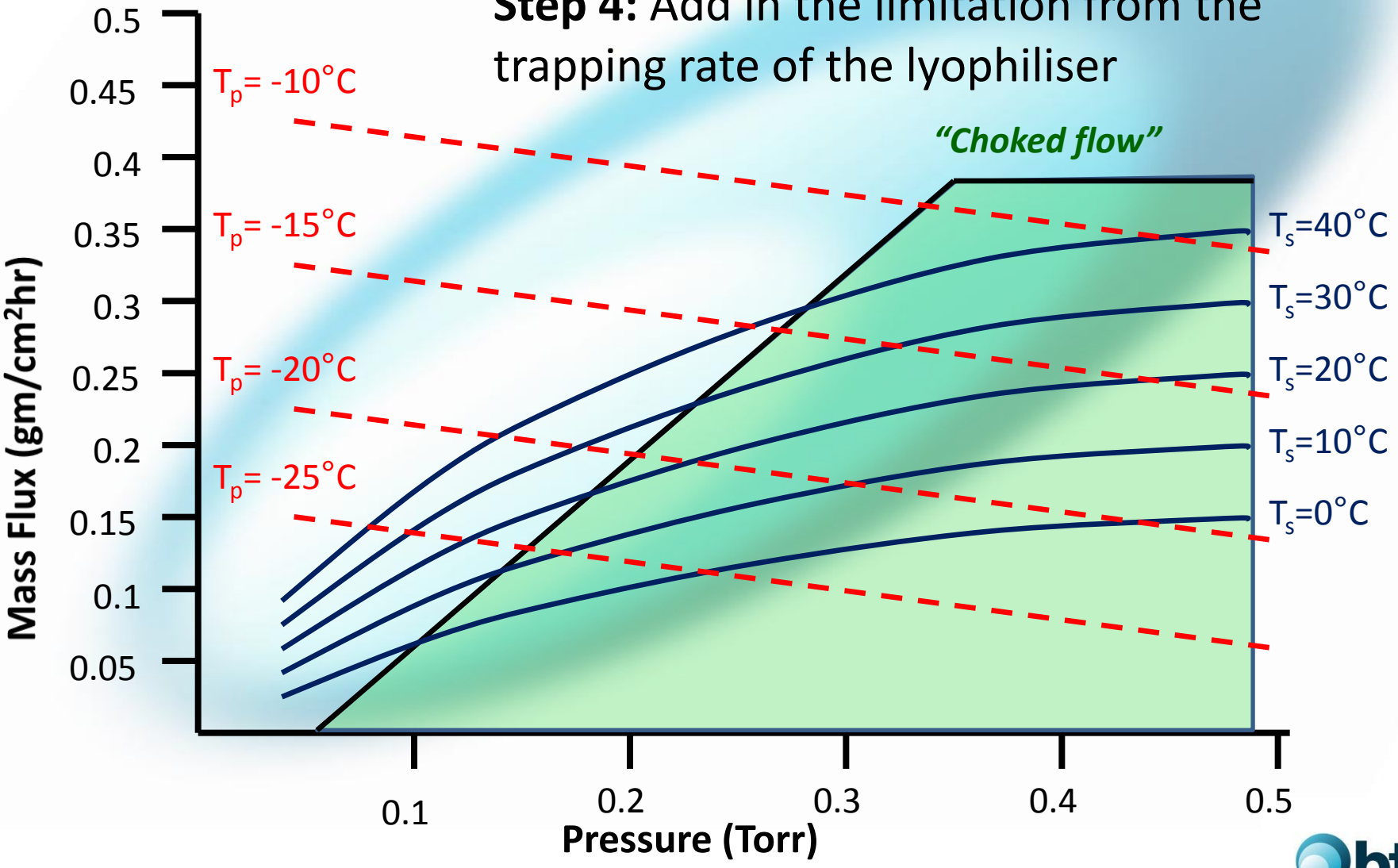
# Building a Design Space

**Step 4:** Add in the limitation from the trapping rate of the lyophiliser

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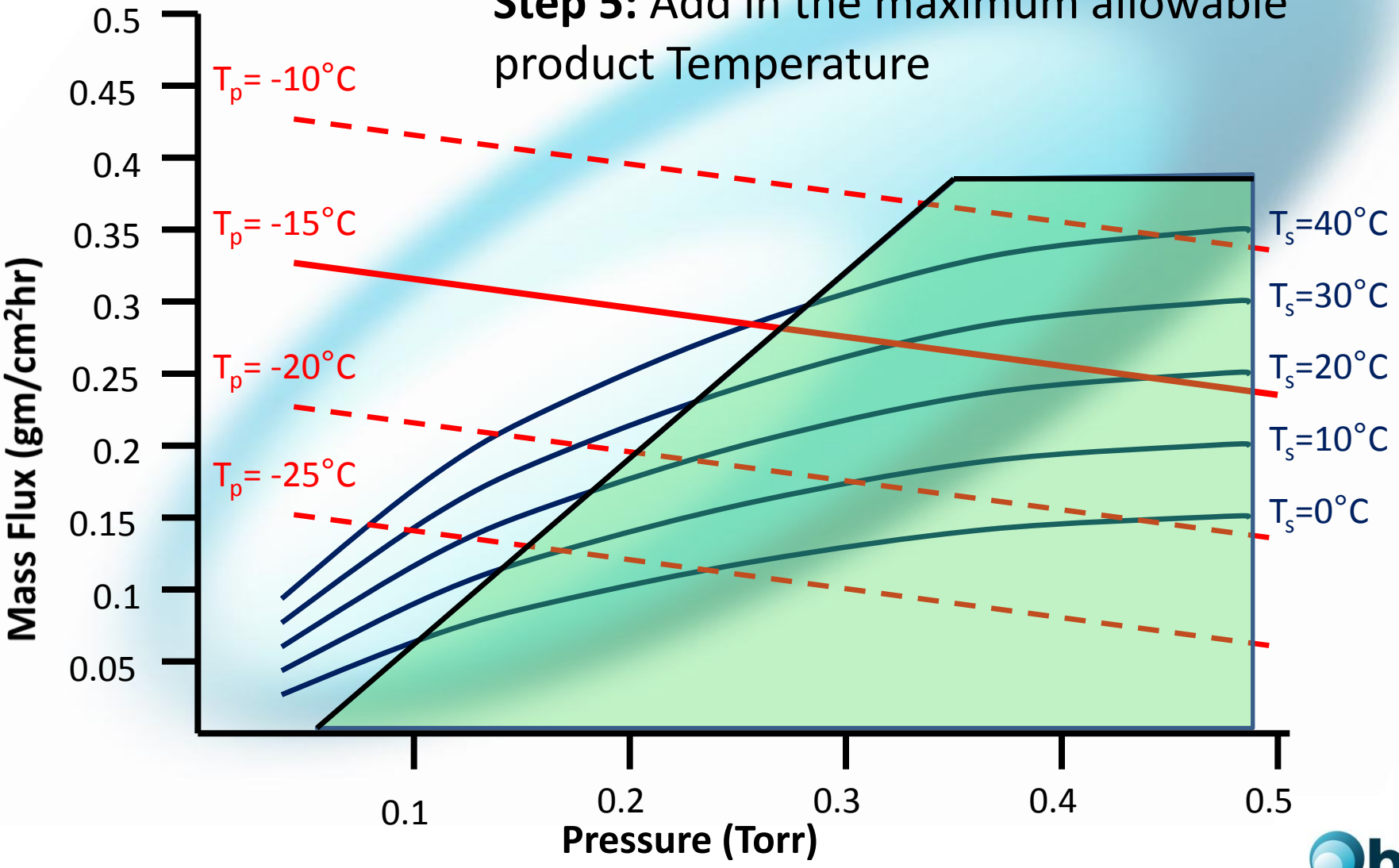
# Building a Design Space

**Step 5:** Add in the maximum allowable product Temperature

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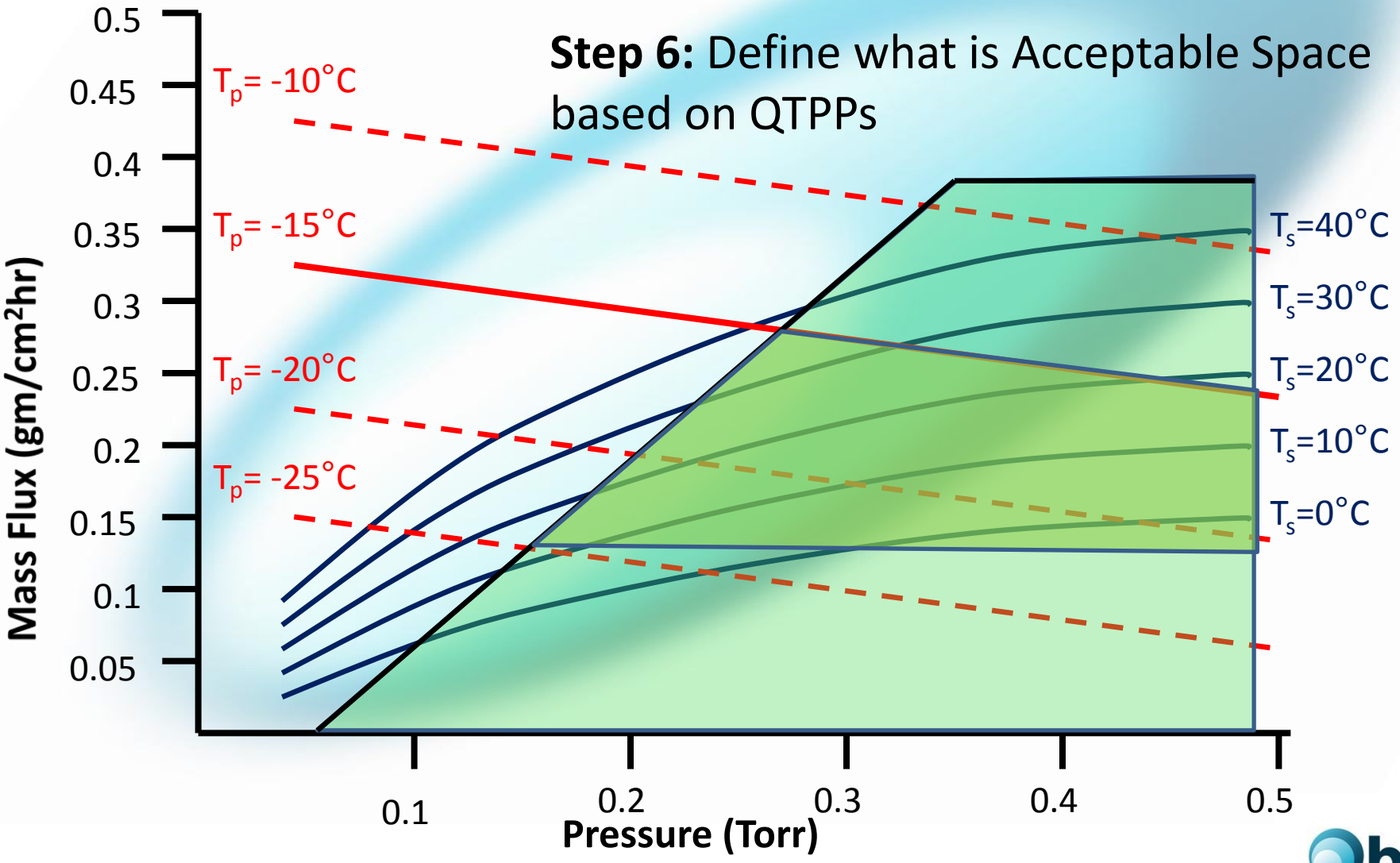
# Building a Design Space

**Step 6:** Define what is Acceptable Space based on QTPPs

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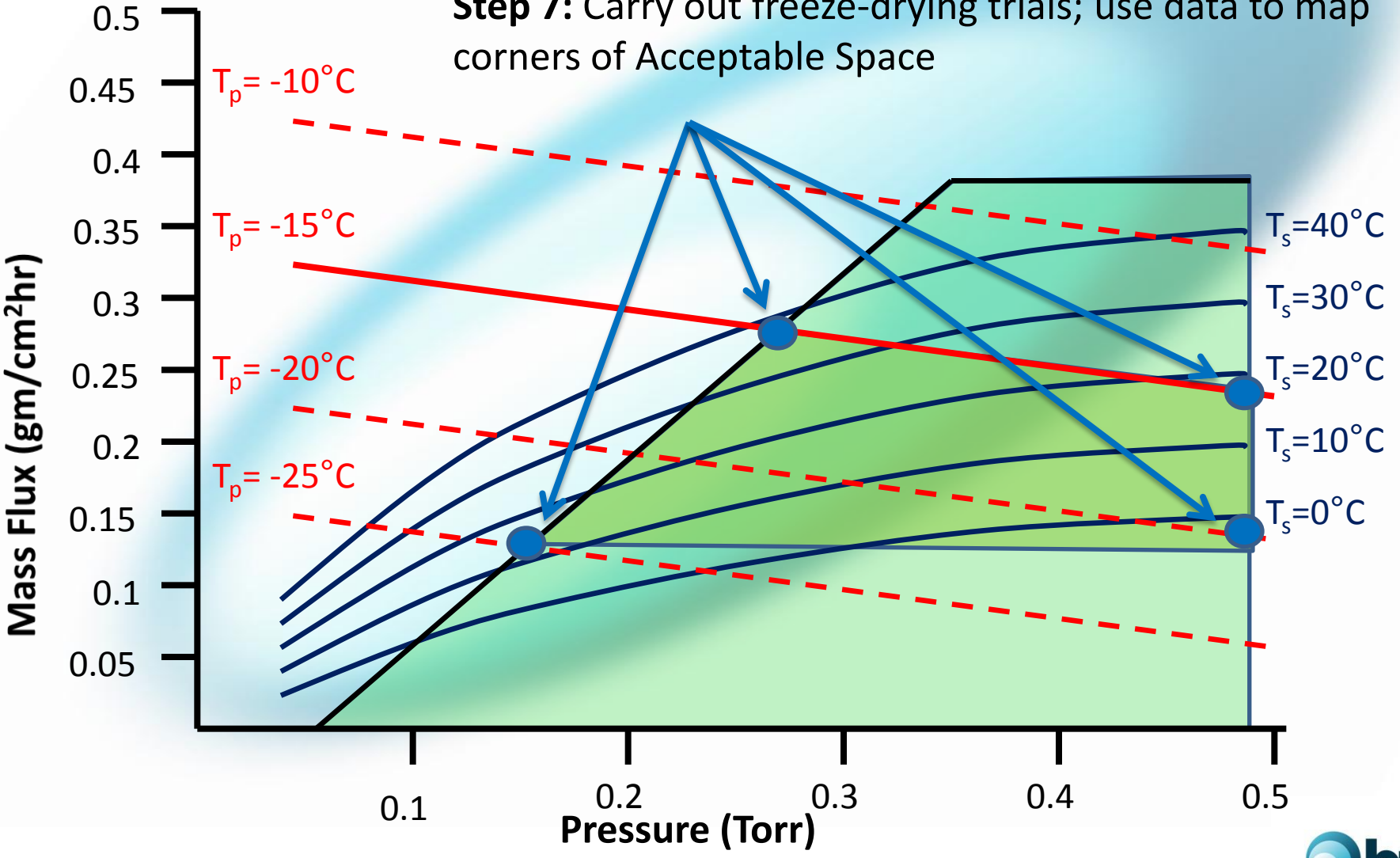
# Building a Design Space

**Step 7:** Carry out freeze-drying trials; use data to map corners of Acceptable Space

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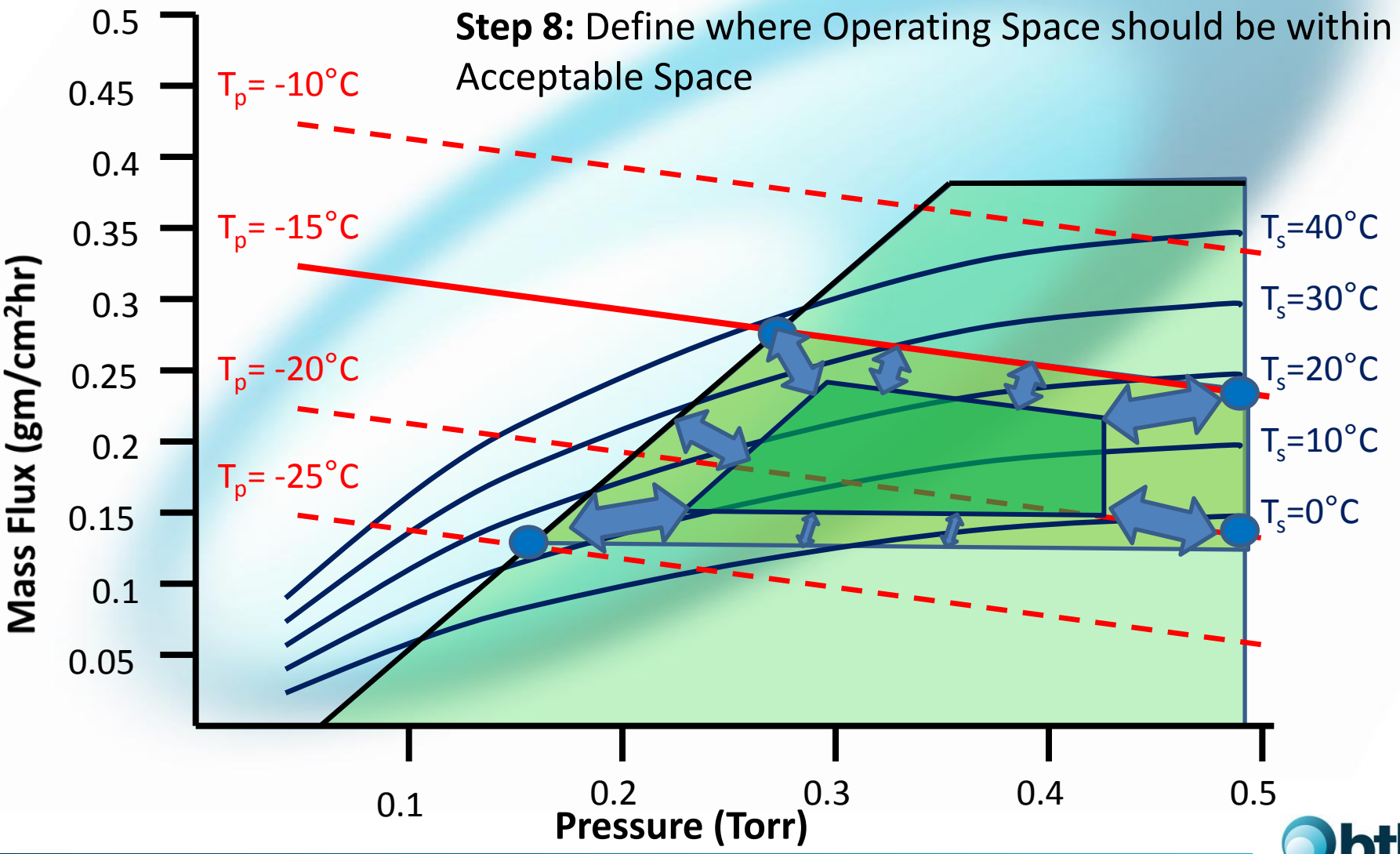
# Building a Design Space

**Step 8:** Define where Operating Space should be within Acceptable Space

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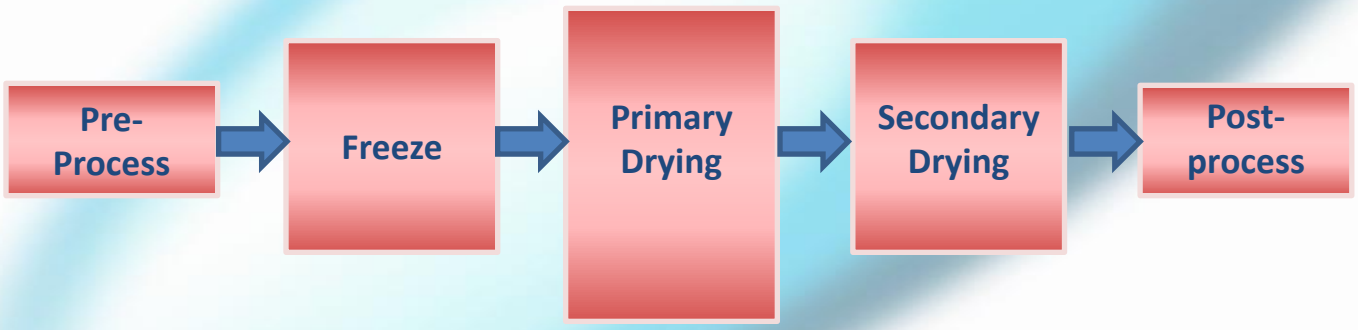
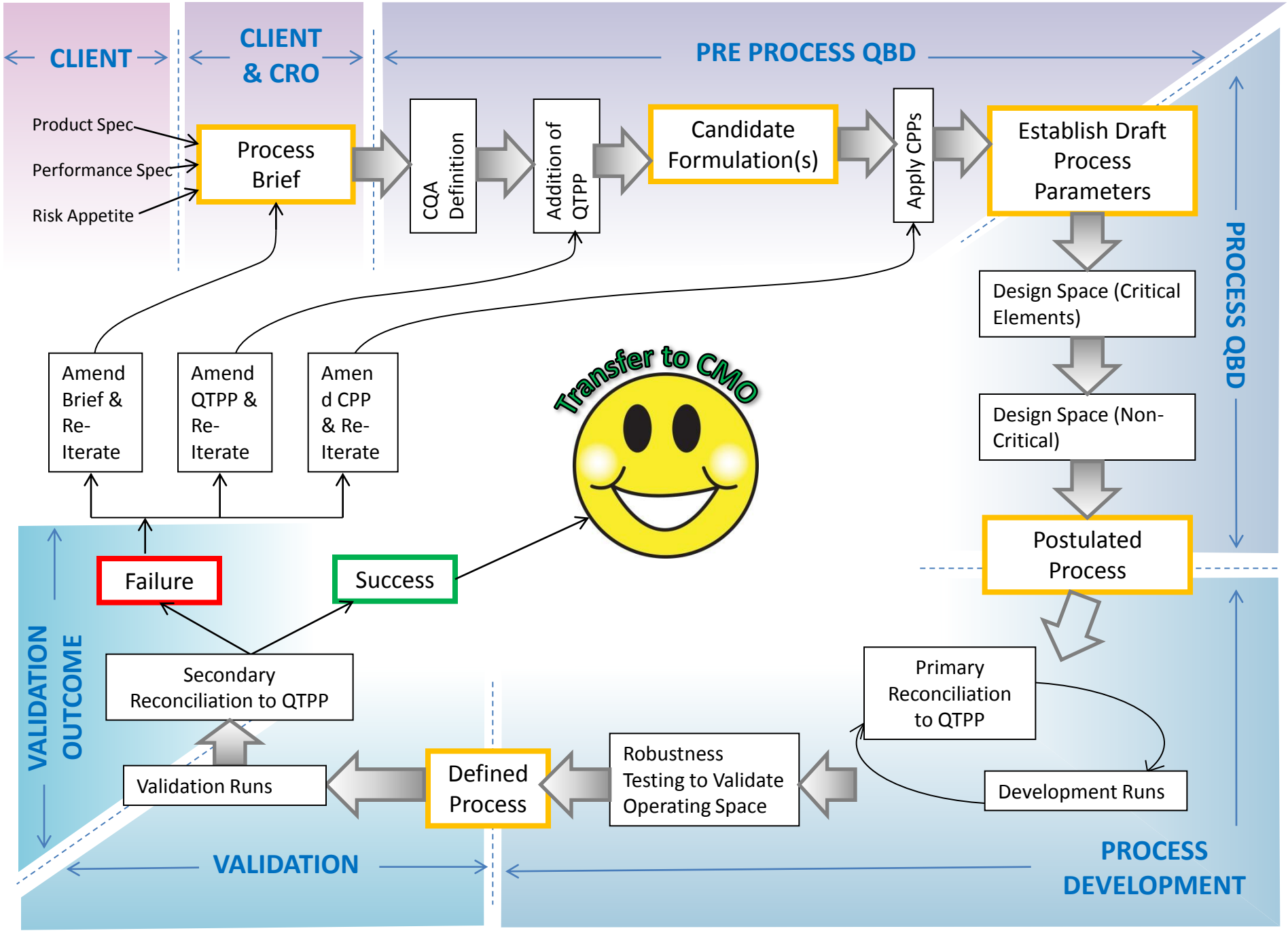
# Assembling the Train

- Segment the freeze drying process
- To what degree – primary drying stage
- Use CQA / QTPP / CPP to identify critical & non-critical segments & relative risks




- Use “Theory of Constraints”
  - Identify point of max risk
  - Provide solution to max risk
  - Subordinate other risks to that solution
  - If that transfers risk pinch-point, reiterate.


CLIENT
CLIENT & CRO
PRE PROCESS QBD
Product Spec
Performance Spec
Risk Appetite
Process Brief
CQA Definition
Addition of QTPP
Candidate Formulation(s)
Apply CPPs
Establish Draft Process Parameters
Design Space (Critical Elements)
Design Space (Non-Critical)
Postulated Process
PROCESS QBD
Amend Brief & Re-Iterate
Amend QTPP & Re-Iterate
Amen d CPP & Re-Iterate
Transfer to CMO
Failure
Success
VALIDATION OUTCOME
Secondary Reconciliation to QTPP
Validation Runs
Defined Process
Robustness Testing to Validate Operating Space
Primary Reconciliation to QTPP
Development Runs
VALIDATION
PROCESS DEVELOPMENT

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