Joint BWP / QWP workshop with stakeholders in relation to **prior knowledge and its use in regulatory applications**

Session 2-Product Design

FIM to commercial for a lyophilised (NBE) product

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efpia
European Federation of Pharmaceutical Industries and Associations

ebe
european biopharmaceutical enterprises

Vaccines Europe
An industry for healthy lives

medicines for europe
better access. better health.

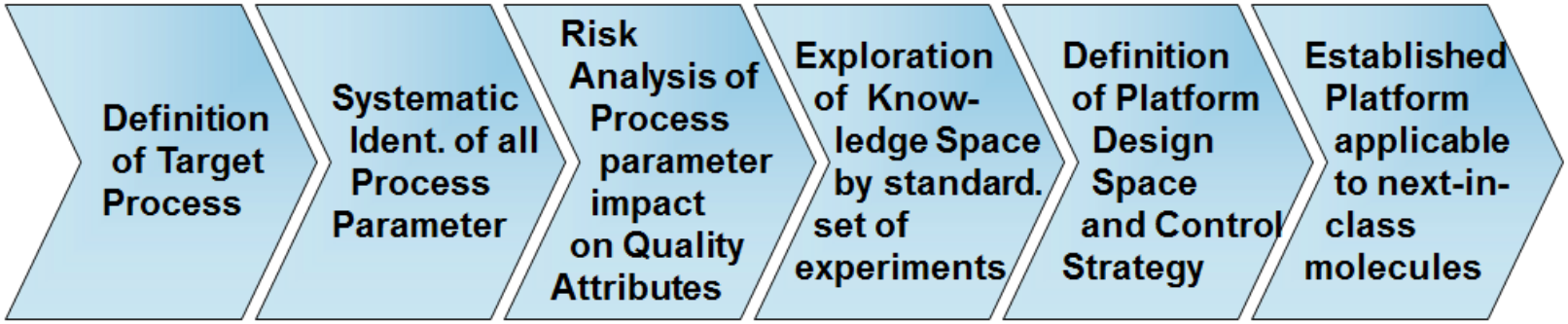
How can prior knowledge support the product development and manufacturing strategy?

Outline of case study (insert word document if needed)	Purpose*
• Efficiency gains by optimal use of prior knowledge for the development of lyophilized drug product from first in human to commercial. • We will present an approach (QbD case study) where prior knowledge is tied into molecule specific development activities via detailed risk assessments eliminating the need for confirmatory molecule specific studies such as formulation development, lyo process development, CCI and process validation. • The approach starts with systematic drug developability assessment of the molecule ensuring fit for platform. • A similar approach would be applied for definition of lyo process and shelf life setting alleviating the need for actual testing.	• Is there agreement that this systematic approach justifies no further development activities? • What are the regulatory perspective/specific concerns with such an approach for FIH studies? • Does the agency agree that for a break through therapy such an approach would be feasible for MAA submission? • What level of prior knowledge documentation would be acceptable in this context?

** Purpose = Issues to be addressed, questions to be raised, impact assessment*

Definition of technology platforms

- A systematic approach to **leverage Prior Knowledge** for **standardized processes** that have been demonstrated that the multidimensional combination and interaction of input variables can be applied for a class of molecules with comparable characteristics to provide assurance of quality.
- A technology platform follows the concept of Quality by Design to improve Product and Process understanding.



Pre-requisites for Utilizing Prior Knowledge in the form of a Technology Platform

- Standardized formulations, primary packaging components and manufacturing process to be applied for all molecules.
- Adequate justification studies to establish the technology platform for the intended class of molecules (*Platform* Design Space) and to provide assurance of quality.
- A systematic approach to assess & select molecule candidates with comparable characteristics (next-in-class molecules).
- Adequate risk assessment to justify that the target molecule can be considered a next-in-class molecule and falls into the Design Space of the established platform.

Example of stand. Formulation & primary packaging components

Example of Lyo Stand. Formulation:

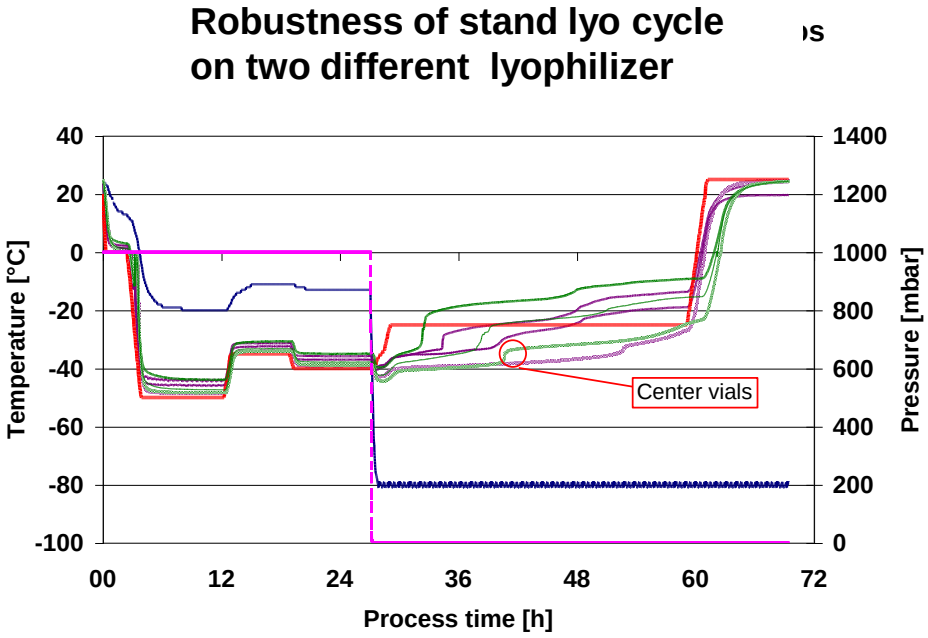
Ingredient	Bulk formulations[1] (prior to lyophilization)	DP formulations [2] (*after reconstitution*)
Antibody	55 mg/mL	100 mg/mL
Buffer	2.33 mg/mL	4.23 mg/mL
Stabilizer	46.0 mg/mL	83.6 mg/mL
Polysorbate80	0.10 mg/mL	0.18 mg/mL

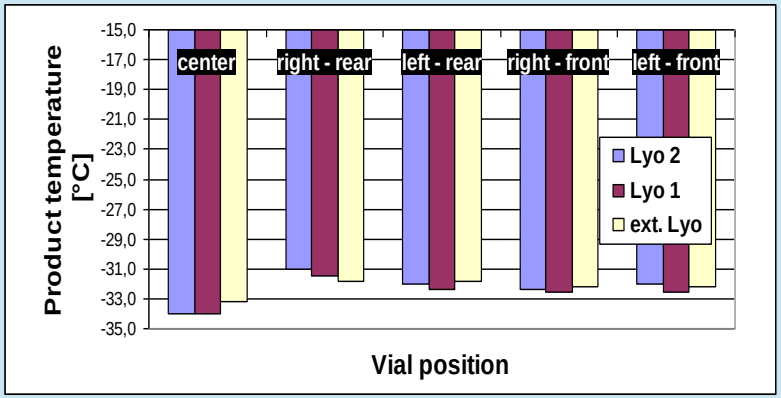
[1]Fill Vol.: 2.45 ml; [2]after reconstitution with 1.2 mL WFI

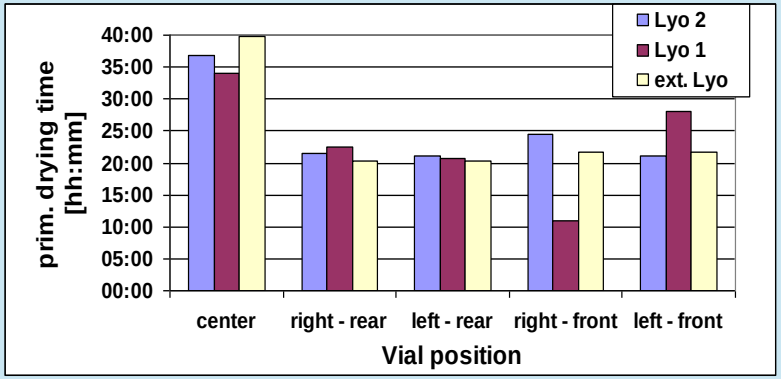
Example of Lyo Stand. Primary packaging components:

6R vial and lyo stopperl

Example of a Standard Lyophilization Cycle Robustness Evaluation







Characterization of lyo equipment

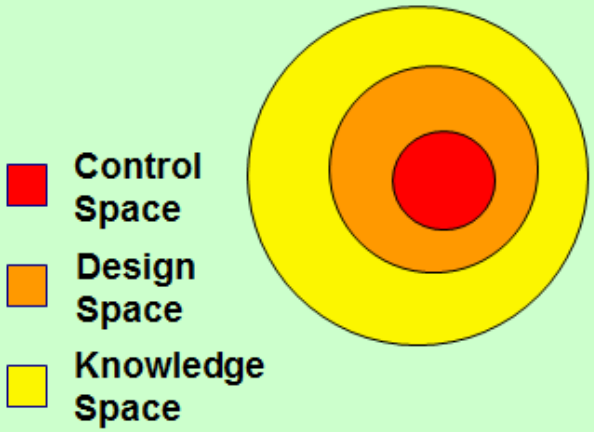
Position dependent product temp. at -25°C shelf temp and corresponding primary drying time

Concept of a Platform Design & Control Space

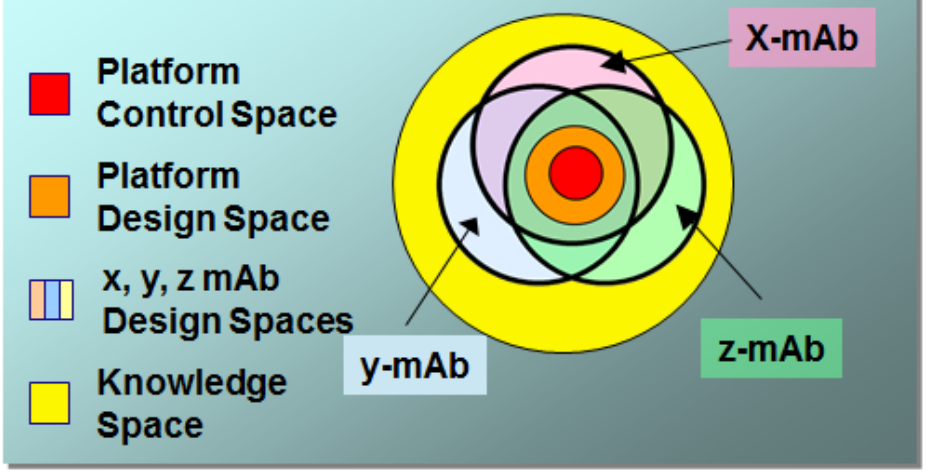
If molecules exhibit comparable characteristics (e.g., stability profile) and standardized process are applied for drug product manufacturing, the respective Design Spaces will overlap.

Within the overlap, a smaller *Platform Design & Control Space* can be defined applicable for all following "next-in-class molecules".

Conventional Approach to define Design & Control for X-mAb



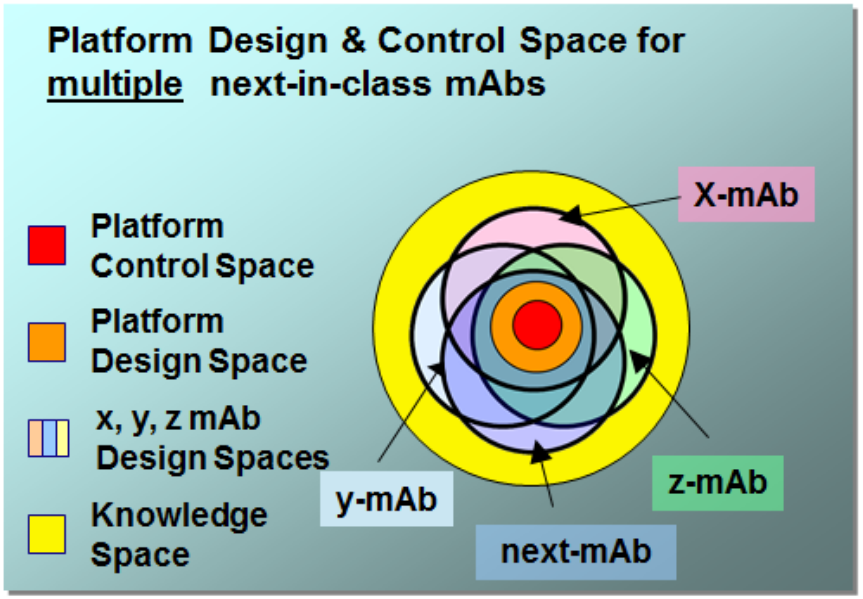
Platform Design & Control Space for multiple next-in-class mAbs



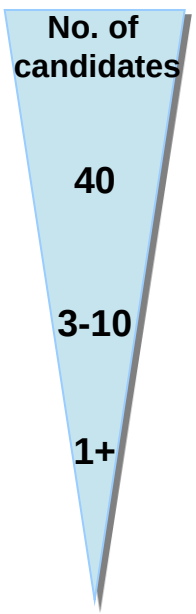
Concept of a Platform Design & Control Space cont.

- The new molecule has comparable characteristics to those used to establish the platform, (*next-in-class-molecule*).
  => It falls into the established *Platform* Design & Control Space.

- The validity of the Platform / Prior Knowledge will be demonstrated by a molecule specific risk assessment combining the QTTP, the Platform risk assessment & molecule developability data



Selection of Next-In-Class Candidates



Discovery

- Candidate selection based on affinity & potency

Preformulation

- Determination of molecule physicochemical properties
- Selection of candidate matching target molecule profile (next-in-class characteristics)

Comparison to previous mAbs database
Justification of DP Technology Platform

Comparability with established DS & DP platform processes

Yes

Platform molecules

Extensive use of Prior Knowledge & Verification of Design Space

- Standardized Formulations,
- Generic Manufacturing Processes
  - Ph I - Lyophilisate

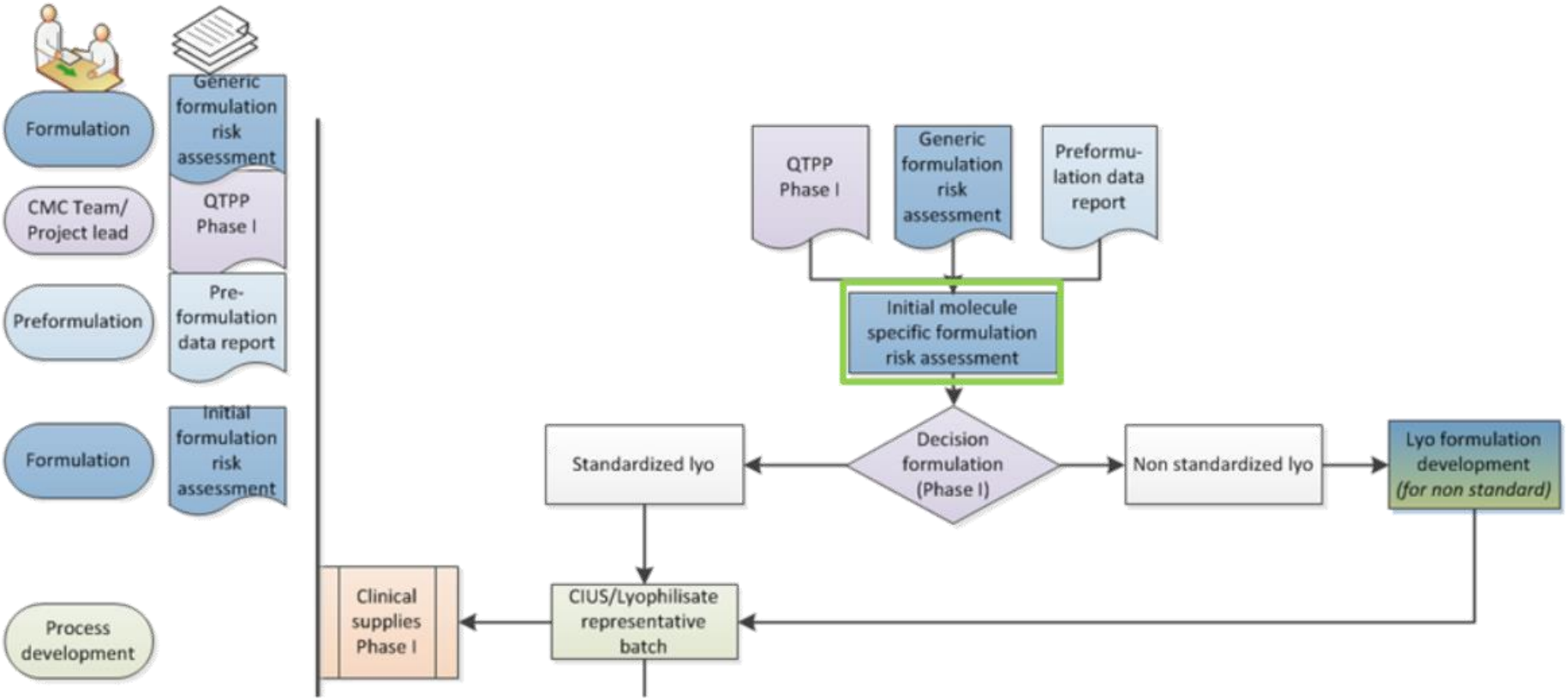
No

non-Platform molecules

Limited Prior Knowledge

- DoE/HTS Formulation Screening
- Process Development Activities
  - Ph I - Lyophilisate

Process Flow to evaluate & decide on Lyo Platform Suitability for a New Molecule



Generic Initial Risk Assessment for Formulation Parameter

	General pCQAs										
Criticality scale	10	5	7	5	7	7	7	5	10	10	...
pCQA / Parameter	Size variants (Monomer)	Size variants (Reversible self-association)	Size ariants Aggregate	Size varian (Fragment	Charge variants (Main isoforms)	Charge variants (Acidic species)	Charge variants (Basic species)	Oxidation-related variants	Protein Content	Potency /Biological activity	
Protein concentration	7	7	7	1	7	7	7	7	10	5	
pH	10	7	10	10	10	10	10	5	1	5	
Buffer selection	7	7	7	5	7	7	7	5	1	1	
Isotonizer selection	7	7	7	5	5	5	5	1	1	5	
Isotonizer concentration	10	7	7	7	5	5	5	1	1	5	
Surfactant selection	7	5	7	5	5	5	5	7	1	7	
Surfactant concentration	10	5	10	5	10	10	10	7	1	10	
Antioxidant selection	5	1	5	5	5	5	5	10	1	5	
...	5	1	5	5	5	5	5	10	1	7	

Rationale for formulation parameter selection and potential impact on critical quality attributes

Parameter	Assumptions / Comments	Criticality x Risk
Protein concentration	As a general phenomenon with increasing protein concentration the colloidal stability could become an issue resulting in potential challenges such as solubility, aggregation, particles and immunogenicity. Furthermore, the increase in concentration could result in an increase in viscosity most pronounced for high conc. formulations (>100 mg/mL). The achievable conc. also might impact the feasible s.c. volume.	1029
pH	The pH of the formulation will have a strong impact on the physical and chemical stability of the protein and will also affect the viscosity of the formulation.	1213
Buffer selection	The function of the buffer system is to maintain the pH of the protein solution within the optimal range, especially at low protein concentrations with limited self-buffering properties. Beyond that the buffer system is not significantly affecting to the overall stability. However, based on prior knowledge there might be an impact on color and clarity. There is also an proven effect on the pain associated with the injection (e.g. citrate buffer)	829
Isotonizer selection	The type of isotonizer could increase or decrease the physical and or chemical stability of the protein especially, during freeze/thawing. The isotonizer selection is also important in case of achieving an acceptable appearance of a lyo cake as well as the pain on injection of the drug product. It could also affect the colloidal stability at high concentrations such as for nanocluster formulations.	825
Isotonizer concentration	The concentration of isotonizer could increase or decrease the physical and or chemical stability. The isotonizer concentration is also important in case of achieving an acceptable appearance of a lyo cake as well as the pain on injection of the drug product. It could also affect the colloidal stability at high concentrations such as for nanocluster formulations.	905
…		

Overview of prior knowledge for formulation parameters and assessment whether the new molecule will fall within established Design Space based on the QTTP

Parameter	Score	Prior Knowledge lyo formulations	Prior Knowledge Standard Lyo formulation – Parameter	QTPP requirements mAb Z	Formulation studies required for mAb Z lyo formulation
Protein conc.	**1029**	*Standard lyo formulation:* Experience with the concentration range for standard lyo bulk drug product solution (15 mM histidine, 46 mg/ml sucrose, 0.1 mg/ml polysorbate 80) has been generated between 20 mg/ml - 55 mg/ml for the following projects: x,y,z	**Bulk drug product solution:** 20 - 55 mg/ml **Reconstituted solution:** 20 - 100 mg/ml	50 mg in 1 ml after reconstitution	no
pH	**1213**	*Standard lyo formulation:* Experience for mabs and DVDs that were processes with the standard lyo formulation e.g. x,y,z show that the optimal pH range for histidine based formulation is between pH 5.5 to 6.0 to minimized protein degradation. *Further lyo formulations:* However some experience with other buffer systems is available for molecules that have been processed at a different pH e.g., x,y,z using histidine	pH 5.2 to 6.0 (Target +/- 0.5) for histidine buffer system	not defined	no, pH 6 tested in preformulation, standard lyo bulk solution pH
….					

Example of the Justification of Lyo Standard Formulation

	Protein Content	Potency	Size variants (Monomer)	Size variants (Rev. self-association)	Size variants (Aggregates)
Prior Knowledge of CQA relevance for stand. Lyo Formulation Feasibility	Protein conc. is defined according to the QTPP and has no impact on protein stability in the defined range of 20-55 mg/ml in F2 formulation in 6R vial; 20 mg/ml in 20R vials in F2 (prior to lyophilisation)	The bioactivity will not be altered by the selected excipients for the stand lyo.	Molecule specific evaluation required	Optional molecule specific evaluation required	Molecule specific evaluation required
Requirements of QTPP	20-55 mg/ml in F2 formulation in 6R vial); 20 mg/ml in 20R vials in F2 (prior to lyophilisation)	Determine molecule function as part of ICH stability (stand. Requirements: ELISA 50 - 150 % Bioassay 70 - 143 %)	≤ 2 % monomer loss (4x F/T) ≤ 3.5 % Monomer loss over 7 days, storage at 25 °C (to allow for fill & finish operations)	Part of an optional extended characterization to be performed by preformulation group.	≤ 1.0 % increase aggregates loss (4x F/T) or ≤ 2.0 % increase aggregates loss over 7 days, storage at 25 °C (to allow for fill & finish operations)
Preformulation data	n/a	n/a	2 F/T cycles: -0.2 % 4 F/T cycles: 0 % 4 °C 7 days: -0.2 % 4 °C 21 days: -1.4 % 40 °C 7 days: -6.6 % 40 °C 21 days: -17.6 %	not tested	2 F/T cycles: +0.2 % 4 F/T cycles: -0.25 % 4 °C 7 days: +0.2 % 4 °C 21 days: +0.9 % 40 °C 7 days: +3.7 % 40 °C 21 days: +13.6 %
Feasibility of standard lyo formulation	✓	✓	!	✓	!
Remarks	-	-	no stability data available for 25 °C , therefore the suitability of the standard lyo formulation needs to be confirmed as part of the representative batch characterization and/or the clinical in-use stability	-	no stability data available for 25 °C , therefore the suitability of the standard lyo formulation needs to be confirmed as part of the representative batch characterization and/or the clinical in-use stability

Summary

- A technology platform following the concept of Quality by Design is the most systematic approach to leverage prior knowledge.
- During establishing a technology platform one has to follow the respective QbD principles.
- A technology platform requires the standardization of the formulation, the primary packaging components & the manufacturing process (e.g., lyo cycle). **-> more product & process understanding across projects**
- In order to use a technology platform most efficiently, “Development” starts in candidate selection by an appropriate “developability screening” to assure a new molecule will fit the technology platform.
- A technology platform will be come more robust & can be broaden with every new molecule. **-> Continuous improvement**
- It eliminates the need for redundant confirmatory molecule specific studies such as formulation development, lyo process development, CCI and process validation.
- A continuously growing technology platform is a very efficient way for knowledge management.