Fast Track Lyophilization Development for Early Phase Programs

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Introduction

- Lyophilization may serve as a critical enabling technology for efficient, rapid initiation of First-in-Man (FIM) trials of Small Volume Parenterals (SVPs).
- Successful application of lyophilization in early phase development involves overcoming significant managerial and technical challenges, especially with start-up sponsors.
- Risk mitigation provides a beneficial dimension to the option of lyophilized dosage form for FIM trials.
- Several case studies illustrate the feasibility of applying fast-track lyophilization development to early phase SVP programs.

Technical Challenges

- Preformulation defines constraints and requirements
  - Stability: can lyophilization enable target shelf-life?
  - Solubility: can lyophilization overcome solubility?
- Complexity of lyophilization process
  - Many individual and interacting critical process parameters define the complexity of the lyophilization process.
  - DOE required; elapsed cycle time is a constraint for number of combinations that can be tested.
- Complexity of lyophilization product
  - The lyophilization process may produce a physically complex solid matrix: local heterogeneity, amorphous and crystalline regions.

Lyophilization: Evaluation, Appearance

Evaluation Characteristic	Description
Melt back	A form of cake collapse caused by the change from solid to liquid state
Collapse	Collapse occurs when product cake begins to lose its original structure.
Incomplete Drying	High moisture content in cake may result in cake collapse after cycle completion
Shrunken Cake	The cake volume and shape will not match the fill volume, and the cake shape may not be uniform.
Surface Quality	Various topographical irregularities on cake surface: for instance, glaze on surface, peak, cracks, bumps.
Cake Color	Observation, should match expectation from experience with product.
Dense/Porous	Cake structure exhibits small pores and densely packed structure, vs relatively large pores and "lacey" appearance.
Friability	Sufficiently fragile cake structure leads to cake breaking up upon vial agitation.

Technical Solutions

- Use solid state via lyophilization to retard decomposition pathways that cannot be easily controlled just by modifying solution recipe
- Physical instability (precipitation) due to poor solubility may be solved by limiting hold periods in solution to processing steps prior or post-lyophilization
- Complexity of lyophilization process can be eliminated as an early phase development problem by adopting a conservative standard cycle and foregoing cycle development
- Complexity of lyophilization product can be reduced by empirically screening a wide range of recipes using a single conservative cycle as the screening mechanism

Case Studies: Overview

Cases are drawn from early phase, small volume parenteral (SVP) projects where lyophilization may be an enabling technology to initiate First in Man (FIM) trials.

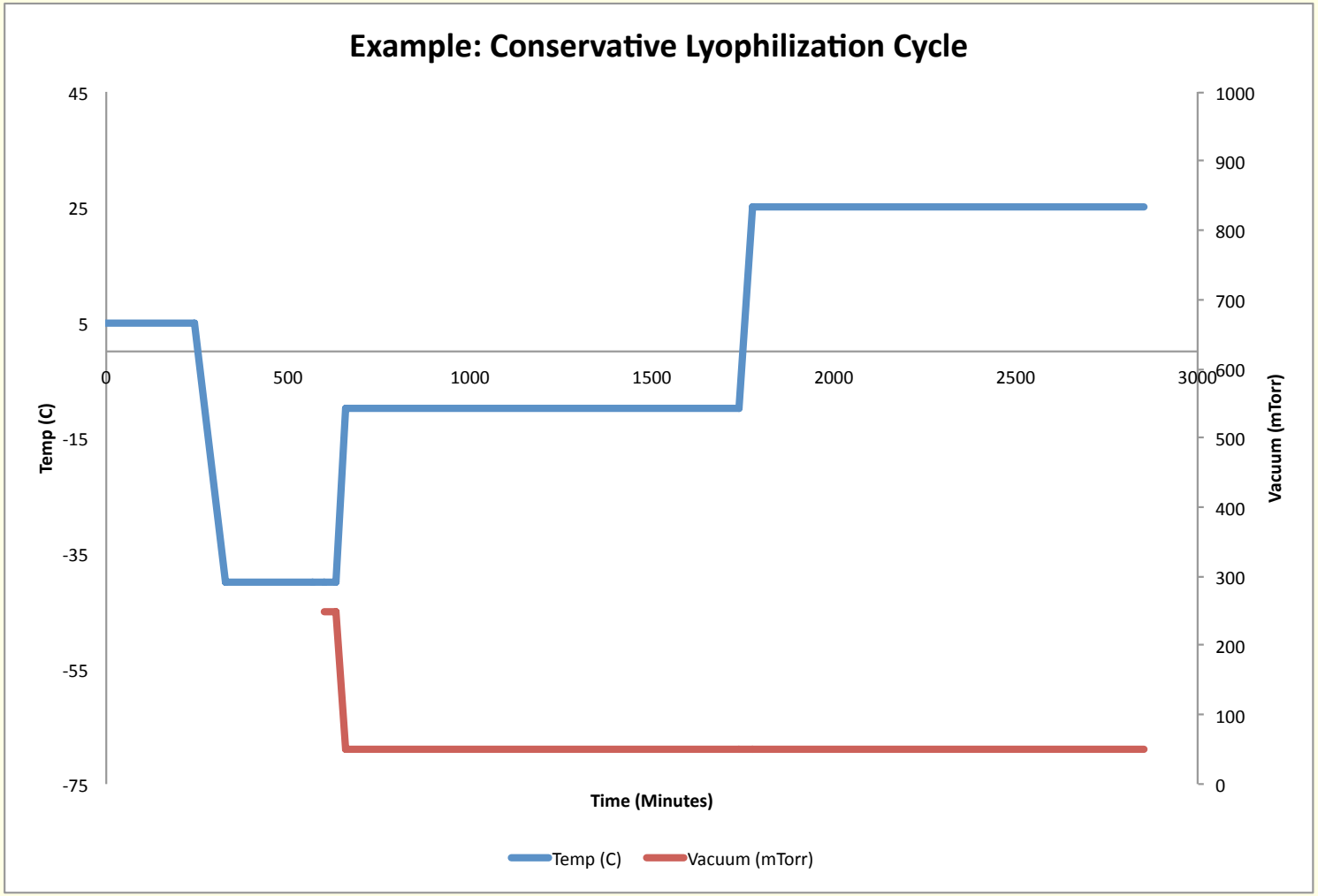
Disclaimer. *The cases present general and disguised information about actual projects. The data as presented are representative models that fairly support the points of this presentation, but any resemblance to actual data is coincidental.*

- Cases
  - A: stabilization of a high concentration peptide
  - B: solubilization and stabilization of four peptides with different solubility properties
  - C: stabilization of enzyme reagents

Fast Track Program Design

- Necessary information (constraints and opportunities)
  - Preformulation data: solubility, stability, compatibility: what are the known constraints to formulation design
  - Acceptance criteria (FIM-specific): requirements from Quality, Regulatory, Manufacturing, and Clinical that restrict acceptable product characteristics.
- Experimental design
  - DOE at screening level where appropriate
  - Avoid optimization DOE unless absolutely necessary.
- Minimize number of lyophilization runs
  - 1-3 runs in laboratory lyophilizer (1-2 screening runs, 1-2 runs limited to replication of lead candidates)
  - 1-3 runs in GMP suite (engineering (non-GMP) test run, 1-2 GMP batches for Clinical Trial Material (CTM)

Example: Typical Conservative Lyophilization Cycle



Case Study A. Target Product Profile (Phase 2)

- Benchmark: Ph 1 prototype, want improvements for Ph 2
  - Solution, recipe (per mL): 250 mg peptide, 1 mg acetic acid, 0.5 mg EGTA, adj to pH 5.3 (base)
- Dosed solution: 500 mg/mL peptide for SC administration
  - Goal incompatible with Phase 1 adverse injection site reaction due to hyperosmolality
  - Maximize drug concentration by minimizing excipient concentrations, will also reduce osmolality
- Stable for at least 2 years, room temperature
  - Goal incompatible with Phase 1 solution stability data, pH 5.3: deamidation is the primary decomposition path, and pH will already minimize deamidation (little room for improvement).
  - Improve stability with solid state (lyophilized) dosage form, will reduce deamidation relative to solution

Case Study A. Analysis, Critical Formulation Variables

- Excipient screen: > stability, <osmolality
  - EGTA (metal chelating agent) in Phase 1 formulation as a "stabilizer"-verify
  - Test potential peptide stabilization: ±5% sucrose
  - Test counterion requirement: acetate, citrate, none
  - Compare pH 5.3 (Phase I formulation) and 6.0
- Drug concentration
  - Establish the maximum concentration achievable.
  - Evaluate osmolality, aggregation, syringability, and injectability as well as purity.
- Counterion removal: Lyophilization alternative
  - Test lyophilization feasibility: apply conservative cycle
  - Test lyophilization to >stability (solid state)
  - Test lyophilization to reduce acetate from API

Case Study A. Summary Results, Critical Variable Analysis

- Established that none of the excipients significantly improved drug stability, but had the disadvantage of >osmolality. pH 6.0 stability was > pH 5.3.
- Lyophilization reduces osmolality to <0.5x by reduction of API acetate
- Solution formulation, no additives, pH 6.0, 250 mg/mL: 15% drop in purity in 1 wk, 40°C
- Lyophilized formulation, no additives, pH 6.0, 250 mg/mL: 0% drop in purity in 12 wk, 40°C
- Therefore, the equivalent solution formulation is >10x more stable post-lyophilization

Case Study A. Analysis, Lyophilization Feasibility

- Good quality cakes do not require bulking agents, because the peptide concentration is sufficiently high.
- pH adjustment followed by lyophilization produces stable target pH: buffer is unnecessary.
- Pure peptide, pH adjusted, may not require any additional excipients.
- Detailed lyophilization cycle optimization does not seem necessary at this development stage either.

Case Study A. Manufacturing Development Timeline

- Screen critical variables: initiation-week 4
- Lyophilization feasibility test, multiple test formulations: weeks 4-8
- Lyophilization feasibility test, acetate removal: weeks 4-8
- Test pilot scale lyophilization, prototype formulation: weeks 8-10
- Stability: pilot lot, accelerated, week 10 through week 18
- *In 1 Quarter completed formulation screening and lyophilization feasibility tests, ready for technology transfer of process to CMO for first CTM batch*
- Technology transfer to CMO: month 1
- CMO engineering batch: month 2
- CMO GMP batch #1: month 3

Case Study B. Compatibility in a Multi-Peptide Product

- Problem
  - The target formulation needs to be compatible with SVP constraints. The multiple active ingredients lack compatible solubility profiles. The product solution is physically unstable.
- Diagnosis
  - A traditional lyophilized solid or particle-free solution will be very difficult to formulate. Lyophilization provides a means to achieve multi-product compatibility as well as physical stability.
- Development path
  - Use the different solubility properties of the active ingredients in conjunction with the physical chemistry of a co-solvent system to produce a physically stable system.

Case Study B. Solubility Pre-Formulation

Solvent	Peptide A	Peptide B	Peptide C	Peptide D
aqueous pH 8-9				
aqueous pH 4-7				
aqueous pH 3				
Glacial acetic acid				
50% acetic acid				
DMSO				
ethanol				

Solubility, mg/mL	Code
> 0.5	
0.2-0.5	
< 0.2	

- Solubility differs greatly between peptide pairs A/B and C/D
- Peptides C and D are not soluble in a vehicle suitable for subcutaneous (SC) administration
- Look for opportunities to take advantage of lyophilization to allow initial dissolution of Peptides C/D in volatile acid that will be removed with water during lyophilization

Case Study B. Solubility
Two, Two-Peptide Solutions

Solvent	Peptide A	Peptide B	Peptide C	Peptide D
aqueous pH 8-9				
aqueous pH 4-7				
aqueous pH 3				
Glacial acetic acid				
50% acetic acid				
DMSO				
ethanol				

Solubility, mg/mL	Code
> 0.5	
0.2-0.5	
< 0.2	

- Solubility is good in all cases, considering the required peptide concentrations
- The solubility behavior is sufficiently similar for each of the two sets of two peptides to allow initial co-formulation
- Two clear colorless solutions result

Case Study B. Formulation Screening Design (DOE)

- Component A. pH/buffer.
  - Only combination: pH 8.0 sodium phosphate/ glacial acetic acid, 1/1, v/v
- Component B. amorphous phase:
  - sugars (2 choices, 2 concentrations each plus 0)
  - polymer (2 concentrations plus 0)
- Component C. crystalline phase:
  - mannitol, mannitol alternative (2 concentrations each plus 0)
- Component D. surfactant
  - one choice/ two concentrations (0 and typical)
- One selection from each component is mixed to produce test formulations

Case Study B. Initial Formulation Screening, DOE

- Based design on preformulation data and dosage form requirements
- Mixed 2-level screen: just determine necessary excipients and excipient combinations.
- Screen includes three levels (0, Low, High) of some excipients to allow concentration assignment.
- 34 formulations were prepared, dispensed to 10 vials each, and all lyophilized in the same run.
- Vial positions are randomized to avoid bias.

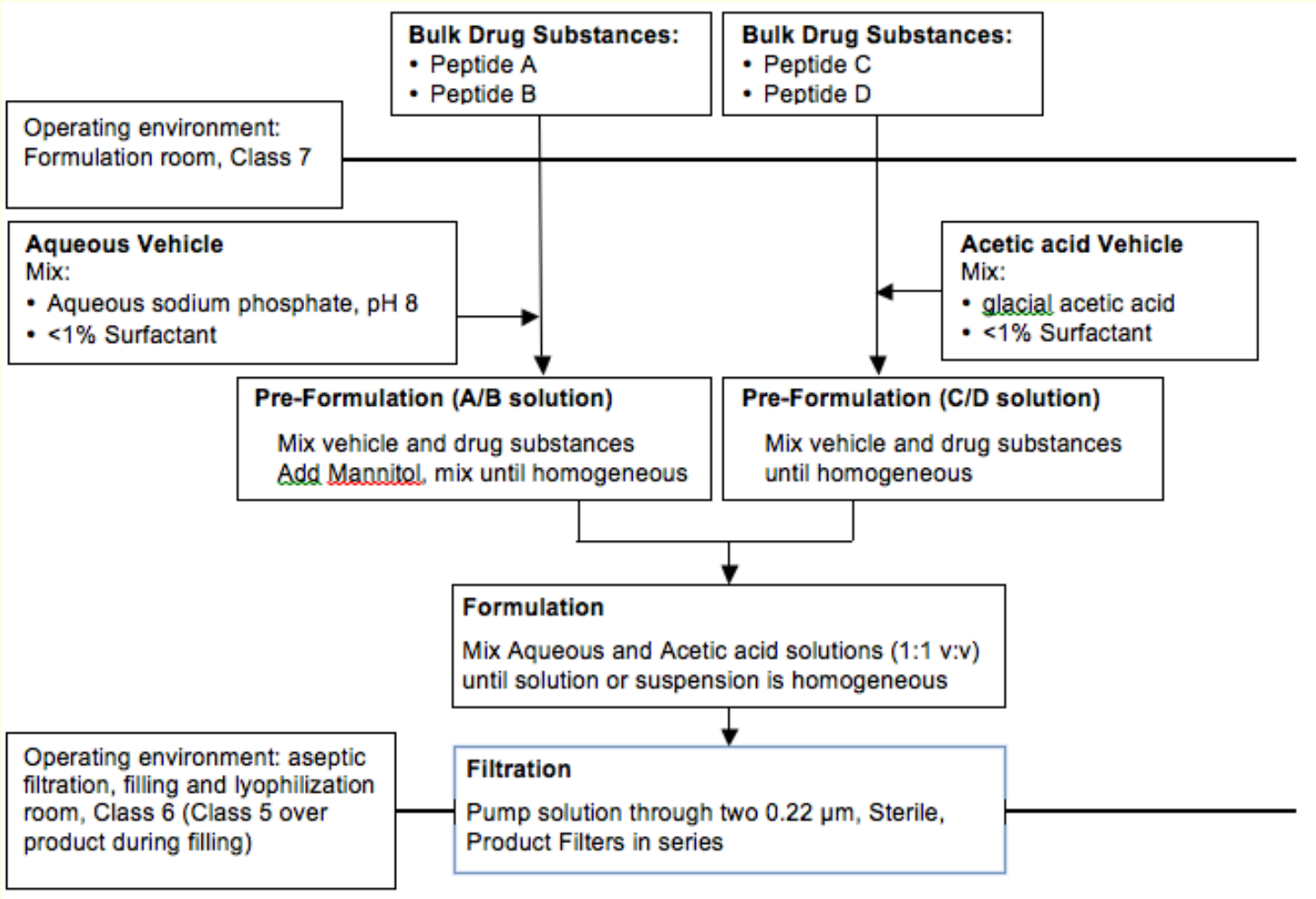
Formulation	Neutral Peptide	Neutral Peptide + Surfactant	Mannitol	Stabilizer A	Stabilizer B	Sugar A	Sugar B	Acid Peptide	Acid Peptide + Surfactant
1	x							x	
2		x							x
3	x		Hi					x	
4	x		Lo					x	
5	x			Hi				x	
6	x			Lo				x	
7	x				Hi			x	
8	x				Lo			x	
9	x					Hi		x	
10	x					Lo		x	
11	x						Hi	x	
12	x						Lo	x	
13	x		Hi		Lo			x	
14	x		Hi			Lo		x	
15	x		Hi				Lo	x	
16	x			Hi	Lo			x	
17	x			Hi		Lo		x	
18	x			Hi			Lo	x	
19		x	Hi						x
20		x	Lo						x
21		x		Hi					x
22		x		Lo					x
23		x			Hi				x
24		x			Lo				x
25		x				Hi			x
26		x				Lo			x
27		x					Hi		x
28		x					Lo		x
29		x	Hi		Lo				x
30		x	Hi			Lo			x
31		x	Hi				Lo		x
32		x		Hi	Lo				x
33		x		Hi		Lo			x
34		x		Hi			Lo		x

Case Study B. Initial Formulation Screening, DOE: Results

- Only one lyophilization run required
- No analytical testing needed at this stage, just Appearance and Reconstitution
- Quickly showed only a few combinations were feasible, even using a conservative cycle.
- Performed a second run to confirm top candidate recipes, add moisture and HPLC testing.
- Second provided sufficient support to propose the lead candidate recipe for the engineering batch.

Formulation	Bulk Formulation Appearance	Cake Appearance	Reconst. Soln Appearance
1	Clear	P	F
2	Clear	P	P
3	Particulates	P	P
4	Clear	P	F
5	Particulates	P	P
6	Clear	P	P
7	Clear	F	X
8	Clear	F	X
9	Clear	F	X
10	Clear	P	F
11	Clear	P	F
12	Clear	P	F
13	Particulates	F	X
14	Particulates	F	X
15	Particulates	F	X
16	Particulates	P	P
17	Particulates	P	P
18	Particulates	P	P
19	Particulates	P	P
20	Clear	P	F
21	Particulates	F	X
22	Clear	F	X
23	Clear	F	X
24	Clear	F	X
25	Clear	P	P
26	Clear	F	X
27	Clear	P	P
28	Clear	P	F
29	Particulates	F	X
30	Particulates	F	X
31	Particulates	F	X
32	Particulates	P	P
33	Particulates	P	P
34	Particulates	P	P

Case Study B. Process Flow Diagram



Case Study B. Solubility
Formulated Four-Peptide Bulk

Solvent	Peptide A	Peptide B	Peptide C	Peptide D
aqueous pH 8-9				
aqueous pH 4-7				
aqueous pH 3				
Glacial acetic acid				
50% acetic acid				
DMSO				
ethanol				

Solubility, mg/mL	Code
> 0.5	
0.2-0.5	
< 0.2	

- Solubility is marginal but sufficient for the target peptide concentrations
- Solution is filterable through 0.2 micron filters with good peptide recovery
- Solution has limited physical stability and must be filled within a day of formulation to avoid precipitation

Case Study B. Innovative Lyophilization

- A trial lyophilization using a default conservative cycle showed lyophilization of the four-peptide acid solution was feasible.
- The bulk formulation is 50% acetic acid
- Acetic acid, like water, crystallizes and may be removed by sublimation during lyophilization.
- Acetic acid vapor, unlike HCl, is relatively non-corrosive and (with proper precautions) may be used in large scale lyophilization.

Case Study B. Solubility
Reconstituted Four-Peptide Product

Solvent	Peptide A	Peptide B	Peptide C	Peptide D
aqueous pH 8-9				
aqueous pH 4-7				
aqueous pH 3				
Glacial acetic acid				
50% acetic acid				
DMSO				
ethanol				

Solubility, mg/mL	Code
> 0.5	
0.2-0.5	
< 0.2	

- Lyophilized dose readily reconstitutes as a fine solid dispersion: acceptable for a SC injection
- Two peptides are in solution
- Two peptides reconstitute as finely dispersed solids
- The reconstituted product will be mixed 1:1 with adjuvant to produce a combined oil-in-water emulsion and solid dispersion

Case Study B. Manufacturing Development Timeline

- Initiate First screening study: week 0
- Screen lead lyophilization candidates: complete end week 4
- Test pilot scale lyophilization: week 6
- Stability: pilot lot, accelerated, week 6 through week 18
- Initial GMP batch Date of Manufacture: week 10
- Initial GMP batch release: week 18
- Second GMP batch Date of Manufacture: week 18
- Second GMP batch release: week 26

- *In 1 Quarter went from formulation screening to release of first CTM batch*

Case Study B. Outcomes

- Application-specific opportunity
  - Two peptides are not completely dissolved upon reconstitution, and two are water soluble. The reconstituted product is a finely divided homogeneous solid suspension, which is acceptable for SC injected vaccine applications-an unusual opportunity.
- Lyophilization-specific opportunity
  - Lyophilization allows staging of peptide processing to accommodate the different solubility profiles of the four component peptides.
  - Acetic acid, a solvent that would be unsatisfactory for finished SVPs, could be used for initial dissolution of Peptides C/D. Lyophilization beneficially removes acetic acid as well as water, leaving a stable dry formulation.
  - An innovative lyophilization development strategy produced an acceptable solution to a complex technical challenge while meeting aggressive timelines.
- GMP Manufacturing
  - Passed acceptance criteria for two GMP batches to date (yield, release testing)
- Stability
  - The product has exceeded nine months stability, real-time. Decomposition is highly non-linear, with less than one month at 40C and > six months at room temperature.

Case C Program Overview

- Goal: reproducible preparation of enzyme raw materials for xIMAB process: Enz A and Enz B
- Stability and quality requirements
  - >1 year at selected temperature
  - after reconstitution, no precipitation
  - ≤2% soluble aggregates
  - ≤5% for all degradants combined
  - <10% loss of activity
  - recovery of 90-110% of mass
- Constraints:
  - restrict excipients (additives) to those used in commercial parenteral products (so removal is not critical)
  - excipients must be compatible with xIMAB reaction

Case C Lyophilization Workplan

- Do not develop a cycle: starting point is a conservative, non-optimized (but practical for scale-up) lyophilization cycle
- Run many recipes (>50) in the same cycle
  - Test both Enz A and Enz B in the same run: 2 for the price of 1!
  - Focus on proven excipients, most at one high and one low concentration
  - Recipes that produce acceptable product form the basis for further development
  - Compensate for variable lyophilization as a function of placement in lyophilizer by doing ten vials of each recipe, distributing the vials randomly in the dryer

Enz A Lyophilization: One Excipient Results-Cake Appearance

All contain: 0.5 mg/mL Enz A

Code	Buffer	NaCl	Excipient 1	Excipient 1	Pass/Fail
	20 mM, pH 7.0	mM		%w/v	
Placebo	MOPS	150	sucrose	2	P
Enz A-1	Amm Bicarb	150			P(6), 0(1), F(1)
Enz A-2	MOPS	150			F
Enz A-3	MOPS	150	trehalose	10	F
Enz A-4	MOPS	150	trehalose	2	F
Enz A-5	MOPS	150	sucrose	10	F
Enz A-6	MOPS	150	sucrose	2	F
Enz A-7	MOPS	150	raffinose	10	P(2), 0(4), F(3)
Enz A-8	MOPS	150	raffinose	2	F
Enz A-9	MOPS	150	PVP (40k)	10	SHRUNKEN
Enz A-10	MOPS	150	PVP (40k)	2	F
Enz A-11	MOPS	150	PEG 400	10	F
Enz A-12	MOPS	150	PEG 400	2	F
Enz A-13	MOPS	150	glycerol	2	F
Enz A-14	MOPS	150	glycerol	0.2	F
Enz A-15	MOPS	150	gly	10	P(6), F(2)
Enz A-16	MOPS	150	gly	2	F
Enz A-17	MOPS	150	mannitol	10	P(9)
Enz A-18	MOPS	150	mannitol	2	F
Enz A-19	MOPS	150	arg	10	F
Enz A-20	MOPS	150	arg	2	F

Enz A Lyophilization: Two Excipients Results-Cake Appearance

All contain: 0.5 mg/mL Enz A, 20 mM MOPS, pH 7.0

Code	Excipient 1	Excipient 1 %w/v	Excipient 2	Excipient 2 %w/v	Pass/Fail
Enz A-21	trehalose	2	gly	10	P(9)
Enz A-22	sucrose	2	gly	10	P(8), 0(1)
Enz A-23	raffinose	2	gly	10	P(9)
Enz A-24	PVP (40k)	2	gly	10	P(8), F(1)
Enz A-25	PEG 400	2	gly	10	P(8), F(1)
Enz A-26	glycerol	0.2	gly	10	P(9)
Enz A-27	trehalose	2	mannitol	10	P(8), F(1)
Enz A-28	sucrose	2	mannitol	10	P(8), F(1)
Enz A-29	raffinose	2	mannitol	10	P(8), F(1)
Enz A-30	PVP (40k)	2	mannitol	10	P(8), F(1)
Enz A-31	PEG 400	2	mannitol	10	P(8), F(1)
Enz A-32	glycerol	0.2	mannitol	10	P(8), F(1)
Enz A-51	sucrose	2	mannitol	10	P(9)
Enz A-52	sucrose	2	mannitol	10	P(8), F(1)

Enz A Lyophilization: Two Excipients Results-Cake Appearance

All contain: 0.5 mg/mL Enz A, 20 mM MOPS, 150 mM NaCl, pH 7.0

Code	Excipient 1	Excipient 1 %w/v	Excipient 2	Excipient 2 %w/v	Pass/Fail
Enz A-33	trehalose	2	Tween 20	0.02	F
Enz A-34	trehalose	2	Tween 20	0.02	F
Enz A-35	sucrose	10	Tween 20	0.02	F
Enz A-36	sucrose	2	Tween 20	0.02	F
Enz A-37	raffinose	10	Tween 20	0.02	SHRUNKEN/ VARIABLE
Enz A-38	raffinose	2	Tween 20	0.02	F
Enz A-39	PVP (40k)	10	Tween 20	0.02	SHRUNKEN/ VARIABLE
Enz A-40	PVP (40k)	2	Tween 20	0.02	F
Enz A-41	PEG 400	10	Tween 20	0.02	F
Enz A-42	PEG 400	2	Tween 20	0.02	F
Enz A-43	glycerol	2	Tween 20	0.02	F
Enz A-44	glycerol	0.2	Tween 20	0.02	F
Enz A-45	gly	10	Tween 20	0.02	P(9)
Enz A-46	gly	2	Tween 20	0.02	F
Enz A-47	mannitol	10	Tween 20	0.02	P(9)
Enz A-48	mannitol	2	Tween 20	0.02	F
Enz A-49	arg	10	Tween 20	0.02	F
Enz A-50	arg	2	Tween 20	0.02	F

Enz A Lyophilization: First Screen Results (Cake Appearance)

The following recipes are carried forward to assessment by UV (280, 320), post-filtration recovery, SEC, activity, SDS PAGE

Code	Buffer	NaCl	Excipient 1	Excipient 1	Excipient 2	Excipient 2	Pass/Fail
	20 mM, pH 7.0	mM		%w/v		%w/v	
Placebo	MOPS	150	sucrose	2	mannitol	10	P
Enz A-1	Amm Bicarb	150					P(6), 0(1), F(1)
Enz A-15	MOPS	150	gly	10			P(6), F(2)
Enz A-17	MOPS	150	mannitol	10			P(9)
Enz A-21	MOPS	150	trehalose	2	gly	10	P(9)
Enz A-22	MOPS	150	sucrose	2	gly	10	P(8), 0(1)
Enz A-23	MOPS	150	raffinose	2	gly	10	P(9)
Enz A-24	MOPS	150	PVP (40k)	2	gly	10	P(8), F(1)
Enz A-25	MOPS	150	PEG 400	2	gly	10	P(8), F(1)
Enz A-26	MOPS	150	glycerol	0.2	gly	10	P(9)
Enz A-27	MOPS	150	trehalose	2	mannitol	10	P(8), F(1)
Enz A-28	MOPS	150	sucrose	2	mannitol	10	P(8), F(1)
Enz A-29	MOPS	150	raffinose	2	mannitol	10	P(8), F(1)
Enz A-30	MOPS	150	PVP (40k)	2	mannitol	10	P(8), F(1)
Enz A-31	MOPS	150	PEG 400	2	mannitol	10	P(8), F(1)
Enz A-32	MOPS	150	glycerol	0.2	mannitol	10	P(8), F(1)
Enz A-45	MOPS	150	gly	10	Tween 20	0.02	P(9)
Enz A-47	MOPS	150	mannitol	10	Tween 20	0.02	P(9)
Enz A-51	MOPS	0	sucrose	2	mannitol	10	P(9)
Enz A-52	MOPS	300	sucrose	2	mannitol	10	P(8), F(1)

Evaluation: Lyophilized Enz A Recovery

- Reconstitution screening: each vial (n=3) was reconstituted with water to the filled solution concentration. Criteria: a uniform, stable solution or suspension should be achieved in < 5 min (preferably < 1 min)
- Solutions were evaluated by UV/VIS at 280 nm (protein), 320 nm (scattering adjustment for protein) and 600 nm (scattering; evidence of particulates).
- Solutions were filtered (0.45 µm) and reassessed. Filterable protein recovery was calculated.
- Formulations were ranked on the basis of recoverable protein post-filtration.

Enz A Lyophilization: Second Screen

The following recipes that passed visual inspection were analyzed for recoverable protein after filtration.

	Post-Filtration recovery based on UV, corrected for scattering	Mean
Enz A Sample	Formulation	Recovery
45	20mM MOPS, 150mM NaCl, pH7, 10% glycine, 0.02% tween 20	96%
47	20mM MOPS, 150mM NaCl, pH7, 10% mannitol, 0.02% tween 20	94%
51	20mM MOPS, pH7, 10% mannitol, 2% sucrose	83%
24	20mM MOPS, 150mM NaCl, pH7, 10% glycine, 2% PVP	83%
21	20mM MOPS, 150mM NaCl, pH7, 10% glycine, 2% trahalose	80%
23	20mM MOPS, 150mM NaCl, pH7, 10% glycine, 2% raffinose	79%
26	20mM MOPS, 150mM NaCl, pH7, 10% glycine, 0.2% glycerol	78%
1	20mM Ammonium Bicarb, 150 mM NaCl, pH 7	78%
7	20mM MOPS, 150mM NaCl, pH7, 10% raffinose	77%
30	20mM MOPS, 150mM NaCl, pH7, 10% mannitol, 2% PVP	74%
17	20mM MOPS, 150mM NaCl, pH7, 10% mannitol	73%
22	20mM MOPS, 150mM NaCl, pH7, 10% glycine, 2% sucrose	71%
28	20mM MOPS, 150mM NaCl, pH7, 10% mannitol, 2% sucrose	67%
27	20mM MOPS, 150mM NaCl, pH7, 10% mannitol, 2% trahalose	66%
29	20mM MOPS, 150mM NaCl, pH7, 10% mannitol, 2% raffinose	61%
52	20mM MOPS, 300mM NaCl, pH7, 10% mannitol, 2% sucrose	61%
32	20mM MOPS, 150mM NaCl, pH7, 10% mannitol, 0.2% glycerol	60%
15	20mM MOPS, 150mM NaCl, pH7, 10% glycine	59%
31	20mM MOPS, 150mM NaCl, pH7, 10% mannitol, 2% PEG 400	39%
25	20mM MOPS, 150mM NaCl, pH7, 10% glycine, 2% PEG 400	27%

n=3

The Quality by Design Paradigm

- Supported by US, EU, and Japan regulatory authorities.
- Scientific, risk-based, comprehensive, proactive approach to pharmaceutical development.
- Deliberate design effort from product conception through commercialization.
- Full understanding of how product attributes and process relate to product performance.
- Increases product quality assurance

Linking QbD to Practice

- Design the initial preformulation database to cover a large experimental space
  - Initially including extreme endpoints for variable ranges allows the workplan to be adjusted to accommodate resource and time constraints.
  - Fast track early phase programs can be accommodated with this approach by looking for ways to selectively populate the database in regions of experimental space that look the most promising.
- As the project develops, a more comprehensive QbD approach may be achieved by selectively increasing the data density within the regions of the previously explored experimental space that have shown the most promise for additional improvement in Quality, but off the critical path.

Summary

- Understand what is necessary (but not necessarily perfect)
  - Product constraints
  - Process constraints
  - Quality Criteria for Clinical Trial Supply
- Build for Success (while minimizing resources and time)
  - Create a working database that preserves the opportunity to transition to a fuller QbD approach as the program develops
  - Integrate risk reduction into product design
- Value Added for the Sponsor (preserves program options)
  - Fast to FIM
  - Resource- and Timeline-Efficient
  - Builds value of the program in the event of acquisition

Fast Track Lyophilization Development for Early Phase Programs

THANKS!

FOR YOUR ATTENTION

Questions and Answers…