Technology Transfer of Aseptic Processes in the Modern Age

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Our purpose

We enable people with life-altering conditions to lead better lives.

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Technology Transfer (per ICH Q10)

"The goal of technology transfer activities is to transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realization. This knowledge forms **the basis** for the manufacturing process, control strategy, process validation approach, and ongoing continual improvement."

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Guiding Principles

Pharmaceutical Quality Systems
ICH Q9/Q10/Q12

API

ICH Q7/Q11

Raw Materials

Process and Product

ICH Q8

Product Specs

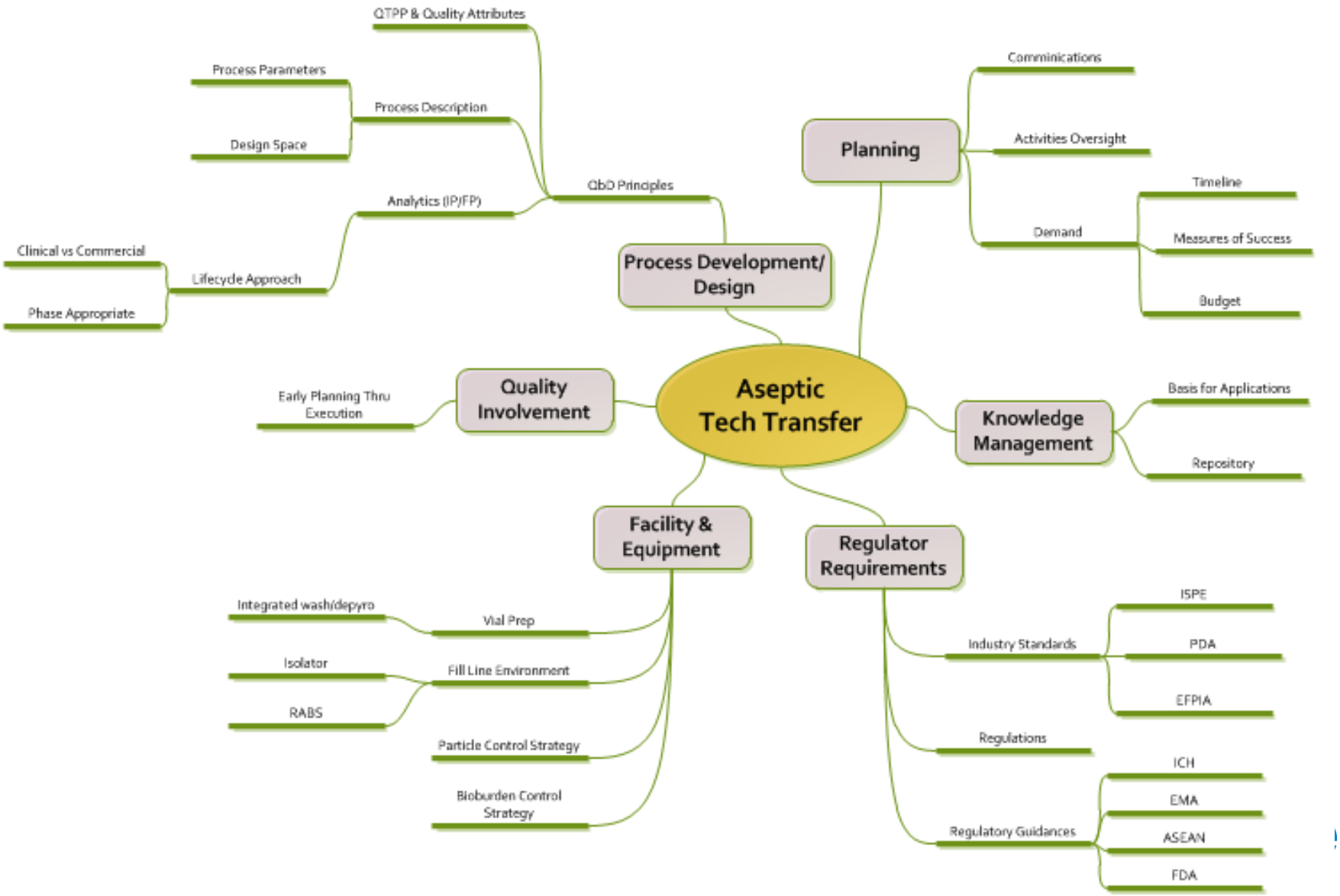
ICH Q5/Q6

Stability

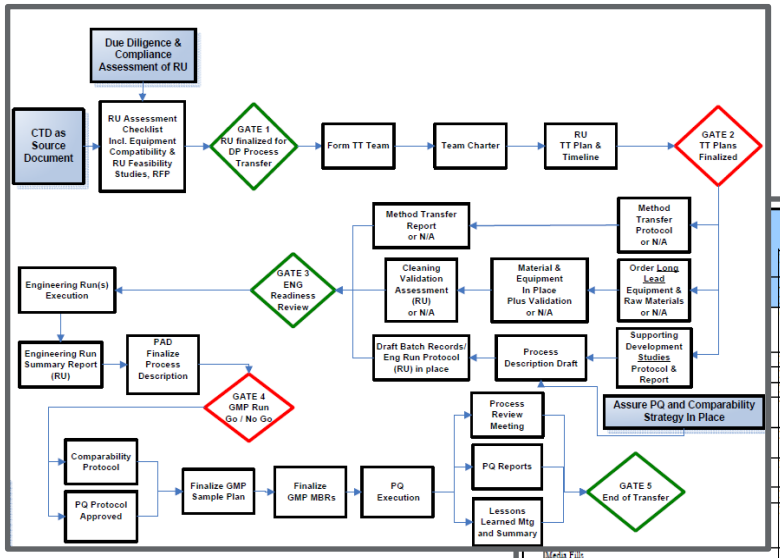
ICH Q1

ICH Q2
Analytical Methods

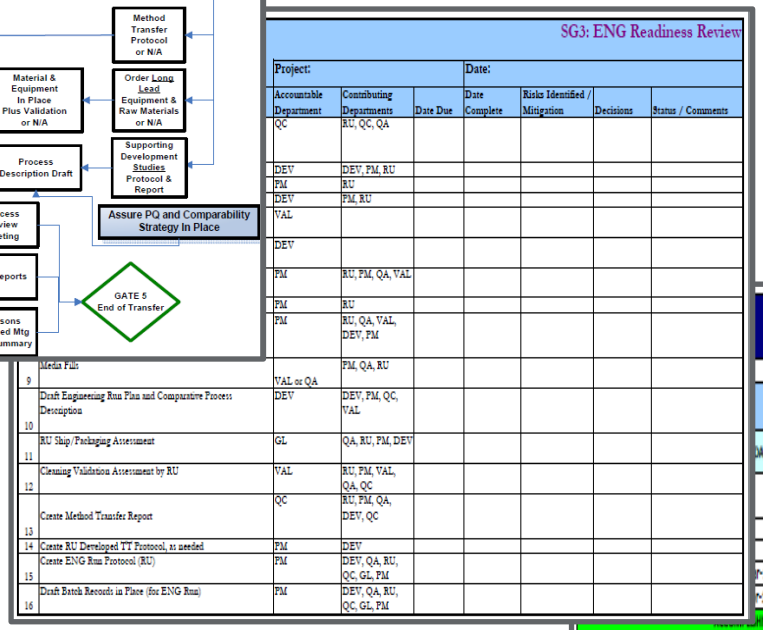
Complexities of Technology Transfer



Technology Transfer Management



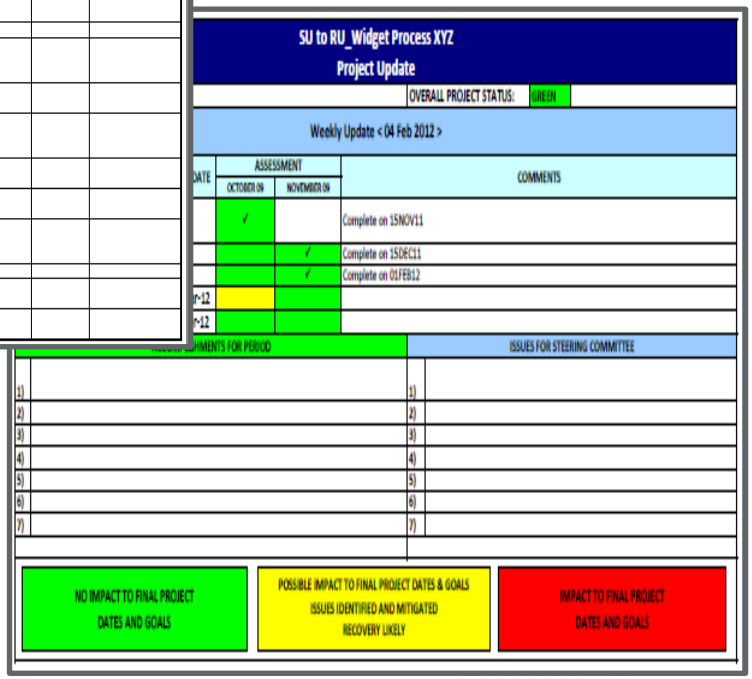
- ROADMAP -



SG3: ENG Readiness Review

Project: Date:

	Accountable Department	Contributing Departments	Date Due	Date Complete	Risks Identified / Mitigation	Decisions	Status / Comments
	QC	RU, QC, QA					
	DEV	DEV, PM, RU					
	PM	RU					
	DEV	PM, RU					
	VAL						
	DEV						
	PM	RU, PM, QA, VAL					
	PM	RU					
	PM	RU, QA, VAL, DEV, PM					
9	Media Fills	VAL or QA	PM, QA, RU				
10	Draft Engineering Run Plan and Comparative Process Description	DEV	DEV, PM, QC, VAL				
11	RU Ship/Packaging Assessment	GL	QA, RU, PM, DEV				
12	Cleaning Validation Assessment by RU	VAL	RU, PM, VAL, QA, QC				
13	Create Method Transfer Report	QC	RU, PM, QA, DEV, QC				
14	Create RU Developed TT Protocol, as needed	PM	DEV				
15	Create ENG Run Protocol (RU)	PM	DEV, QA, RU, QC, GL, PM				
16	Draft Batch Records in Place (for ENG Runs)	PM	DEV, QA, RU, QC, GL, PM				



SU to RU_Widget Process XYZ
Project Update

OVERALL PROJECT STATUS: GREEN

Weekly Update < 04 Feb 2012 >

DATE	ASSESSMENT OCTOBER 09	ASSESSMENT NOVEMBER 09	COMMENTS
	✓		Complete on 15NOV11
		✓	Complete on 15DEC11
		✓	Complete on 01FEB12
r-12			
r-12			

ISSUES FOR STEERING COMMITTEE

1) 2) 3) 4) 5) 6) 7)

NO IMPACT TO FINAL PROJECT DATES AND GOALS

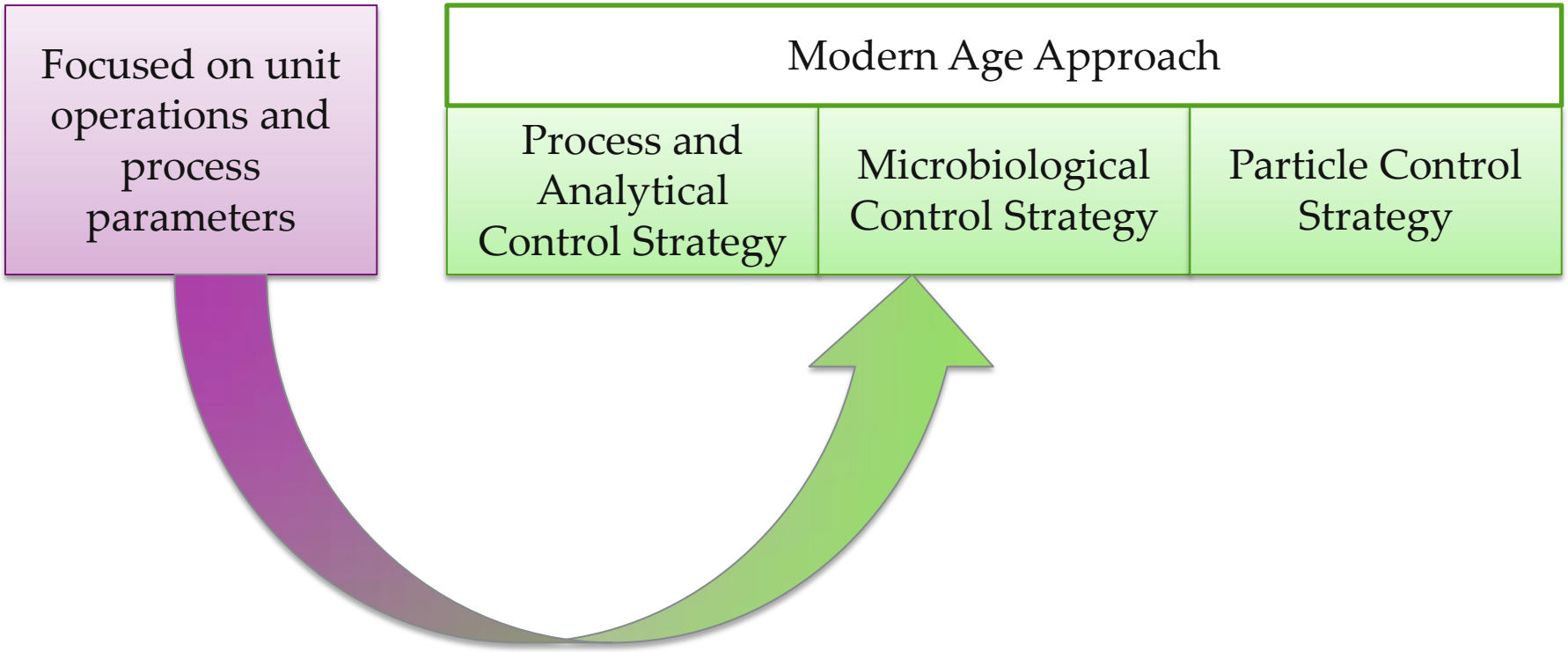
POSSIBLE IMPACT TO FINAL PROJECT DATES & GOALS ISSUES IDENTIFIED AND MITIGATED RECOVERY LIKELY

IMPACT TO FINAL PROJECT DATES AND GOALS

- Visibility – How's the team doing?
- Management Awareness
- Outline Hazards and Mitigation Planning

- Stage Gates
- Key Milestones
- Clear Decision Points
- Consistency Across Projects

In the Modern Age…



In the Modern Age…

- Heavy Reliance on External Partners
  - DS/DP Manufacture
  - Product and Process Development
- Facility Design is KEY – RABS/Isolators are the new STANDARD for aseptic processing
- QbD: Greater Product and Process Understanding using a Risk-Based Approach
  - Understand the Product
  - Understand the Process
- Control strategies are EXPECTED

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Foundational Pillars

Successful Tech Transfer

Facilities & Equip.

- Understand facilities and equipment
- Are they current?
- Do they meet the needs of the process and intended usage?

Manufacturing

- Process description
- Raw materials – grade and sources (options)
- Filtration pre-work on site & filterability issues
- Scale - flexible to match demand & DS supply
- Process flow diagram
- Sampling plan

Testing

- Compendia testing (e.g. pH, osmolality, sterility, etc.)
- Product specific testing (protein concentration)
- Sample plan and site of testing

Supply Chain

- DS to the site
- DP from the site
- Samples to and from site
- FDP to patients

Finding the Right Fit: CMO Selection

Partnership
- Responsibility
- Trust
- Flexibility
- Experience
- Communication
- Reputation

Quality
- Agency Compliance
- Strong Quality Systems
- Strong Adherence to SOPs
- Quality Culture

Capabilities
- Manufacturing Facility & Capabilities
- Process Expertise
- Analytical Capabilities
- Development Capabilities

Select a CMO that embodies the right Capabilities, Quality, and Partnership Characteristics, but remember that

NO ONE IS PERFECT!

Set your Priorities
Find the Balance
Assess the Risks

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Goals of Technology Transfer

A tech transfer that is well designed and executed should result in a process that is ready for its intended purpose .

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A tech transfer that is well designed and executed should result in a process that is ready for its intended purpose .

- Define Metrics
- Knowledge Transfer
- Continuous Improvement!
- Process Understanding
- Product Understanding
- Analytical Plan & Method Transfer
- Develop Knowledge Database
- Understand Materials & Excipients
- Expand Supply Network

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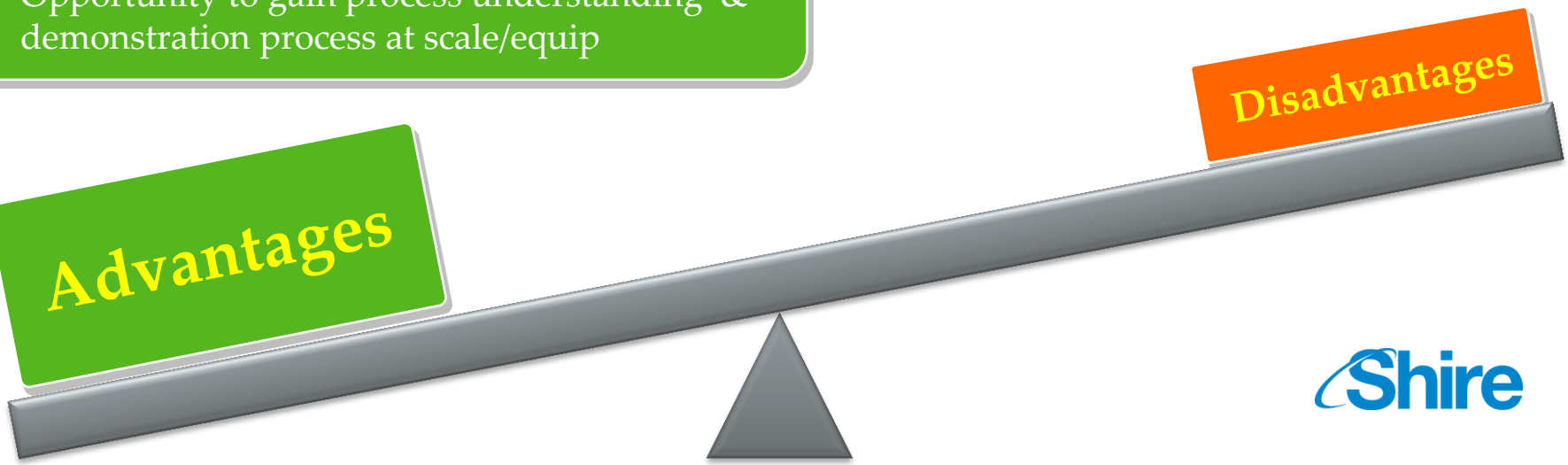
Value of Engineering Runs

- Mitigation strategy to "de-risk GMP production"
- Optimize generation of process understanding & baseline process data supportive of GMP
- Confirm scale
- Demonstrate impact to CQAs
- Demonstrate process & product comparability
- Generate stability data to support shelf life
- Confirm effectiveness of risk mitigation efforts
- Train operators & analysts
- Test batch documentation for improvements
- Perform cleaning verification
- Produce material for development studies
- Opportunity to gain process understanding & demonstration process at scale/equip

- Cost
- Time
- Material generated only for development purposes
- Perception of need



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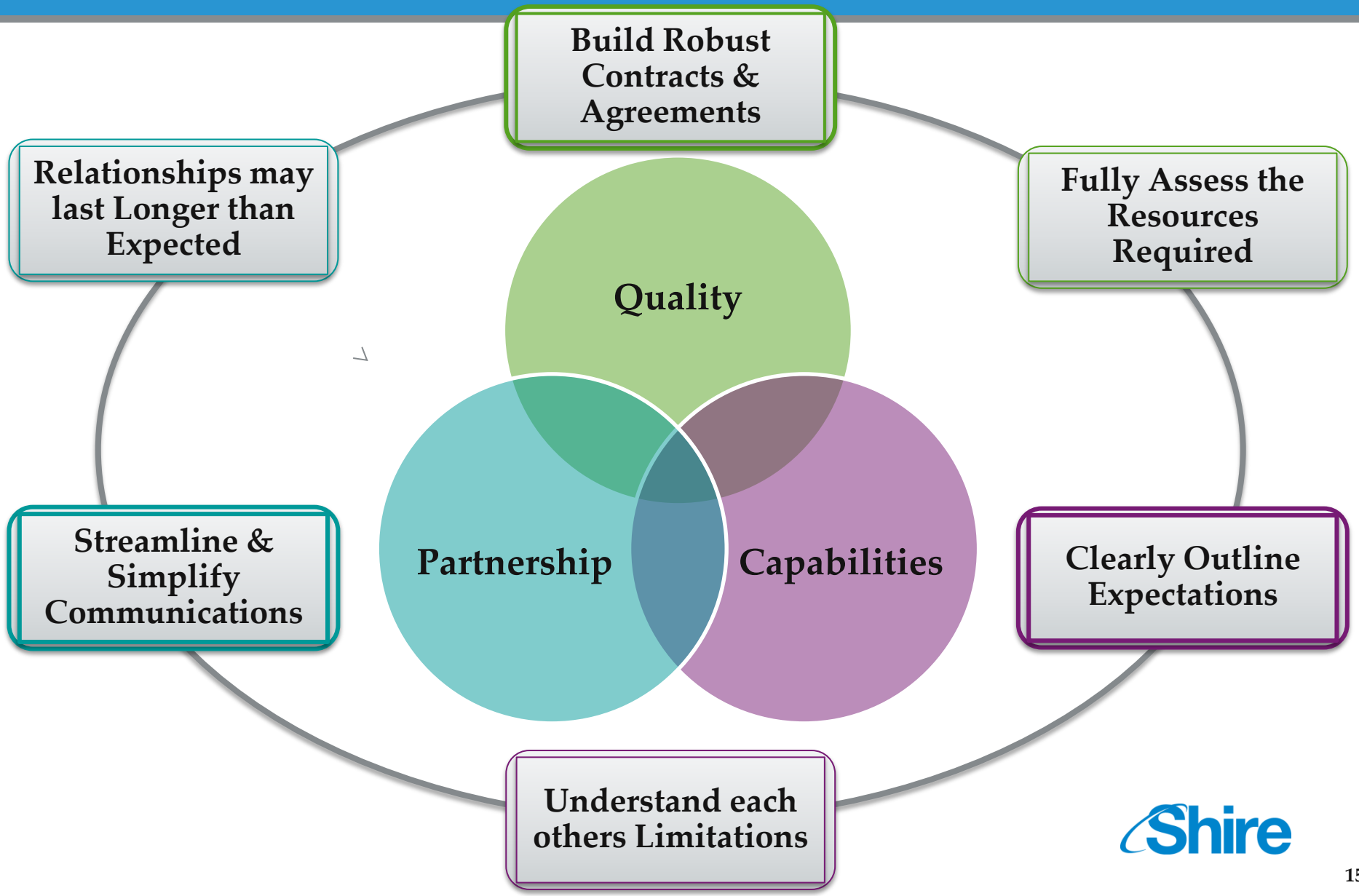
Making it Work, Building a Partnership



Field Ex. #1 - Filtration Schemes

- **Parenteral products require sterilization**
  - Terminal sterilization by heat – preferred by Health Authorities
  - Filtration – used for thermal labile products

- **Filtration different schemes**
  - Two sterilizing grade filters in series
  - A single sterilizing grade filter after a bioburden reduction filtration step.

- **Two key differences when transitioning from one scheme to another**
  - Sequence of filtration steps & testing for bioburden (risks)
  - Effect on product quality (product concentration)

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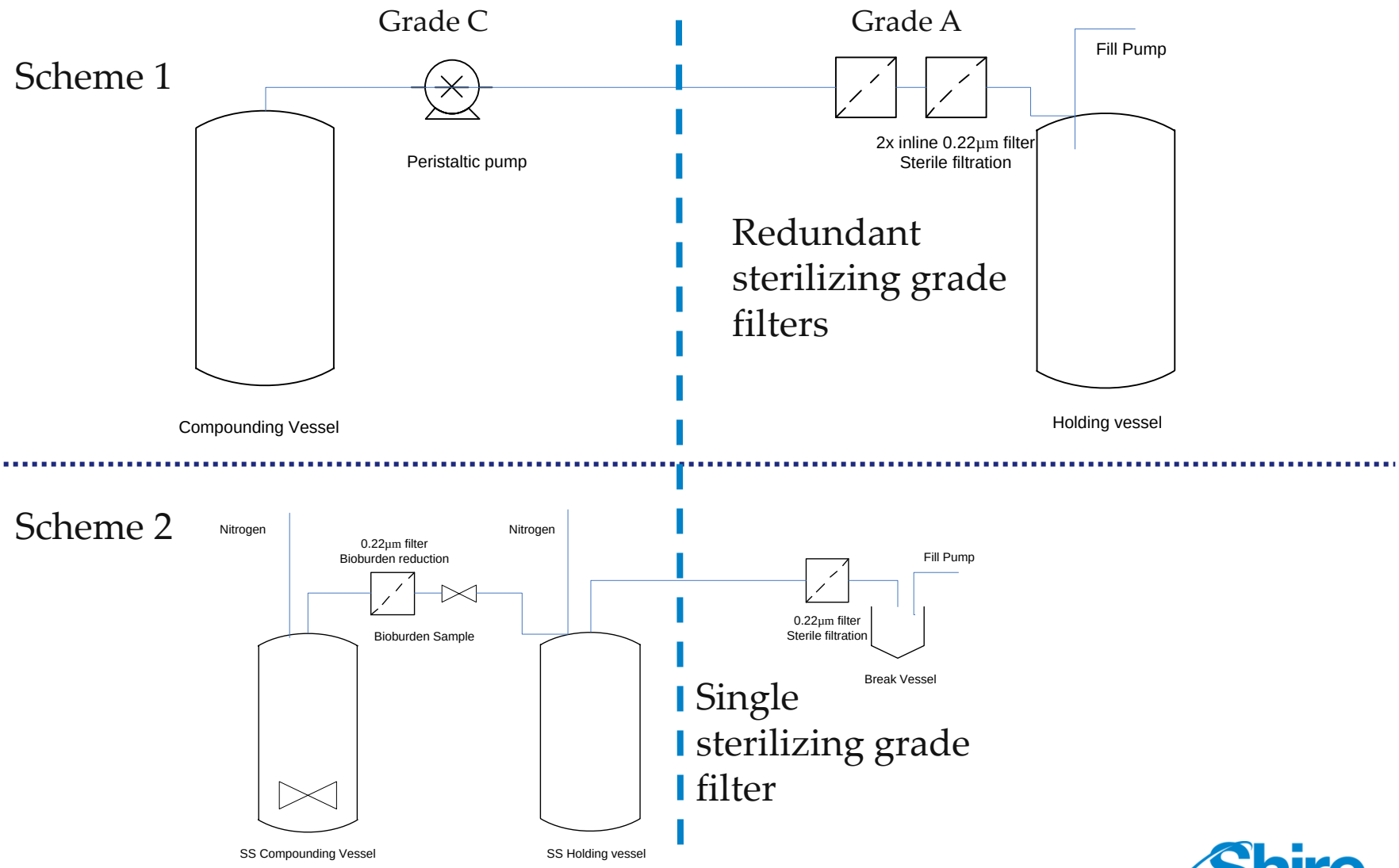
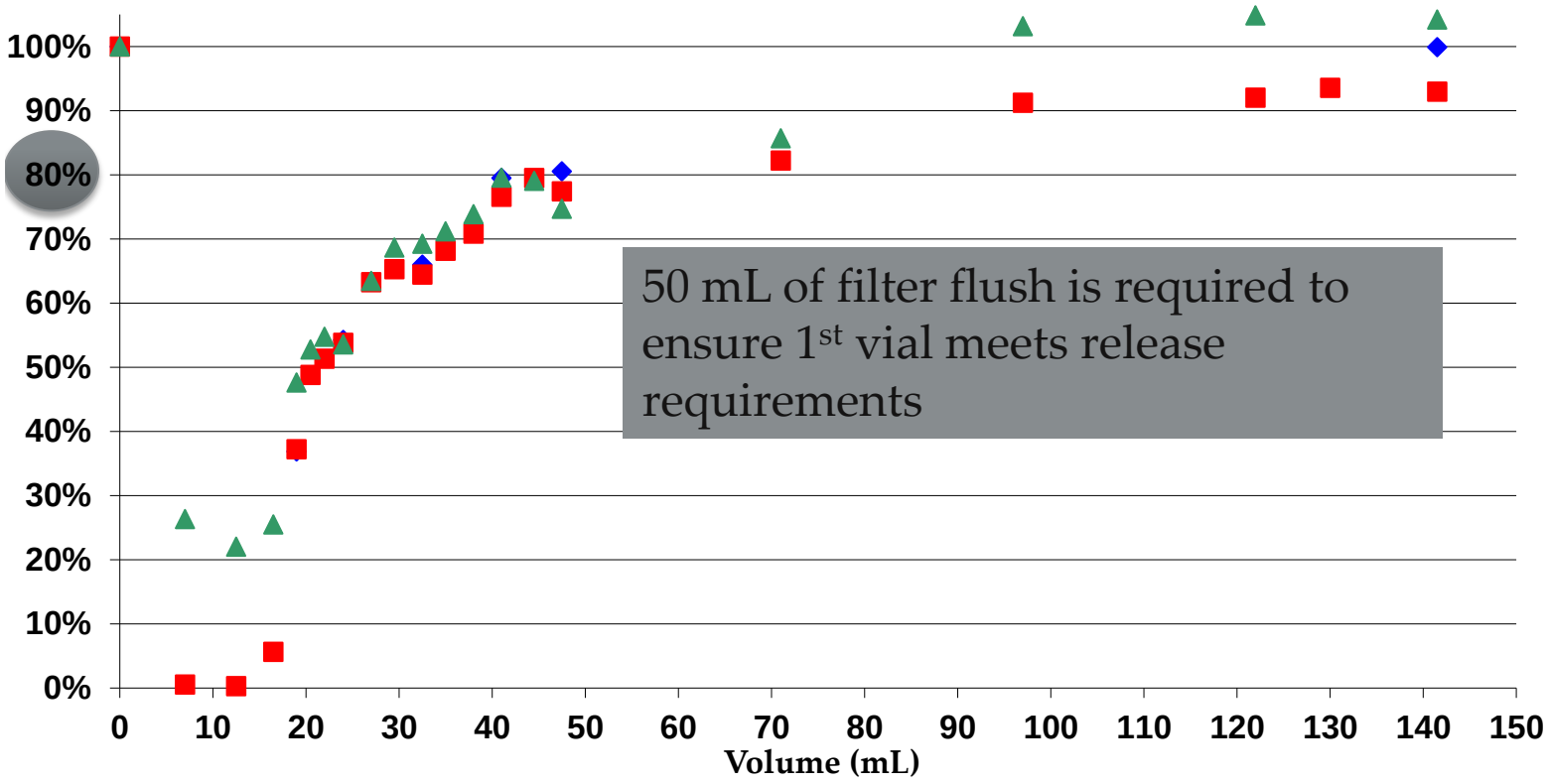
Thinking…

- **Understand the change**
  - Impact to process
  - Impact to product quality
- **Consider risks of changing from one scheme to another.**
  - Microbial control strategy
    - Connection to current best practices
  - Impact on sterility assurance approach
- **Collect necessary data and implement**

Comparison of Filtration Schemes



Effect of Filtration on Product Quality



Field Ex. #2 - The Lyophilizer Surprise

- Product requires lyophilization for required shelf life
- Development lab study confirmed transferable lyophilization process
- Engineering run was conducted to ensure production scale unit produced same product quality

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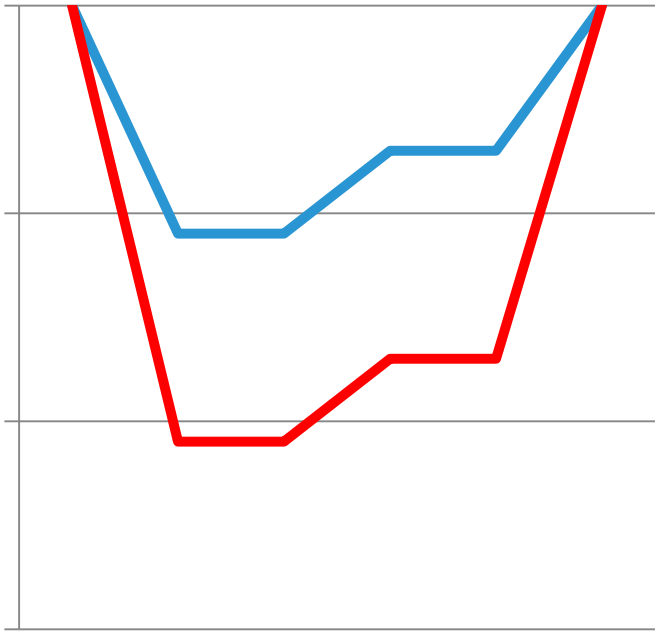
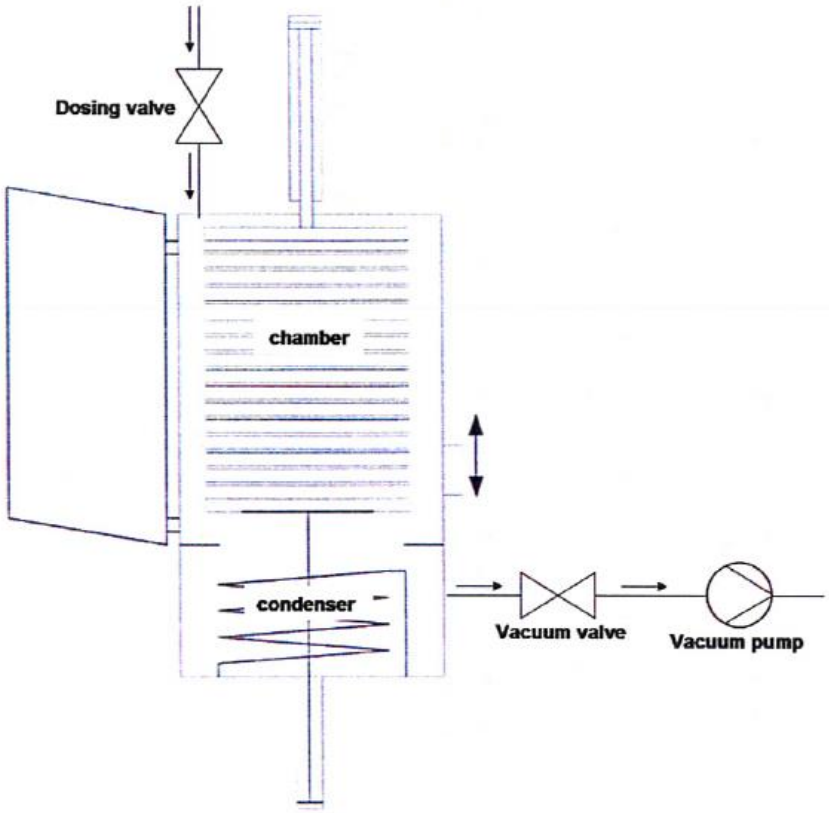
Engineering Run Results





When working with a lyophilizer always ask detailed questions about the control system.

What went wrong?

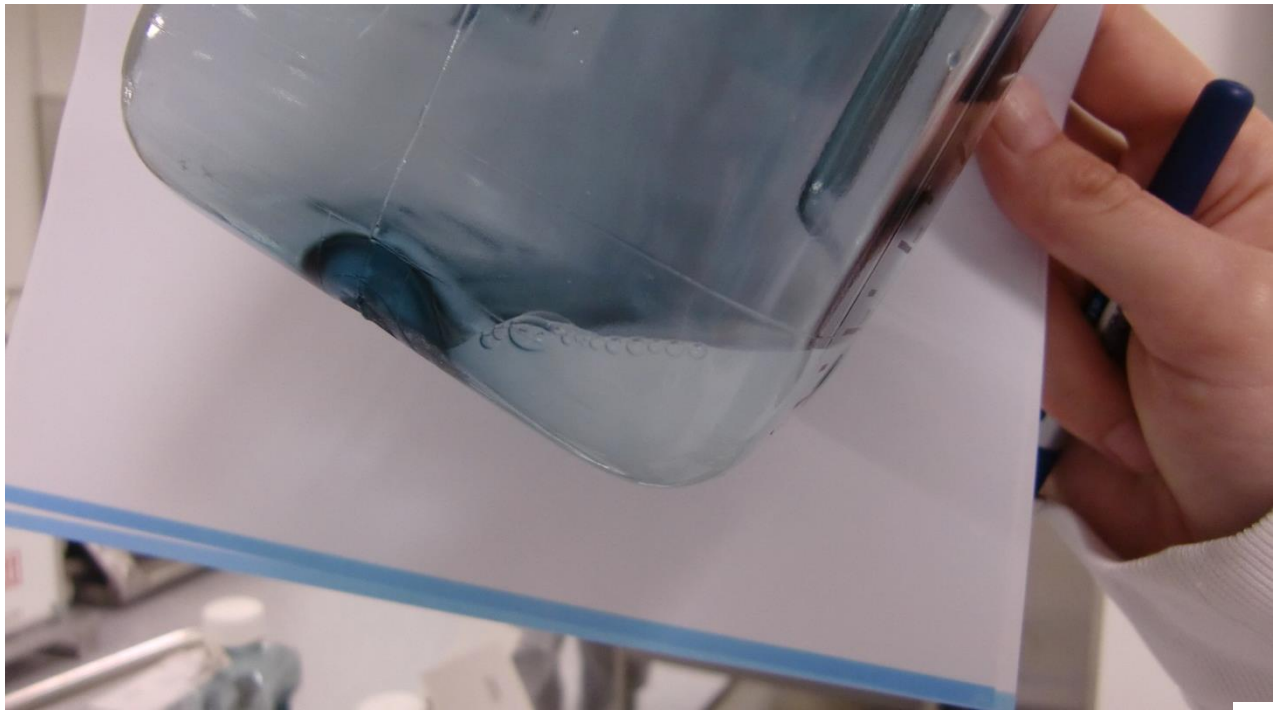
- Technical questions were not asked because assumptions about the equipment were not challenged/assessed.

- Risk assessment for change was not conducted.

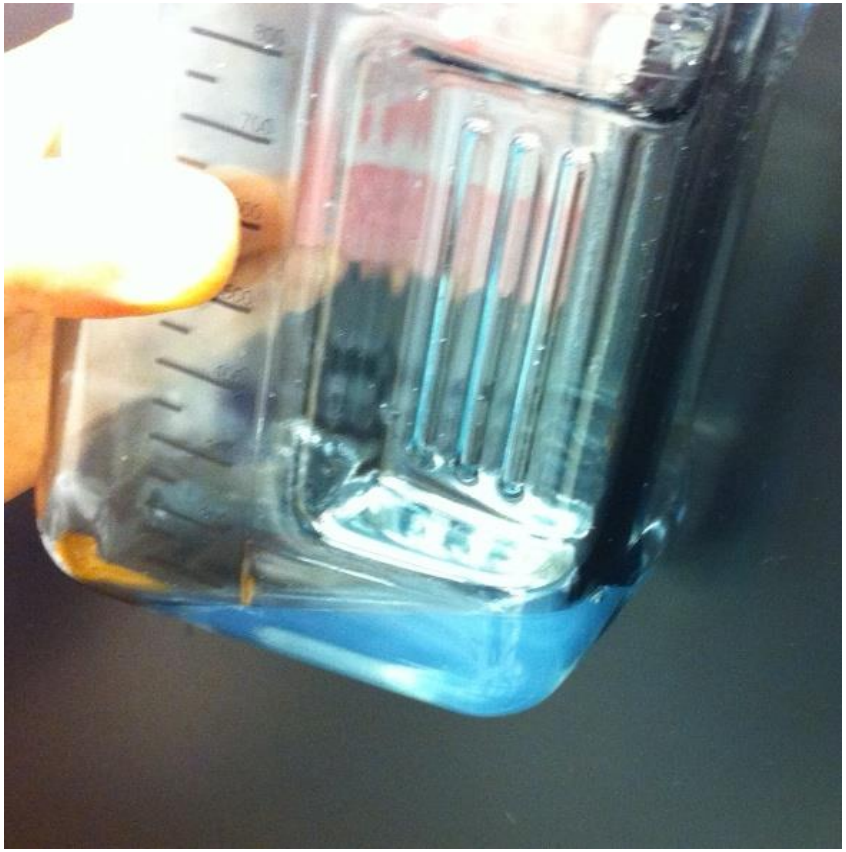
Perspective…

- **Filtration**
  - Proactive
  - Assessed risk
  - Identify ways to understand new process and new risks associated
  - Considered appropriate process controls
- **Lyophilization**
  - Reactive
  - Didn't assess risk
  - Didn't ask important questions to gain better process understanding.
  - Did not consider appropriate process controls

Field Ex. #3 – Particles in DS bottles!



Can we replicate the phenomena?



API After Thawing

API After Storage for 45 minutes

Yes we can replicate the phenomena!

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So What Happened?

- Particles were confirmed to be API
  - Additional intrinsic particles were identified
- Combination of factors contributed to this issue
  - formulation vulnerabilities
  - shipping conditions
- Risk assessment for entire process was not conducted.

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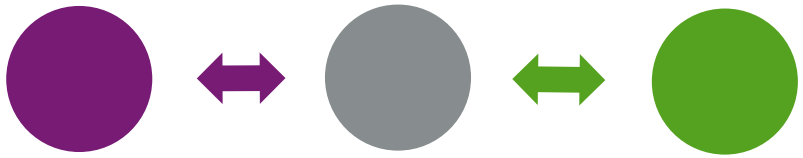
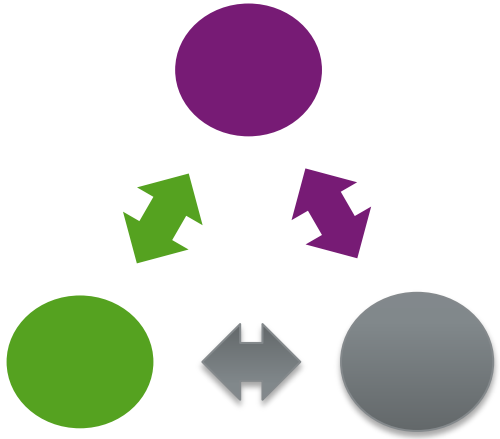
Field Ex. #4- Analytical Method Transfer

- Transfer of an Analytical Method from one site to another during late-phase Tech Transfer
- The receiving site unable to successfully complete System Suitability
  - New equipment
  - Tedious assay
  - New reagent



So What Happened?

- Not enough Technical information in the Transfer Documents
  - Sampling Handling
  - Reagent Storage
- Assay was able to be performed successfully after collaboration between companies



Importance of Strong Relationships

- Trouble-Shooting between companies, build the three-way relationship
- Together work through:
  - New Processes, Equipment, Products, etc
  - Tight Timelines (as always)
  - “Tribal Knowledge”
- Ensure correct legal documents are in place!

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Field Ex. 5-Limited Drug Substance

Manage Material Limitations!

- Strong Relationship with Partners
- Explore creative solutions:
  - Use of Surrogates
  - Small-Scale Studies
  - Reduction of Line Losses
- Leverage Prior Knowledge from Similar Programs

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Valuable References

- ISPE Baseline Pharmaceutical Engineering Guide, Volume 3 – Sterile Product Manufacturing Facilities, Second Edition (September 2011)
- ISPE Good Practice Guide, Technology Transfer (2014)
- PDA Technical Report #65, Technology Transfer (2014)
- ICH Q8 Pharmaceutical Development (November 2009)
- ICH Q9 Quality Risk Management (June 2006)
- ICH Q10 Pharmaceutical Quality Systems (April 2009)
- ICH Q11 Development and Manufacture of Drug Substances (November 2012)
- FDA Guidance for Industry, Process Validation: General Principles and Practices (January 2011)
- FDA Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing (2004)
- PDA Technical Report #60, Process Validation: A Lifecycle Approach (2013)
- USP-NF General Chapter <790> Visible Particulates in Injections
- USP-NF General Chapter <1790> Visual Inspection of Injectable Products

Circling Back…

- Beware of Perspective!
  - Clinical process sets stage for PPQ strategy and future commercial process
- Develop the product and process using the tenets of enhanced approaches in ICH

Befriend the "Knowledge Monster"

Face to Face Meetings

Supply Agreement

Quality Agreement

Team Encouragement

Risk Analysis

Intention

Vie to be Better than Yesterday

Risk Assessment

Celebrate Small Successes

Mindfulness

FDA

Regulatory Strategy

Project Monitoring "Visibility"

ISPE

Team Empowerment

Process Standardization

Document Sharing Site

Lessons Learned

Open Communication "Transparency"

Breath

ICH Guidelines

PDA

PLANNING

- Most Importantly -

Continuously reinforce project purpose and importance of each team members contribution to the overall project, the business, and impact to the Quality of the Patient's Life.

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Final Thoughts

- BREATH…
  - Inhale fully…
  - Pause…
  - Exhale fully…

Repeat as needed

- At the beginning…and throughout the project…
  - Whenever you feel the anxiety build…
    - » Before you know it, it'll be time to celebrate SUCCESS…as a TEAM!

Shire