Technology Transfer of Aseptic Processes in the Modern Age

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“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.”
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 -

- 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...

Focused on unit operations and process parameters

Modern Age Approach

Process and Analytical Control Strategy

Microbiological Control Strategy

Particle Control Strategy

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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
**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

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**Successful Tech Transfer**

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**Foundational Pillars**
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
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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- Define Metrics
- Knowledge Transfer
- Continuous Improvement!
- Process Understanding
- Product Understanding
- Analytical Plan & Method Transfer
- Develop Knowledge Database
- Understand Materials & Excipients
- Expand Supply Network
Value of Engineering Runs

**Advantages**

- 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

**Disadvantages**

- Cost
- Time
- Material generated only for development purposes
- Perception of need
Making it Work, Building a Partnership

- Build Robust Contracts & Agreements
- Fully Assess the Resources Required
- Relationships may last Longer than Expected
- Clearly Outline Expectations
- Understand each others Limitations
- Streamline & Simplify Communications
- Quality
  - Partnership
  - Capabilities
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)
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

Scheme 1

Grade C
- Peristaltic pump

Grade A
- 2x inline 0.22µm filter
- Sterile filtration

Redundant sterilizing grade filters

Scheme 2

Nitrogen

Grade C
- 0.22µm filter
- Bioburden reduction

Grade A
- 0.22µm filter
- Sterile filtration

Single sterilizing grade filter
Effect of Filtration on Product Quality

50 mL of filter flush is required to ensure 1\textsuperscript{st} vial meets release requirements
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
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!
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.**
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!
Field Ex. 5-Limited Drug Substance

Manufactured Drug Substance

DP Stability

In-Process Sampling

Clinical Supply

Analytical Method Qualification

Development Studies

Release Sampling

DS Stability
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
Valuable References

- 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)
- USP-NF General Chapter <790> Visible Particulates in Injections
- USP-NF General Chapter <1790> Visual Inspection of Injectable Products
• 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”
Vie to be Better than Yesterday

- 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.
Final Thoughts

• BREATHE…
  • 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!