An Industry Perspective on the Challenges of Modern Sterile Product Manufacturing and the Opportunities for Change

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Industry Current State

- Sterile manufacturing, without preservatives, has become wide spread
  - necessitating special capabilities for microbial control.
- Across the industry, performance varies widely.
  - opportunities for improvement abound.
- Regulations and GMPs are continually tightening.
- New therapeutic trends exacerbate existing challenges

Note on nomenclature: I will use "sterile manufacturing" to refer to the manufacture of sterile product. It does not necessarily mean that all environments and processing elements are sterile.

Regulations and GMPs are Continually Tightening

Process Simulations
- staff participation requirements
- interventions challenged
- number of runs
- action limits

Personnel Monitoring
- sample points
- frequency of sampling
- action limits

Environmental Monitoring
- sample points
- frequency of sampling
- action limits

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Manufacturing Processes: New Therapeutic Areas

Potential Challenges:

- cross-contamination risks (e.g. blood processing)
  - extensive ***single-use technology*** use
- many aseptic operations
  - expect ***closed processing*** to be widely implemented
- processing in non-traditional settings (e.g. hospitals)
  - will accelerate adoption of ***robotics***
  - expect ***isolators*** to be widely implemented
- very small scale operations
  - will challenge paradigms for demonstrating microbial control
    - process simulations, environmental monitoring, etc.

Successful Sterile Manufacturing

There is no secret…no magic bullet.

It requires a ***multifaceted program*** of controls and measures that are operated with high ***diligence*** and strong subject ***knowledge***.

Elements Include:

- Technology
- Microbiological Knowledge
- Process Knowledge
- Systems and Procedures

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The Role of Technology

Proven, ***available*** technologies dramatically reduce risk.

Technologies:

- filling isolators
- VHP transfer isolators
- single use technology (e.g. closed system operations)
- VHP room sanitization
- rapid micro analytics
- sterile connectors and welders

Benefits:

- reduce risk from open operations and humans
- reduce amount of Grade A/B space and associated EM and PM testing
- improved sanitization effectiveness environmental control

Introducing New Technology: Challenges

Industry is ***intensely*** interested in introducing new technology.

<u>But there are challenges….</u>

- can be difficult to retrofit
- lead time and change management work
  e.g. changes to Single Use Technology items
- lack of industry standards
- increased operational/reliability risk
- regulatory process

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Introducing New Technology: Industry Opportunities

- Industry standards with suppliers
  - components
  - equipment
- Industry standards
  - ISPE
  - PDA
  - etc.
- Joint Industry / regulatory road mapping

Introducing New Technology: Strategies

Company Opportunities:

- design into the process from the beginning
  - during initial product development & startup
- prospective regulatory consultation
- prioritize based on impact and implementation feasibility
  - e.g. upgrade RABs to true "closed door" set up and operation
- manage risk: use standard designs, dual sourcing
- pursue "functional equivalence" for Single Use Technology
  - per PDA Technical Report #66

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Technology: Example

Opportunity: upgrade RABs (Restricted Access Barriers) to true ***closed-door set-up and operation***

Line Set-Up:

1) map sequence of steps in detail
2) re-engineer to allow covering removals and connections with doors closed

Operations:

1) identify all interventions
2) re-engineer to eliminate or execute through glove port

Technology: Final Thoughts

Technology can be powerful but it is not the whole solution.

-> Modern technology that is operated badly …fails.

-> Older technology that is operated well …succeeds.

The Role of Microbiological Knowledge

The application of microbiological knowledge is both powerful and necessary.
Opportunity: better leverage microbiological science.

Applications:

- Process design
  - microbial control strategy
  - EM Risk Based design
- Investigations
  - root cause determination
  - CAPA design
- Risk Assessment and Mitigation
- Microbial Trend Analysis
  - as a leading performance indicator

Microbiological Knowledge: Use in Investigations

Contamination Identification

- micro ID testing

Informs about:
1) **potential sources**
- **water source**
- **human source**
- **environmental**

2) **trend history**

Investigational Testing

- special EM testing
- micro characterization testing
  - growth & viability studies
- genotyping

Informs about:
1) **source identification**
2) **root cause hypothesis testing**

Risk Assessment & CAPA Generation

microbiological aspects of root cause

Inform how to:
1) **eliminate source**
2) **eliminate route of entry**

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Microbiological Knowledge: Monitoring

Microbiological Trends are the best available gauges of control and leading indicators of performance.

Examples:

- personnel monitoring
- environmental monitoring
  - Including grade C/D space and micro-laboratories
- water systems
- material transfers

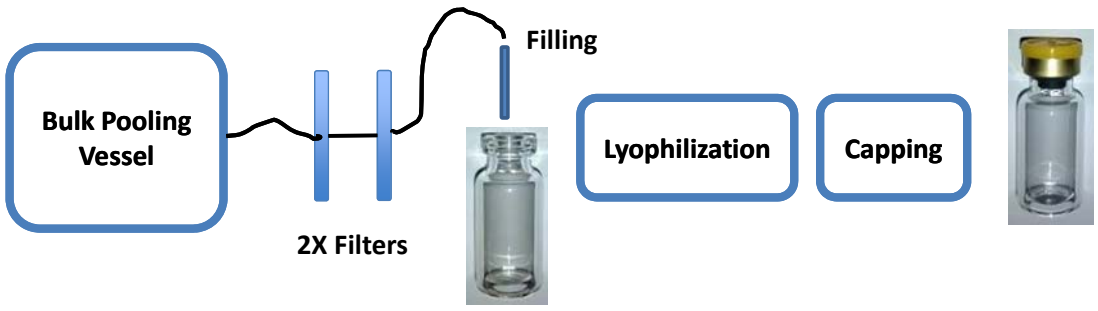
The Role of Process Knowledge

A deep understanding of the process and the technologies is necessary…. for everyone involved.

Examples:

- Where is the "sterile boundary"?
- How does VHP sanitization work and what are processing risks?
- What are potential routes and mechanisms of microbial ingress?

Process Knowledge: Sterile Boundary



Where is the sterile boundary? ***IT DEPENDS…***

Everyone involved must understand the ***designated*** sterile boundary.

A key design goal should be to minimize the size of the "sterile envelope"

Process Knowledge: VHP

Example: VHP Technology is complex. Execution problems can easily shut down operations:

- prevention and response to "rogue" VHP BI
- periodic requalification of aeration and affect of airflow
- impact of residual VHP on the product
- VHP adsorption and release from silicone tubing
- capabilities and limitations as a sanitizing / sterilizing process

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The Role of Procedures and Systems

Too big a topic to cover in detail…

but two key messages are important:

1) necessary to be paying attention at an organizational level
   - via formalized systems
2) it is necessary to react
   - response limits, trending, escalation, decision making

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Connection to Annex I

All of these concepts can be found in the revised Annex I

		Annex I Examples
Technology	→	RABs, Isolators, Closed Systems
Microbiological Knowledge	→	Personnel, Knowledge & Expertise
Process Knowledge	→	Quality Risk Management
Procedures and Systems	→	Contamination Control Strategy