New England Chapter

# Accelerating Process Scale-Up through Enhanced CCS and Vendor Management

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# Zeroing In

Process and Product Development,
Equipment procurement,
Facility, Facility Modifications,
Outsourcing → CMC

- Transition from pre-clinical to clinical
- Transition to late phase
- PPQ
- Commercial

# Optimal flow

- TPP/CQA
- Process/Analytical Platform
- Risk Assessment/Gap Assessment
- Control Strategy
- Monitor/Verify
- Process Knowledge

**Iterate!**

# Types of Risk – simplified

## PROBLEM

- Business
- Risk to Patient
- Compliance
- Process
- Facility-Specific
- EHS


**Should be APRIORI (to start)**

## TYPICAL ISSUES

- No Integrated Vision
- Silos
- Implicit not Explicit
- Personality Driven
- Not First-Principles Based
- Done Too Late – Typically late phase or after facility design, etc.

# Risk Assessment (RA)/Gap Assessment (GA) Approach

- Standardized
- Data and Process Driven – Not Personality Driven
- Documented
- Live or Discrete but Cycled (must fit the iterative model)
- Nested and Connected

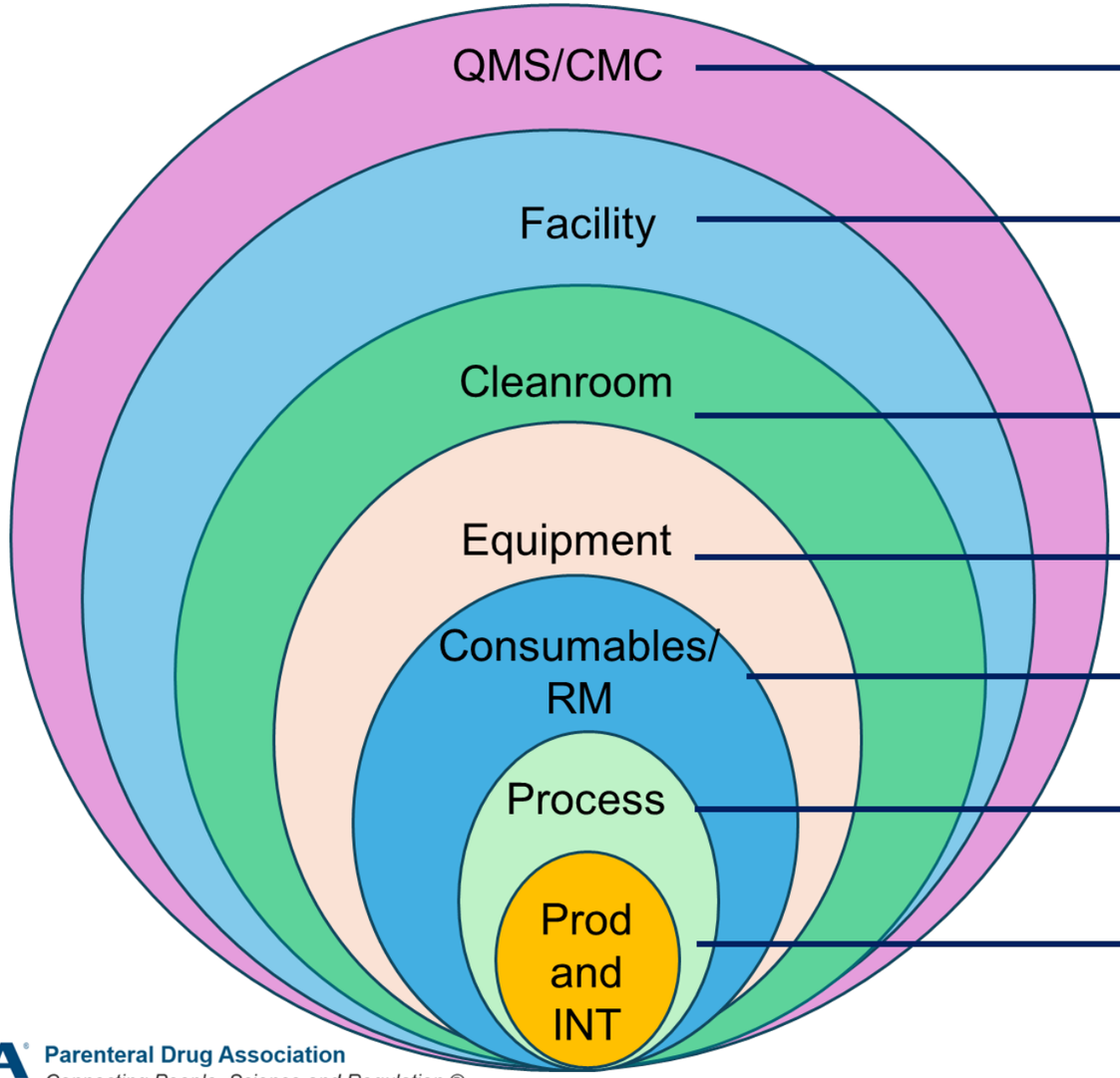
**Note: Not and excuse for non-compliance—directs controls to achieve compliance necessary for a specific set of risks**

# Goal (Measure of Success)

## Improved Schedule, Cost, and Quality


- RA / GA Identifies (or you have the wrong tool or approach)
- What must be controlled
- To what extent it must be controlled
- How is it measured
- What is not sufficiently controlled

# CONTROL ONION Modules




QMS Module: CAPA, Trending, RCA, Deviation, Change control, Risk Management, Continuous Improvement

Facility Module: Interactions outside of direct process housing, flows, mulit-product operation, Utilities, Sustainability,

Cleanroom Module: Appropriate Grade for contained operations, Interface Mgmt (transactional risk)

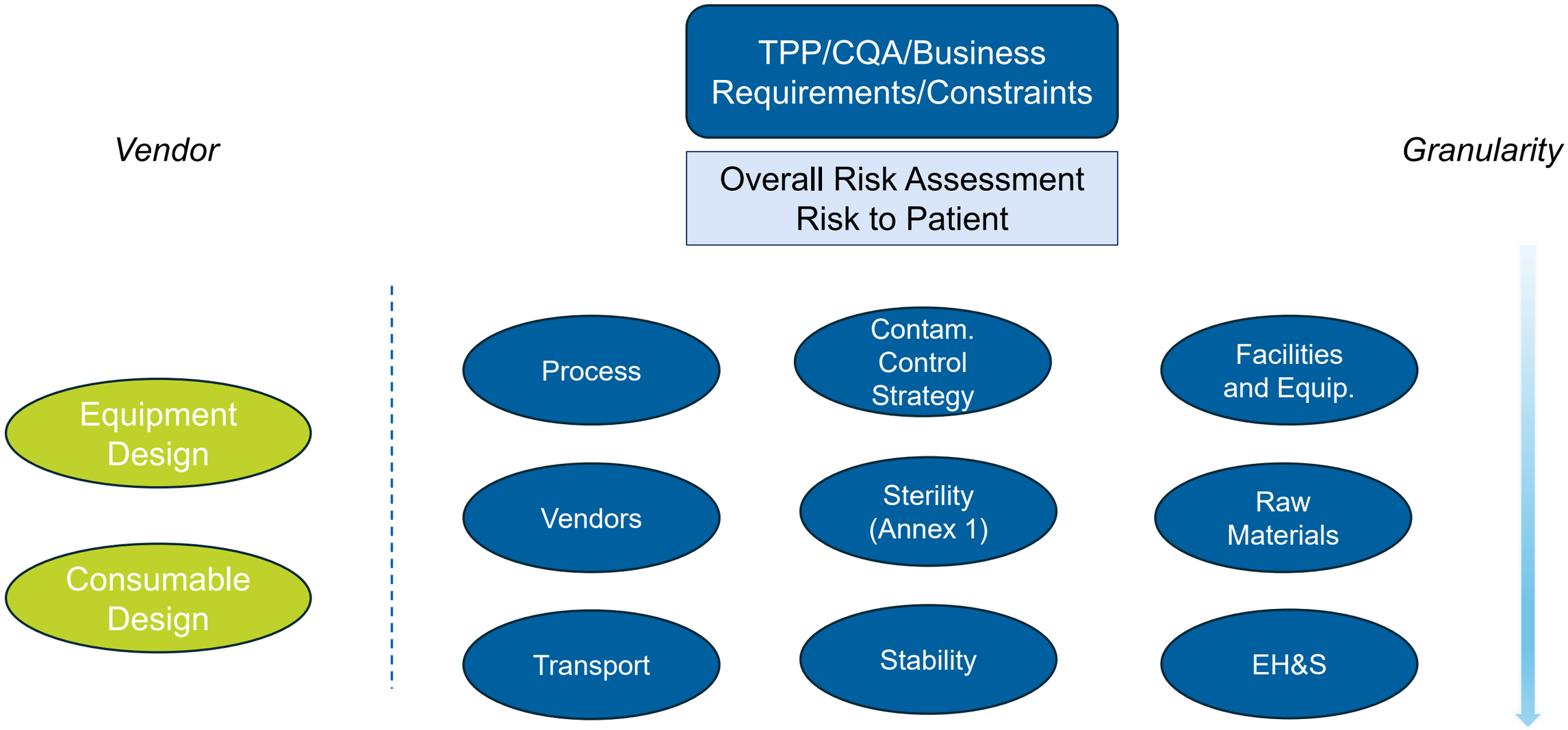
Standardized Modules: Std Packaged Equipment

Raw materials, Supply Assurance
Product dedicated contact surfaces

Process Module: Dynamics Process knowledge
CPP

Product and Intermediate: TPP/CQA, Stability

# Nested Risk Assessment Hierarchy



# BioPhorum Example: (Pre-Publication April ’25)

## HACCP of mAb manufacturing clarification step

**Node:** Clarification **Suite #:** CC-1304 **Room classification:** Grade D

**Design conditions/parameters:** Axenic cell culture is transferred to a harvest vessel that feeds a disk-stack centrifuge for initial clarification. The supernatant is further clarified by depth filtration, then sterile filtered into the clarified harvest vessel, which will serve as the chromatography feed vessel. The clarified broth is considered cell free for subsequent purification.

**Closure methodology:** Clarification is a controlled condition operation. The harvest vessel is SIP'd, the centrifuge is CIP'd, and the depth filters are conditioned with high volumes of sterile buffer. The sterile filtered depth filtrate is collected in a vessel that was previously SIP'd.

**Crossover prevention strategy:** The process is BSL1. The process is protected from the environment. The process pathway is integrated through to the clarified harvest vessel.

| Hazard scenarios | Critical limits | Causes | Detection methods | Safeguards | Consequences | RISK BEFORE REDUCTION | | | | | CCPs | | | | | Recommendations for risk mitigation | RISK AFTER MITIGATION | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | S | L | RI | D | RPN | Q1 | Q2 | Q3 | Critical to quality? | Controlled or uncontrolled? | Attention required? | | S | L | RI | D | RPN |
| 1. contaminated clarified harvest | | 1.1 contaminated production cell culture | offline bioburden testing | *summary item(s), see below:* | A. harm to patient | 4 | 1 | M | 2 | M | Y | N | N | Yes | Uncontrolled | Yes | *Risk mitigation recommendation required* | 4 | | | 2 | |
| | | 1.2 open operations | | | B. loss of batch | 3 | 2 | M | 2 | M | | | | | | | | | | | | |
| | | 1.3 breach of closed system integrity | | | C. loss of product yield | 2 | 1 | L | 2 | L | | | | | | | | | | | | |
| | | | | | D. high bioburden in feed to chrom | 3 | 2 | M | 2 | M | | | | | | | | | | | | |
| 1.1 contaminated production cell culture | Axenic | | | | A. contaminated clarified harvest | 3 | 1 | L | 2 | M | Y | Y | N | Yes | Controlled | No | 1. ALARP | 3 | 1 | L | 2 | M |
| 1.2 open operations | | contaminated depth filter | | depth filter is flushed post assembly | A. contaminated clarified harvest | 3 | 2 | M | 2 | M | Y | N | N | Yes | Uncontrolled | Yes | *Risk mitigation recommendation required* | 3 | | | 2 | |
| | | contaminated centrifuge | | centrifuge is CIP'd prior to use | | | | | | | | | | | | | | | | | | |
| | | | | sterile filtration of centrate/depth filtrate | | | | | | | | | | | | | | | | | | |
| 1.3 breach of closed system integrity~~contaminated clarified harvest~~ | 1 CFU/mL | 1.3.1 contaminated harvest vessel | offline bioburden testing | depth filter is flushed post assembly | ~~1~~A. harm to patient | 4 | 1 | M | 2 | M | Y | N | N | Yes | Uncontrolled | Yes | 2. re-evaluate the need for a surge vessel between the centrifuge and depth filter as it adds to the duration of the controlled condition process, resulting in the potential risk of the product | 4 | 1 | M | 2 | M |
| | | 1.3.2. contaminated centrifuge | | centrifuge is CIP'd prior to use | ~~2~~B. loss of batch | 3 | 2 | M | 2 | M | | | | | | | | | | | | |
| | | 1.3.3. contaminated surge vessel | | sterile filtration of centrate/depth filtrate | ~~3~~C. high bioburden in feed to protein-A | 3 | 2 | M | 2 | M | | | | | | | | | | | | |
| | | 1.3.4. contaminated depth filter | | duration of operation limited | | | | | | | | | | | | | | | | | | |
| | | 1.3.5. contaminated buffer feeds | | SIP of harvest vessel | | | | | | | | | | | | | | | | | | |
| | | 1.3.6. sterile filter failure | | FIT of sterile filter | | | | | | | | | | | | | | | | | | |
| | | 1.3.7. contaminated suite | | | | | | | | | | | | | | | | | | | | |
| 1.3.1 contaminated harvest vessel | Sterile | | | | A. contaminated clarified harvest | 3 | 1 | L | 2 | M | Y | Y | N | Yes | Controlled | No | 1. ALARP | 3 | 1 | L | 2 | M |
| 1.3.2 contaminated centrifuge | 1 CFU/mL | | | | A. contaminated clarified harvest | 3 | 2 | M | 2 | M | Y | N | N | Yes | Uncontrolled | Yes | *Risk mitigation recommendation required* | 3 | | | 2 | |

# Focusing on Closed Single Use Manufacturing

- Modern Approach to Risk Control
- Closed Processing
- Standardized, Packaged Equipment
- SU Components
- Automation
- Process Intensification
- Digital Twins
- Simplified Facilities with Reduced Use of High-Grade Space (A,B,C)

# Vendor Management - Ordering

URS - User Requirement Specification

Audience:

- Done after purchase or before?
- Junior Engineer Copying the vendor SPEC sheet?

URS -> Convert to a set of pre-set quality specifications with a single engineering-driven sizing specification (no QA required)

For example:

- QA + Matrix approved: DI, Automation, Environmental, etc.
- ENG approved: Size requirements (which size XDUO, etc.)

Vendor will then be required to do trace matrix

Leverage Vendor to the maximum

# Vendor Management - Consumables

Consumable vendors—Creating the most important control—Closed systems


Survey Audience

- How many are running closed processes?
- How Many have SU suppliers rated as critical vendor?
- How were they audited?

  - QA only
  - Technical Audit
  - Identified critical aspects that feed into your risk-based requirements?
  - Have you challenged their ability to reproducibly create the components and integrated flow paths

# Example Issue

Closed System Connectors
Approximately 100 are used per 2k mAb upstream

Hmmm…..
Math happening…..
I really want to target <0.1% failure rate (instant contamination)

So…..
1 per 1000 BUT we are using 100 so that means 1 per 100000!!!!!
99.999%. 5 NINES!
How sure are you that the vendor CS meets 5 nines?

**Now how do we feel about our Vendor Management Programs?**

# Vendor Management - Equipment

Standard Packaged Equipment Vendor MUST be made to provide design RA USERS did not make design choices and are not SME's

The old model of procurement and validation is outdated, inefficient and counter-productive

- WHY is the user performing equipment design qualification or IOQ for that matter?
- WHY should there be any difference between users if equipment properly ordered?
- WHY is equipment not supplied pre-validated?

# Optimal flow

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# Thank you!

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# Thomas C. Page, PhD

- Dr. Thomas Page brings over 35 years of Life Sciences experience, having worked at clinical development and CDMO companies in roles supporting cmc, operations, engineering, process development, and business development.

- His expertise spans a range of products, including blood-based therapies, vaccines, recombinant proteins, monoclonal antibodies (mAbs), and advanced therapy medicinal products.

- Over the course of his career, Dr. Page has led the design, construction, validation, and operation of assets valued at over $1 billion in both the public and private sectors.

- He holds numerous patents and publications and is passionate about advancing faster, better, and more cost-effective responses to pandemics and emerging health threats. Additionally, he is committed to supporting the next generation of biotechnologists and developing biotechnology hubs.