Annex 1 in Practice:

Based on an interview with Jim Polarine, Principal Consultant, STERIS

The revised EU GMP Annex 1 has rapidly become one of the most influential regulatory updates in sterile medicinal product manufacturing. Its impact is global, its expectations far reaching, and its interpretation still evolving. In a recent episode of the Pharma Conversations podcast, we sat down with Jim Polarine, Principal Consultant at STERIS one of the industry's most respected voices on contamination control, to explore how organisations are navigating Annex 1 in real world environments.

Several themes repeatedly emerged: the criticality of a robust contamination control strategy (CCS), the growing maturity gap between regions, the importance of a robust risk assessment, and the operational challenges that continue to surface in cGMP (current Good Manufacturing Practices) drug and device manufacturing facilities. What follows is a comprehensive analysis of the key takeaways from Jim's insights offering a practical, experience driven perspective on Annex 1 implementation today.

CCS Is No Longer a Document – It's a Mindset

Contamination control strategy is the backbone of Annex 1. It is not a checklist, not a binder on a shelf, and not a regulatory afterthought. It is a holistic, cross functional framework that must integrate every aspect of sterile manufacturing.

Organisations that excel in CCS share several traits:

- Cross departmental ownership
- Continuous improvement culture
- Data driven decision making

A CCS must be a living system that is reviewed, challenged, and refined regularly. The organisations that treat CCS as a culture rather than a compliance exercise are the ones seeing the strongest outcomes.

A Growing Global Maturity Gap

One of the most interesting insights from Jim's perspective is the regional disparity in Annex 1 readiness.

European cGMP manufacturing sites particularly in Ireland and Belgium are described as early adopters of EU Annex 1 with strong CCS maturity. Many have already embedded risk based thinking into their operations.

In contrast, United States (U.S.) facilities face a steeper learning curve. Annex 1 introduces concepts not historically emphasised in Food and Drug Administration (FDA) centric environments, including:

- Integrated risk-based decision making and frequent utilisation of risk assessments
- Expanded environmental monitoring expectations
- Enhanced gowning requirements
- Deeper CCS integration

This difference is not about capability; it's about mindset shift. Annex 1 requires organisations to move from a compliance driven approach to one that is proactive, science based, and risk oriented.

Risk Assessment: The Heart of Annex 1

If CCS is the backbone, risk assessment is the heartbeat.

Annex 1 expects risk assessment to be embedded in:

- Process design
- Environmental monitoring
- Cleaning and disinfection
- Material transfer
- Validation strategies

Large multinational companies tend to excel here, using structured methodologies to identify worst case scenarios and optimise validation scope. Smaller organisations, however, often struggle with either over-testing due to fear of non compliance or under testing due to lack of expertise.

Jim's advice is clear: invest in training. Risk assessment is not just a regulatory expectation; it is a tool for smarter, more efficient operations.

Residue Management: The Silent Contamination Risk

Residue management has become a major focus under the revised Annex 1.

Although residues on non-product contact surfaces are not considered a major risk, a residue management strategy is an important part of Annex 1. Residues can:

- Contribute to particulate contamination
- Interfere with biodecontamination
- Jim highlighted the need for:
- Routine rinsing with WFI or 70% IPA
- Documented residue management strategies

This is an area where many organisations are still adapting and where regulators are increasingly focused.

Personnel: The Largest Source of Contamination

Operators remain the number one contamination risk.

Annex 1 reflects this reality with heightened expectations for:

- Gowning
- Behaviour



- Movement
- Training
- Qualification

A key change is the requirement for sterile gowning in Grade B areas supporting isolators or Restricted Access Barrier Systems (RABS), a departure from previous norms which included scrubs or non-sterile gowning.

Jim shared examples of how minor behavioural lapses can escalate contamination risk, reinforcing that training is not optional; it is foundational.

Material Transfer: The Hidden Weak Link
Material transfer is responsible for a significant proportion of contamination events, yet it is often inadequately designed.

Jim highlighted recurring issues:

- Carts and trolleys moving between uncontrolled and controlled areas
- Inadequate cleaning protocols
- Poorly defined transfer pathways
- Inconsistent disinfection practices

Annex 1 expects organisations to treat material transfer with the same rigor as aseptic processing and many are only now recognising the extent of this gap.

Legacy Facilities:
When Infrastructure Becomes the Risk
Ageing facilities face structural and mechanical challenges that can undermine even the strongest CCS, including:

- Degraded surfaces
- Compromised seals
- Outdated HVAC systems
- Water ingress
- Mold outbreaks

These issues are real, recurring, and costly.

Annex 1 forces organisations to confront a difficult question: Is continued operation viable without significant investment?

For resource constrained companies, Jim recommends prioritising these areas:

- Critical infrastructure repairs
- Enhanced maintenance
- Targeted risk assessments
- Interim mitigation strategies

Environmental Monitoring:
A More Proactive Era
Annex 1 expands expectations for environmental monitoring (EM), particularly in Grades C and D.

Jim emphasised two major shifts:

1. **Trend analysis over point data**
   Organisations must identify potential bioburden patterns early before they reach Grade A/B cleanrooms. This includes more identification of bioburden in the Grade C and Grade D cleanrooms.

2. **Increased focus on lower grade areas**
   Contamination rarely originates in Grade A areas; it migrates from elsewhere.

Jim also pointed to rapid microbiological methods (RMMs). While adoption is still limited, regulatory acceptance is growing, and technology is advancing quickly.

Isolators, RABS, and the Complexity of Modern Containment
Advanced containment technologies reduce operator intervention but they introduce new challenges.

The most misunderstood requirement: cleaning before Vaporised Hydrogen Peroxide (VHP) bio decontamination.

This raises questions about:

- Compatible cleaning agents
- Residue management
- Equipment integrity
- Cycle development

Emerging technologies like UV disinfection offer promise but come with limitations such as shadowing. UV is best viewed as a complementary tool, not a replacement for common biodecontamination methods such as Vaporised Hydrogen Peroxide (VHP).

Process Mapping:
The Foundation of a Strong CCS
Organisations cannot build an effective CCS without deep process understanding.

Process mapping enables teams to:

- Identify contamination risks
- Define critical control points
- Align controls with real world operations
- Eliminate blind spots

This is especially important in complex manufacturing environments where interactions between steps can create hidden risks.

Practical Prioritisation for Resource Limited Organisations
Not every organisation has the budget of a multinational. Jim offered pragmatic guidance for smaller companies:

Start with the highest impact areas:

1. Personnel training
2. Gowning
3. Material transfer
4. Environmental monitoring
5. Infrastructure repairs

These foundational elements deliver the greatest risk reduction for the time and resources invested.

The Future of Annex 1:
Continuous Evolution
Annex 1 is a positive force that elevates standards and drives better science. But it is not static. Updates and clarifications will continue, and industry groups like Parenteral Drug Association (PDA) will play a critical role in shaping interpretation and sharing best practices.

Annex 1's future will be shaped by:

- Technological innovation
- Regulatory evolution
- Industry collaboration
- Continuous learning

Conclusion
Jim Polarine's insights reveal an industry in transition that is moving from compliance driven behaviours to science based, risk oriented, and holistic contamination control. Annex 1 is challenging, but it is also transformative. Organisations that embrace its principles are not just meeting regulatory expectations; they are building stronger, safer, and more robust cGMP drug and device manufacturing operations.



Jim Polarine

Jim Polarine is a Principal Consultant, Technical Services at STERIS Corporation, widely recognised as one of the leading global experts in contamination control, cleaning and disinfection, disinfectant validation, and microbial excursions in sterile manufacturing.