Featured Article

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The Question of Quality: Implementing Quality by Design Principles

A QUESTION OF QUALITY

Implementing quality by design principles

Jason Rossi from AST discusses how a systematic approach, "Quality by Design", is used to design and develop of drug product manufacturing environment that prioritises product quality and QRM principles

AST's ATO (Automatic Tub Opener)

In the world of pharmaceutical development, the journey of the drug product to commercialisation is largely defined by a single word: quality.

A key point that's clear in the revised Annex 1 is the expectation that the entirety of the sterile product manufacturing process be based and consistently revised upon sound principles of Quality Risk Management (QRM) to minimise contamination risks and ultimately ensure the quality of the drug product.

Annex 1 formalised expectations that had long been held throughout the industry and by other regulatory presences: that the design and execution of manufacturing operations and facilities should be designed around the scope of the product, and not the product around the facility.

Regulatorily strong, sustainable drug manufacturing now requires a deep understanding of the overall drug product, quality attributes, and the processing measures necessary to achieve consistent, high-quality production throughout the product lifecycle.

Quality: What is it, and why is it important?

Throughout my career, I've seen the gradual progress towards product-centred design firsthand. The pharmaceutical industry has seen profound advancements in treatment modalities, including the emergence of patient-centred medicine through high-yield, highly targeted products.

No longer tenable—and, in many cases, no longer compliant—is a facilities-first approach that attempts to constrain product needs to the limitations and capabilities inherent in whatever equipment and premises may be available.

Best practices now dictate a proactive, product-first approach in the strategy, design, and implementation of a drug manufacturing operation.

Here, the concept of quality comes

> **Quality by Design is a systematic approach to design and development that prioritises product quality and QRM principles**

into focus; the more clearly and concisely product quality is defined and all the risks that could adversely affect that quality are understood, the more effectively the processes, equipment, and facilities can be designed to support the realisation of a product.

So, what exactly are we talking about when we discuss quality? Simply put, Quality is how appropriate and effective a drug is for its intended use and definitionally includes attributes like purity and strength (ICH Q8). Once identified, a process and strategy can be developed that supports and controls the product's critical quality attributes (CQA) and critical process parameters (CPP), and considers the full scope of the operation and all its potential variables related to quality and repeatability of production.

The end goal is to ensure that sterile products are effective, safe, and available to patients.

Since quality is the priority, it's necessary to understand how to assess these variables in relation to potential harm to the product and the associated risks. How do we correctly identify risks and evaluate them in a proportional manner? And how do we resolve risk, either preemptively or mitigate it during development and production? The answer is robust, science-based QRM principles.

The two tenets of QRM are that risk evaluation and decision-making should be based on scientific justification and that the level of effort and protocol of any risk-informed process should be proportional to the risk itself. As Annex 1 highlights, QRM principles should be applied to every aspect of an operation that results in the final product, including facilities, equipment, processes, and personnel. How, practically speaking, are these principles applied to an operation? By implementing Quality by Design (QbD) solutions.

Quality by Design is a systematic approach to design and development that prioritises product quality and QRM principles in clearly defined processes and objectives based on the specifications of the product. A proactive and preemptive approach, Quality by Design is how QRM principles are brought to bear on the operation as a whole, and on related quality management initiatives like Contamination Control Strategies.

Fundamentally, QbD is based on ongoing scientific feedback and is a key vehicle for pursuing continuous improvement throughout the product lifecycle. An active, effective QbD strategy equips stakeholders with solutions based on the product quality needs and practical avenues for designing out risk throughout the product life cycle, accelerating major milestones in drug development and commercialisation.

Annex 1 and recent regulatory findings

The discussion on QbD is particularly relevant in light of the revised Annex 1 and recent findings over the past 18 months. There have been persistent themes around both the implementation and interpretation of CCS and QRM principles observed by regulators. Some key findings include:

- Risk analyses were too generic
- The scientific basis for both RA and CCS wasn't sound
- In some cases, QRM was used to justify bad practice
- CCS wasn't expansive enough, unidentified risks were present
- CCS was static/with no programme in place for feedback or updates
- QRM process was predetermined or not active

It's important to note that while it's easy enough to view these findings strictly from the viewpoint of compliance, the broader context is the clear progress that the industry has made in these areas. Higher standards and new regulatory concepts are downstream of the refined processes, collective knowledge, and innovations that make those standards attainable.

Our industry is at a place in time where we can address and resolve risk at an incredibly high level and where it's possible to enact a holistic strategy that addresses all variables of contamination.

One observation that's apparent, and an approach I would strongly advocate for based on my time in the field, is a strategy for applying active feedback and continuous updates to all relevant protocols and processes of an operation; if a CCS is expected to be an active, living programme, the parameters that inform it (QRM) and solutions that make it a reality (QbD) should be actively and continuously improved and revised. A set cadence with designated resources for assessing risk and the robustness of an operation's CCS is a must and should be enacted across relevant stakeholder groups, including operations, materials science, tech transfer, etc. Having specialists available to assess microbial and cross-contamination risks and who understand the role of mitigation and QbD strategies is crucial to regulatory compliance and the long-term viability of a project.

Practical considerations for applying QbD

When setting the scope for the design of a project, then, what are some practical applications of QbD principles? Starting with product requirements and associated risks to quality, teams should be analysing the necessary risks that need to be mitigated (material transfer, cleanroom personnel, planned and unplanned interventions, airflow movement, etc.) and risks that can be designed out of an operation completely (various human interventions, sterility processing for containers, reusable product-contacting parts, etc.) and assessing those solutions based on their approximation to effort, resources and documentation needed for that QRM-based process.

One of my earliest experiences in leading a QbD facility construction project was for a multiproduct facility in Europe in 2013, where our team completed a comprehensive risk assessment and analysis before building commenced.

Every mode of risk, from contamination to the handling of materials to personnel and environmental risks, was designed for. And one of the first issues to resolve when planning a multiproduct facility is not only the mitigation of microbial contamination, but also cross-contamination. Do the products require separate pathways in and out of the facility, or with the right control measures, can they utilise the same airlock?

When our team analysed the question, we considered the scope of having two separate product pathways and the similarity of products (a significant factor), and determined that, with the

proper controls and protocols, the risk from utilising a shared airlock could be successfully mitigated and was a more viable option. This is the type of science-based balance between risk and resources that a comprehensive QbD approach encourages.

The beauty of these principles is that they apply to every aspect of the facility and cleanroom environment. Are your floors suitable for operation? Are they cleanable and able to bear heavy equipment? Are there wall guards in place to protect from damage and subsequent microbial havens that a dent can create? Do your doors open automatically, or do they require bodily contact from cleanroom personnel to open? Will you need utilities and equipment for the sterilisation of containers, or will you utilise pre-sterilised RTU containers? What's the allocation and layout of graded space, and what do solutions like isolators mean for those considerations? A QbD framework provides clarity on every question applicable to a product's environment and production.

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When we arrive at the drug manufacturing process, the benefits of advanced technologies become clear, as does the rationale behind the increased regulatory focus on these solutions. The question in every fill-finish setting is how to best protect the product while eliminating major sources of contamination altogether.

This is where, in the past 10–15 years, innovation has taken centre stage with the rise of advanced automation, barrier technologies, decontamination methods, and robotics. The use of robotics alone not only eliminates the majority of operator interventions but also eliminates operator variability, which has long been a major risk factor in aseptic operations. Critical zone operations can now be carried out automatically in meticulously controlled Grade A environments, the full potential of which the industry will explore well into the future.

As regulators continue to advocate for both a science-based approach to risk and quality, as well as advanced technological solutions, our ability to eliminate risk through sound QRM principles will continue to expand. The key in drug manufacturing settings remains a commitment to science-backed protocols and processes, and an active pursuit of continuous improvement throughout the life of the product

For more information

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AST's GENiSYS® R FCM (Fill-Close Module)