

Quality Control

Kate Westwell and Gina Wenham at Eden Biodesign explain how implementing the quality cycle can deliver product value

Quality control is too often perceived simply as the last phase in the many stages of product manufacture; a box ticking exercise to check that what has been made meets the required specification. However, quality control should be considered as a key driver for increasing product value. In a multi-product biopharmaceutical facility that manufactures products using a wide range of technology platforms, efficient, effective and appropriate quality control is fundamental to business success.

Effective quality control begins well before a product or project even enters the manufacturing facility; ensuring the quality of the manufacturing environment, utilities and cleaning are key to determining project success or failure.

The main aim of many quality groups has often been to develop the necessary systems to obtain a license for a facility or product, or to pass a customer or regulatory audit, the goal being for the business to establish the fundamental quality requirements to achieve compliance, whilst maintaining patient safety. More recently, the focus has been shifting towards producing robust systems that are 'quality-focused' and 'fit for purpose' at any level.

QUALITY BY DESIGN

The concept of quality by design (QbD) is not new. It was best explained by Juran as a means of efficient quality control that has been applied to a wide range of goods and services (1). In fact, quality by design was introduced to pharmaceuticals in the International Conference on Harmonization (ICH) Q8 guideline, approved in May 2006, which provides guidance for pharmaceutical process development worldwide (2).



The introduction of the QbD initiative in the US has highlighted the importance of quality control to pharmaceutical and biotechnology companies Stateside (3). Identified as a 'key component' of the US FDA's Pharmaceutical cGMP Initiative for the 21st Century, QbD identifies three factors, or principles, within its make-up:

- Quality of a product should be built by design and cannot be tested into products
- It is not so much about arriving at the finished process parameters, but how you get there and how you demonstrate the robustness of the process

- Tools for QbD include 'design of experiment' (DoE), miniaturisation, process and analytical technology (PAT) and robust quality systems to establish design space and control strategies

As such, a QbD system is based on two interconnecting processes. Firstly, 'process and product design', which is used to:

- Define the desired product performance requirements by identifying the critical quality attributes (CQA)
- Design product and manufacturing processes to meet the CQA

The second process is based on 'development, risk assessment and risk control' which is used to:

- Understand the impact of material and process parameters on the CQA
- Identify and control any variability in materials and processes
- Continually monitor and update processes to assure consistent quality

In its initiative, the FDA has challenged the pharmaceutical industry to achieve a level of process understanding consistent with controlling process variability and assuring product quality in 'real-time', while a batch is being manufactured. Ideally, the appropriate level of quality must be assured by the process in real-time, despite variations in materials and processing. In the past, such variations would have resulted in unacceptable product batches that were prevented from entering the market only by laboratory testing of the finished product. In other words, the ability to achieve the appropriate quality outcome must be 'designed-in' to the process itself, rather than relying on final product testing.

This increased emphasis on QbD requires manufacturers to make larger investments much earlier in the product lifecycle during process development, well in advance of approved commercial operations. The goal is to develop a sound scientific base that accommodates a range of defined variability that may occur in commercial process materials and operations, and still produces the right product quality outcomes.

THE EUROPEAN QUALITY CYCLE

The same philosophies and practices as those being advocated by the US FDA are being implemented throughout Europe, although formally this may be less apparent. The system widely used within Europe is termed 'the quality cycle approach'.

In order to work efficiently, quality control systems and processes must be integrated and, of course, quality-driven. In addition, they should operate appropriately to support the business in its key role to create valuable biopharmaceutical medicines for

maintaining and improving public health. It is also essential to continuously assess and drive improvement to ensure quality standards are met and that changing business objectives are delivered.

These goals can be achieved by applying and continually reviewing the three key factors in the quality cycle:

- Strategy driven by robust quality control systems – quality driven and business efficient. This determines the requirements to consistently provide product that meets customer and applicable regulatory requirements
- Supported through management and leadership – delivered through effective communication and disciplined governance, including continual review and improvement of systems and processes
- Implementation against well-defined and agreed plans that address and consider the critical quality aspects of the product

By comparing the US FDA and European systems, one can identify the common goals being considered:

- Desired product performance
- Product design
- Process design
- Process performance

In essence, this means 'beginning with the end in mind' in order to achieve efficient, effective systems with the required level of quality to keep up with an ever changing and increasingly challenging market (4); a 'desired state' of biopharmaceutical manufacturing where:

- Product quality and performance are ensured through the design of effective and efficient manufacturing processes
- Product and process specifications are based on a mechanistic understanding of how formulation and process factors affect product performance
- Quality assurance is continuous and real-time

- Relevant regulatory policies and procedures are tailored to accommodate the most current level of scientific knowledge

- Risk-based regulatory approaches recognise both the level of scientific understanding and the capability of process control related to product quality and performance

The resultant 'desired state' of biopharmaceutical manufacturing is one which provides processes that consistently produce products of acceptable predetermined quality.

With the recent introduction of the ICH Q9 Quality Risk Management, it is likely that the systems used in the US and across Europe will become much more aligned. Risk assessment is becoming the way forward for most decisions within the biopharmaceutical industry. In addition to the assessment of any risks to patients, assessment of the risks to products, processes, facility and personnel by any actions taken is being used to optimise both the quality system requirements and the required level of inbuilt quality.

DESIGNING AN EFFECTIVE MANUFACTURING PROCESS

By careful consideration of all aspects of quality control it is possible to achieve a streamlined system which, from the outside, appears to require little input and little management, whilst always delivering on time, on budget and to the required level of quality.

In order to achieve this and set up both cost- and use-effective QC laboratories, all aspects of materials, sampling, testing and reporting must be carefully scrutinised to highlight impact and crossover with other disciplines. For multi-product facilities, systems must be put in place that are flexible to allow adaptation to all different sample types, whilst being sufficiently fixed to enable full control. This is achieved by a QbD philosophy, although not necessarily following the formal QbD system.

If you adopt QbD together with a quality system as described in the draft International Conference on Harmonization (ICH) Q10 document on 'Pharmaceutical

Quality Systems', you will be closer to achieving the 'desired state' of pharmaceutical manufacturing (5).

The aim of pharmaceutical development is to design a manufacturing process to consistently deliver a quality product. Each manufacturing cycle begins with inputs that are transformed by a process into a more desired state or into the product. In each process, excessive variations and errors can cause nonconformities, with undesirable consequences. The goal of quality control in every production system is to: eliminate nonconformities and their consequences; eliminate rework and wasted resources; and achieve these goals at the lowest possible cost.

IMPACT OF ROUTINE ACTIVITIES ON QUALITY CONTROL

The implication for laboratory testing is that we must know the analytical quality required for each of the tests we perform, select measurement procedures with the precision and accuracy necessary to satisfy that requirement, and implement QC procedures that will reject runs when the analytical errors exceed the quality requirement.

The quality system needed for one test may be different from that needed for another. QC procedures must be based on the quality required for individual tests and the performance achieved by individual test methods. Therefore we must develop a QC planning process that provides the appropriate QC system for each test, as well as for each sample type. Why subject a sample from upstream processing to the same rigorous quality requirements employed for downstream samples? The answer to this question is very much dependent on the product, and the secret to good business quality control is to perform appropriate testing.

One could take the blanket approach of treating all samples the same. But beware, this then means that in order to achieve the required level of quality for the most quality-sensitive samples, the same rigorous (and often expensive) levels of quality must be achieved for the much less quality-sensitive samples.

For multi-product biopharmaceutical manufacturing facilities, where potentially

every process and product is different, quality control requires a two-tier approach. The first tier is the fixed basic quality control structure, with defined procedures and practices, where method of working, interaction and overlap with other disciplines is fully defined. This is the 'how do we do it?' part of the question, with the aim of ensuring that it is done in the same way every time. The second tier is where the same core procedures, which are specific and fixed for the 'knowns', are set up in a more flexible, but still fully controlled format, for use with the 'unknowns'.



To illustrate this with examples, consider the different quality control requirements for a utilities 'water for injections' sample and that of a Phase I product in manufacture for the first time. For the utilities sample, all handling, storage and testing requirements will be very much prescribed. Indeed, the test method necessary for the testing and the product specification are stated and published in US and European Pharmacopoeias (5,6). Test records and sample log sheets, for example, can all be standardised and issued as fully specific, itemised documents.

Now, consider the Phase I product in manufacture for the first time. There may be no real specification, test methods may still be in development and certainly will not be validated. It will, therefore, be very difficult to have detailed test records, test procedures, specifications and so forth. However, by employing the first tier of the QC system to control operational aspects

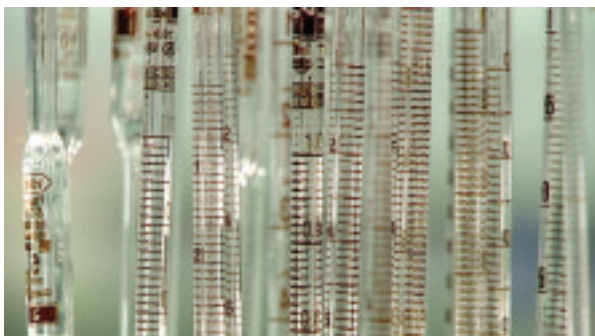
of the sample handling and testing, for example, using generic test records and laboratory notebooks, the second tier of control can be achieved whilst incorporating the flexibility needed.

CASE STUDY

A new fusion protein produced by transient transfection of a mammalian cell line is used in a vaccine product for a novel therapy and shows significant efficacy in early clinical trials. However, during the stability study of the master virus seed stock, productivity is shown to

decrease rapidly due to loss of infectivity of the virus. The plaque assay performed to measure the viral infection is repeated several times and the results support the loss of infectious titre. Due to the nature of the production method, instability of the virus is not detectable in the finished product. The questions that must be addressed are: should the company invest in further costly clinical trials in the hope that the instability shown does not affect the quality of the final vaccine? Should the company embark upon a formulation development programme to stabilise the virus? Or, should the product be shelved? Each route has significant cost implications: from the costs incurred to bring the product to this point, or risking further investment to continue product development or supporting the clinical trials for a product whose continued supply cannot be assured.

Now consider the true impact of the results of the QC testing: the laboratory



carrying out the testing is fully compliant, with well-designed, well-managed systems, where reagents, equipment, consumables, training, laboratory controls and testing and reporting methods are all within a quality system. The result obtained can therefore be accepted as a true and valid result. The consequences of the result are that a stability problem has been identified at the early clinical trial stage and, although it will be costly whether or not the product is taken forward, the damage to the business both commercially and financially is limited.

The laboratory carrying out the testing does not have well-designed or well-managed systems. Aspects of the systems operate outside the quality system resulting in a breach of compliance. This could be as simple as the temperature monitoring of incubators not being in place or expiry dating of reagents not being controlled. The result, which indicates that the product is unstable, could in fact be questionable, due to a change in storage temperature of the media or media being used from a central stock which is not bioburden tested at the time of use. In this case, the result is uncertain and even upon repeat review of

the data the error, for example contamination of media or the instability of a reagent used for the analysis, would not necessarily be identified. The consequences of the results in this case are that the company either loses the product or invests heavily to

overcome the perceived instability issue. Either way, the outcome is costly to the company and, potentially, the loss of an effective treatment for patients.

CONCLUSION

Through a strategy of considered planning of QC systems and procedures, we can accomplish a defined level of quality in daily operation and assure that manufactured products satisfy both patient and customer requirements. We can achieve this by good quality management, employing operable, flexible, but fully controlled systems, regardless of whether government regulations require it. Control procedures that are planned in this way actually build quality into the testing process, in contrast to many current control practices where control rules are often set in an arbitrary way or in response to regulatory requirements, with little or no consideration of their true impact on quality. Implementation of the formulated systems to give both good service and business value is achieved by constant review and improvement of these systems.

Use of this Quality Cycle, much like the implementation of the FDA's QbD, ensures

that not only do we design-in enough quality where needed, but that quality throughout the manufacturing, testing and release process is at the desired level, the desired level being such that there is no risk to the patient, regulators and customers are satisfied, and indirect business costs are minimised. Keep things simple and low cost if possible, only incorporating the higher, more expensive levels of quality where necessary. By using this model, fewer batches will be lost, fail or require investigation, and less documentation will require correction and numerous reviews. The knock-on effect of this is that manufacture to release timelines are shortened, and fewer resources are required which means faster turnaround and bigger profit for the manufacturer with no compromise to patient care.

In many ways, good quality control can become a victim of its own success. Where good QC is achieved, the concept of it being merely a box ticking exercise to check that what has been made meets the required specification can be understood. With effective, well-managed systems, the progression of products through quality control should be an almost effortless process. This, however, will only be the case where the thinking and hard work has been done upfront, and review and improvement of the systems are perpetual activities.

By designing quality into quality control, we achieve the assurance that manufactured products meet the required levels of quality and guarantee patient safety whilst maintaining good product value.

About the authors

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