QA/QC

Quality Assurance (QA) is a wide concept and covers all aspects that could have an impact on the quality of prescribed pharmaceutical products. Anastasia Petropoulu, Radiopharmacy Technician / Clinical Scientist, University Hospital Bristol NHS Foundation Trust, focuses on some of the Pharmaceutical Quality Systems in relation to QA of manufactured medicines.

In terms of QA / QC, specifications and method / process capability are two sides of the same coin, writes Dave P Elder, JPAG Member and Dave P Elder Consultancy.
Quality Assurance / Pharmaceutical Quality Systems in manufacturing medicinal products

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Quality Assurance (QA) is a wide concept and covers all aspects that could have an impact on the quality of prescribed pharmaceutical products. The objectives of QA are: to ensure that the prescribed medicine competently provides the desired effect to the person taking it; to protect patients from accidentally being administered an incorrect or contaminated medication; and to ensure medicines comply with the regulation.

Pharmaceutical Quality Systems (PQS) consist of eight pillars, which are designed to provide high quality finished pharmaceutical products, with QA and PQS working together in synergy (Figure 1). Pharmaceutical companies strive to provide high quality products to enable them to enhance their reputation, maximise profit and to provide high quality drugs to humans and animals. To meet these targets, they rely on well-designed PQS, which involve the coordination of quality through processes, with the aim of producing finished products of the highest quality.1

It is worth noting that the European Medicines Agency (EMA) defines PQS as: “The degree of excellence processed by an item” and “Meeting the requirements of specific customers’ needs”.6

The general model of controlling quality involves standards. Those include: checking the value or degree of the set standards, checking the product for conformity and feeding this back into the initial system and checking stages.2 The control of quality is an essential process and should be applied at all manufacturing stages; starting with the design, through to assembly of raw materials, in-process, post process and finally the finished products including stability testing. This explains why Quality Control is often described as being the most appropriate Total Quality Control (TQC) concept (Table 1).6,7

This article will focus on some of the Pharmaceutical Quality Systems in relation to QA of manufactured medicines. As mentioned previously, the eight pillars of PQS constitute a good foundation for discussion (Figure 1).7

The application of a process performance and product quality monitoring system throughout the product lifecycle is shown in Table 1. This illustrates the most effective monitoring system that provides assurance of the continued capability of processes and controls to produce a product of desired quality and to identify areas for continual improvement, according to PQS Q10.5

Nevertheless, it is not possible to mention high quality finished pharmaceuticals without mentioning Good Manufacturing Practice (GMP) and Validation.1 It is well known that all manufacturing stages need quality assurance actions to ensure successful results; but how can they be achieved, and which is the most important action during all the manufacturing stages?

The answers can be found by applying GMP in each step of the manufacturing process.3 GMP is part of Quality Management that ensures products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorisation or product specification.3

BIOGRAPHY

ANASTASIA PETROPOULU
AMRSC obtained a certificate in Health and Science followed by a BSc Hons degree in Pharmaceutical Science at the University of the West of England. She has gained experience in Quality Assurance / Quality Systems (QA / QS) by completing work in both pharmacy and the food industry. Anastasia has worked in Greece in the food industry as a Quality Assurance technician and in the UK pharmaceutical industry at Norbrook Laboratories Ltd in Northern Ireland and gained experience in testing raw materials as a Quality Control Analyst. She has also worked at NHSBT Bristol and the University Hospital Bristol NHS Foundation Trust, where she assisted in the production of parenteral nutrition and cytotoxic medicines. She currently works in Radiopharmacy as a Radiopharmacy Technician / Clinical Scientist where she applies PQS in the manufacturing process of radiopharmaceuticals.

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Furthermore, it ensures the manufactured products meet the end-user’s needs in terms of safety, quality and efficacy. GMP involves monitoring of processes, equipment, personnel and the environment in pharmaceutical companies. GMP is essential in all cases from initial drug trials to commercial launch. To obtain the best product, a manufacturer needs a system in place to ensure regular formulation, processing and composition. Without regulation of a manufacturing process, the consequences cause confusion that might escape notice in the first instance but at some later point will invalidate the safety of the product. This means someone will get harmed or it will cost the manufacturer money. However, the importance of patient safety is what drives companies to improve quality and prevent unnecessary expenditure on manufacturing. GMP applies to all types of pharmaceuticals. For example, a ‘standard product’ is one in which the unit operation and risk assessment of the end product suggests simple equipment ambient conditions; however, this doesn’t mean that the system can be abused. GMP should be applied, and the product manufactured, according to highly-regimented and regulated procedures. On the other hand, sterile medicines require different processes and equipment. These types of manufacturing processes often include biotechnology derivatives; where the consistency and potency of bio-preparation, that needs validation and constant monitoring, is often highly variable but may also be associated with issues such as purity. Sterile manufacture tends to be more vigorous in terms of equipment and specialised clean rooms. These specialised conditions and the nature of the drug itself often require additional staff training and a stronger reliance on the Qualified Person (QP) to sign-off. Figure 2 shows how Quality by Design embraces an integrated science and risk-based approach with continuous improvement for the entire product lifecycle. Process validation is needed to underpin confidence in the compatibility and coherence of each individual stage in a process of manufacture of pharmaceuticals. This represents the biggest part of the validation process in pharmaceutical products. However, cleaning and analytical validation are equally as important in manufacturing validation as in-process, or on-process, control. The aim is to ensure end-product suitability by fragmenting the process into modules with an appropriate consideration of risk and non-compliance to established standards. As such, the essential considerations of any validation of manufacturing should include:

- The importance of following and establishing an environment of GMP
- The site / building / equipment limitations

**TABLE 1** Application of Process Performance and Product Quality Monitoring System throughout the Product Lifecycle

<table>
<thead>
<tr>
<th>Pharmaceutical Development</th>
<th>Technology Transfer</th>
<th>Commercial Manufacturing</th>
<th>Product Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process and product knowledge generated and process and product monitoring conducted throughout development can be used to establish a control strategy for manufacturing.</td>
<td>Monitoring during scale-up activities can provide a preliminary indication of process performance and the successful integration into manufacturing. Knowledge obtained during transfer and scale-up activities can be useful in further developing the control strategy.</td>
<td>A well-defined system for process performance and product quality monitoring should be applied to assure performance within the state of control and to identify improvement areas.</td>
<td>Once manufacturing ceases, monitoring such as stability testing should continue to completion of the studies. Appropriate action on marketed product should continue to be executed according to regional regulations.</td>
</tr>
</tbody>
</table>
The complexity of routine production, processes, equipment, personnel and aspects associated with packaging / storage / handling of the product.

Additional aspects of higher-end quality in a manufacturing validation include: the probability for consistency of manufacturing and the consequences of inconsistency. Another parameter in the validation process is the use of a pilot trial to identify the point of ‘weakness’ in a particular stage of a manufacturing process where particular attention is required. Pharmaceutical companies should have a system for implementing corrective and preventive actions arising from the investigation of complaints, product rejections, non-conformances, recalls, deviations, audits, regulatory inspections and findings, trends from process performance and product quality monitoring. A structured approach to the investigation process should be used, with the objective of determining the root cause.

A Quality Risk Management system (Figure 3) involves monitoring and assessing the system’s or procedure’s effectiveness. This mainly involves investigating deviations that have occurred during any step of the manufacturing process, or identifying other factors such as damaged or faulty raw materials, devices or equipment.

The root cause analysis is identified and documented and finally an evaluation is undertaken to confirm quality objectives were achieved and the quality of the product was not affected. In other words, this system was built to ensure the quality of products by solving various issues or identifying risks and preventing the same happening again.

Risk management principles are used in many areas of business, including pharmaceuticals. The manufacturing and use of medicinal products, including its components, involves some degree of risk, whereas the risk to its quality is just one part of the overall risk. A robust quality risk management programme can ensure the high quality of pharmaceuticals by providing a proactive means of identifying and controlling potential quality issues during development and manufacturing. Effective quality risk management can provide regulators with greater assurance of a company’s ability to deal with possible risks and can positively affect the level of direct regulatory oversight.

Efficient quality management results from the correct interfacing of quality control, quality assurance and quality improvement initiatives. It is achieved through acting on feedback from the people involved in the product supply chain. A quality cycle is a group of experts who meet with the aim of improving the quality of manufacturing processes, the environment, health and safety etc. Effective communication between the investors in the group can result in an improvement over and above those routine improvements.

Summary

In pharmaceutical manufacturing, QA is the parameter used to ensure prescribed medicine effectively produces the desired effect on the person taking it. The POS, part of QA system, was designed to help manufacturers achieve the target for high quality finished pharmaceutical products; leading to the required level of drug regulations and providing efficacy and safety for patients. The parameters for approaching these targets include:

- The pharmaceutical product is designed to meet the need and performance requirements
- The process is designed to consistently meet product critical quality attributes
- Processes, equipment, personnel and deviations are identified and controlled in an appropriate manner
- The whole manufacturing process is constantly monitored and updated to enable consistency in quality over time.

The application of Pharmaceutical Quality Systems in pharmaceutical products can extend to pharmaceutical development, which should facilitate innovation and continual improvement of prescribed medication. It is the tool with which to achieve product realisation by designing, planning, implementing, maintaining and continuously improving a system, to allow the consistent delivery of pharmaceuticals with appropriate quality attributes.
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Specifications and method / process capability: two sides of the same coin

Specifications are defined as “a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described”.¹

**BIGRAPHY**

**DAVE ELDER** has nearly 40 years of service within the pharmaceutical industry at Sterling, Syntex and GlaxoSmithKline. He is now an independent GMC consultant. Dr Elder is a visiting professor at King’s College, London, and is a member of the British Pharmacopoeia. He is a member of the Joint Pharmaceutical Analysis Group (JPAG) and a member of the Analytical Division Council of the Royal Society of Chemistry.

Hence, the concept of a “universal specification” for a product is often aspirational in nature, rather than a realistic goal.”

**SPECIFICATIONS** establish predefined criteria of the expected quality of a product – Active Pharmaceutical Ingredient (API) or drug product – at that stage of their development. That is, there is, or should be, an expectation that specifications will evolve as process understanding and knowledge increases.

Specifications are therefore a compilation of "critical quality standards (CQSs) linked to overall product performance, which are proposed and endorsed by the applicant and reviewed and approved by the appropriate regulatory or pharmacopoeial authorities".² Despite decades of “harmonisation” initiatives, it is by no means certain that acceptance by one regulatory authority, eg. European Medicines Agency (EMA), will result in acceptance or approval by others, eg. FDA or Pharmaceuticals and Medical Devices Agency (PMDA).

Indeed, applicants often see different opinions from within the same EU regulatory region. Hence, the concept of a “universal specification” for a product is often aspirational in nature, rather than a realistic goal.¹

The link between specifications and the underlying critical process parameters (CPPs) and critical quality attributes, which are generated as part of a QbD-type (Quality by Design) submission²³⁴ have never been fully articulated, although all are part of the overall control strategy. Some commentators have expressed concern that ICH Q6A was never revised to more fully explain the inter-relationship.²

The application of ICH Q6A² during development, particularly early phase development, is one of the key challenges facing applicants and reviewers alike. In general, these guidelines were intended to be applied to marketing approval on new products, except for ICH M7(R1).³ This is sensible as knowledge of CQAs at this early stage of development may be very limited. Significant changes will be expected to both the synthesis / process of the drug substance and to the formulation / process of the drug product as they proceed towards market.² ICH M3(R2)² does provide some clarity of the original intent. It states in connection with impurities: “The approaches for qualifying impurities and degradants are outlined in ICH Q3A(R2)⁴ and Q3B(R2).² If specific studies are warranted to qualify an impurity or degradant, generally these studies are not warranted before Phase III, unless there are changes that result in a significant new impurity profile e.g., “a new synthetic pathway, a new degradant formed by interactions between the components of the formulation”.

However, the reality is that ICH Q6A guidance is often widely used during clinical development by both industry and regulators alike; often inappropriately, ie, requests for full details of impurities to be included on early phase clinical regulatory submission, e.g. investigational Medicinal Product Dossier (IMPD), investigational new drug (IND), without applying some aspects of the ICH Q6A guidance. Nonetheless, great care is needed to ensure that specifications are not constrained at an early stage based on limited data, especially if there is an intention to remove tests specified in early versions.

ICH Q6A does not include any discussions on process capability (Cp). However, it has become clear with the advent of QbD that a comprehensive understanding of the effect of variability of the process and supporting methodologies is required before robust specifications can be set. Process capability measures the output of an ‘in-control’ process by assessing the ratio of the process specification width (or range) to the spread of process values using standard deviation units. As the process capability improves, the variability
Process Capability (Cp) and the Likelihood of Out of Specification (OOS) Consequences (adapted from Elder∗)

<table>
<thead>
<tr>
<th>Process Capability (Cp)</th>
<th>Standard Deviation Range (±)</th>
<th>Probability that data are within specification limits</th>
<th>Occurrence of OOS Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00</td>
<td>6.00</td>
<td>99.73</td>
<td>1 in 370</td>
</tr>
<tr>
<td>1.25</td>
<td>7.55</td>
<td>99.98</td>
<td>1 in 5655</td>
</tr>
<tr>
<td>1.50</td>
<td>9.00</td>
<td>99.99</td>
<td>1 in 147160</td>
</tr>
<tr>
<td>2.00</td>
<td>12.00</td>
<td>99.9999998</td>
<td>1 in 5.1 x 10^6</td>
</tr>
</tbody>
</table>

This perspective is predicated on the view that measurement uncertainty will always be smaller than batch variation.

This assumes that the data are centred within the specification range, ie. 100% for API potency, ± 2% for specified range, ie. 98.0-102.0%. However, this is not typically the case; the presence of impurities means that the drug substance process is off-centred at 100-x%, where x is the total value of all impurities found in the process. This is reflected by the off-target process capability index (Cpk). A process with a Cpk of 2 could have a Cpk of 1.5, which would equate to a failure rate of four defects in every million assessments. Thus, logically process capability or variability (including method variability), is one of the key parameters in setting robust specifications.

However, regulators have indicated that it is “not considered appropriate to add method variability as determined in analytical method validation to the variation seen in batch results as this variability is already included in the batch results and therefore will be counted twice”. This perspective is predicated on the view that measurement uncertainty will always be smaller than batch variation. This is true if the sample size of the number of batches in question are sufficiently large reflecting the total population (typically a minimum of 30 batches). In practice many new drug products will submit regulatory files with a limited number of batches, ie. three at commercial scale, accompanied by a number of development batches at smaller scale. This prompts the key question: “How will it be possible to ensure the variability of the production process is covered by the specification with limited number of manufacturing scale lots that are available at the time of submission?” Are these criteria replicated by the product’s clinical experience or are the limits based on the cumulative process performance, or both?

Thus, if the specification is tightened during the review process and / or takes no account of process / method variability, this can turn a capable process into a non-capable process leading to OOS results or batch failures. Unfortunately, this is an increasingly common incidence during regulatory review, where reviewers consider that by further constraining the proposed specification they will make the process / specification more discriminating ensuring patient safety; simply, all that occurs are more batch failures of product that are of an acceptable quality.

It is widely accepted that method variability is frequently greater than manufacturing process variability, particularly for API processes. Intermediate precision is the most appropriate method validation parameter for assessing Cp and should be taken into consideration when proposing any specification limits, or when assessing the capability of the method when the specifications are “constrained”, as is the case for API assay, ie. 98.0-102.0%. Therefore, a specification of 100.0 ±2% i.e. 4% range for a 3-sigma process is equivalent to a total variability of 0.67%.

This assumes that the data are centred within the specification range, ie. 100% for API potency, ± 2% for specified range, ie. 98.0-102.0%. Therefore, a specification of 100.0 ±2% i.e. 4% range for a 3-sigma process is equivalent to a total variability of 0.67%. Thus the method variability needs to be at least half this value, ie. 0.34% (or less). The allowable method variability is further constrained as the true means of the specification is less than 100%, ie. 100-total impurities.

Thus, the supporting methods need to be 6σ capability (ie. show decreased variability) and hence the total method deviation is required to be < one twelfth of the total allowable range or tolerance, ie. 0.17% (or less). Based on this significant high-performance liquid chromatography (HPLC) method variability, several commentators have expressed significant misgivings about the utility of the standard HPLC assay method to monitor drug substance quality. Kredla et al. commented that, “assay results are simply not stability-indicating (....) due to the large assay variability associated with them”.

In the classical operating scenario, specifications have clearly defined acceptance and rejection zones (Figure 1). The various pharmacopoeias are currently evaluating decision rules based on a probabilistic assessment that acknowledges measurement uncertainty (MU) and the role it plays in decision making, ie. Acceptance / rejection.
based on compliance with a pre-determined specification. These decision rules support the decision-making process by, (i) assessing the measurement result, (ii) the specification limit (both current practices), (iii) the measurement uncertainty, (iv) and assessing the acceptable level of probability of making a wrong decision (where (iii) and (iv) are new approaches). These specification decision rules will introduce the concept of a “guard band” or “transition zone” between the acceptance and rejection zones within a specification. Within the specification “transition zone” a product will be considered non-compliant if the probability of either being above or below the designated upper or lower specification limit exceeds 2.5%. A target MU equivalent to α equal to 1.02 would meet these requirements. However, a bias will impact on this acceptance value. In the case of a non-centred specification or method bias of 1.0%, then α needs to be reduced to 0.6%.

An increasingly common situation that can occur in the QbD paradigm is the setting of specifications based solely on the clinically derived CQAs, without considering Cp arguments where Cp assessments clearly indicate that these proposed specification changes will make this a non-capable process, ie. a 3-sigma process. The recent trend towards tightening dissolution specifications from the typically encountered Q=80% at 30 minutes, to the much tighter Q=80% at 20 minutes is a case in point.

The intrinsically poor hydrodynamics of the dissolution apparatus at time points below 30 minutes ensures that there is significantly increased method variability for methods based on 20-minute (or lower) time points. That is, the method becomes less robust, but not more discriminating.

A potential solution is to move towards the clinically-derived specification in managed stages, ie. post-approval. Applicants would therefore generate data from a meaningful number of batches, ie, 30 batches; allowing an assessment of the population variability and adjust the specification based on a revised Cp assessment. However, for some low volume products these large numbers of manufactured batches, i.e. ≥30 are still very aspirational.

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Current trends in detection of falsified medicines

There is global public health concern over the falsification of pharmaceutical products and the extent to which widespread distribution of substandard drugs has developed. These products are rarely efficacious and can lead to disastrous health consequences, including failed treatment, disability, and even death. Consequently, falsified medicines may negatively impact public confidence in health care systems, health care professionals and the pharmaceutical industry.

THE EU took steps to address these concerns through the introduction of the EU Falsified Medicines Directive (2011/62/EU) (FMD), adopted in 2011, setting out new measures to ensure that medicinal products in the EU are safe and that medicinal trading is properly controlled.1,2 ‘Falsified’ and ‘counterfeit’ medicinal products are closely related terms, which are commonly used interchangeably. In the FMD, the term ‘falsified’ refers to any medicinal product with a false representation of its identity (including its composition, packaging, and labelling), source or history. Counterfeit medicines, on the other hand, are those that do not comply with intellectual-property rights or that infringe trademark law.3,4

Scale of the problem
The extent of counterfeiting / falsification is impossible to quantify. The Pharmaceutical Research and Manufacturers of America (PhRMA) states that it is greater in those regions where ineffective regulatory systems and market control exist.2 The World Health Organization (WHO) estimated that the prevalence of falsified drugs ranges from less than 1% of sales in developed countries, to over 10% in developing countries. In some regions, more than 30% of medicines on sale are falsified. Across the EU alone, it causes the loss of 4.4% of legitimate sales, the loss of €10.2bn in revenue for the pharmaceutical industry, and the loss of €1.7bn in government revenue.5

Technologies and application
Various analytical techniques are used throughout the industry for the screening of falsified medicines, including Fourier-transform infrared spectroscopy (FT-IR), near-infrared spectroscopy (NIRS), Raman spectroscopy, and liquid chromatography-mass spectrometry (LC-MS).6 In the case of falsified drugs that are chemically very similar to the genuine product, authenticity may be determined by differences in the distribution of ingredients within the product using near-infrared microscopy.7

NIRS and Raman are often used as complementary techniques. Chromatographic techniques often require extensive sample preparation, have slow analysis times, and require extensive technical knowledge. NIRS, in comparison, is non-destructive, portable, rapid, and samples can be analysed through plastic bags and glass containers. Additionally, workflow-based approaches can be implemented to enable users of any background to perform the analysis. If a product is deemed falsified based on the initial screen using NIRS, it can then be subjected to further testing using a confirmatory method such as LC-MS.8

When combined with a chemometric algorithm, known as Soft Independent Modelling of Class Analogies (SIMCA), NIRS can be used to verify the identity of a material and detect falsified or suspect materials. SIMCA models the variation found within a collection of reference spectra for a given material.

An example screening application using NIRS is the detection of counterfeit statins. Statins are a class of drug used to lower cholesterol in patients. Approved in 1996 under the brand name Lipitor®, atorvastatin was the most sold prescription drug in the U.S. from 2007 to 2011, with revenue generation of $12.9bn in 2011. In late 2011, the expiration of the patent held by Pfizer allowed generic versions of the drug to emerge.9,10 Falsification / counterfeiting can apply to both branded and generic drugs and NIRS with chemometrics can provide a rapid and simple approach for their detection.

The Medicines and Healthcare products Regulatory Authority (MHRA) is inviting views on the proposed steps that the government intends to take to ensure the UK meets its obligations to transpose the provisions of the FMD requiring safety features to appear on the packaging of certain medicinal products.

Act now by completing a response form, which can be found at the link below. This consultation closes at 3pm on 23 September 2018.


References
To view the references for this article, please visit: europeanpharmacareview.com/4-18-PerkinElmer

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