Moving from Quality Control to Quality Assurance

by Guy Wingate, PhD

This article provides ways to implement an effective quality management system to allow manufacturers to meet their ethical and regulatory obligations.

This article is based on content from the presentation, "Moving from Quality Control to Quality Assurance" held during the ISPE Proactive Compliance Conference on 13-14 January 2014 by Dr. Guy Wingate, VP and Compliance Officer (Global Manufacturing and Supply), GSK. As reflected in the theme of the conference, a collective challenge facing the industry is to achieve proactive compliance. This involves effective management and control of the manufacturing environment to avoid problems rather than just responding to problems after they have happened.

As it applies to many of us, this means assuring sustained higher performance (often during a period of significant change) with no nasty surprises. Central to our thinking must be the person at the end of our supply chain and their trust in us to comply with regulatory requirements and ensure the products we make are fit for purpose. In the pharmaceutical industry, the Quality Department is playing an increasingly pivotal role in running a sustainably profitable business that is also committed to meeting the expectations of the patient and the public. Executive managers, R&D, manufacturing, and sales and marketing all feel the pressures of productivity challenges, organizational changes and increasing regulatory requirements, but the fundamentals of quality and compliance must never be compromised. The implementation of an effective quality management system allows manufacturers to meet their ethical and regulatory obligations. It is good business sense to remove defects, reduce deviations and eliminate waste. To achieve the highest level of safety, purity, and efficacy of drug products, quality management teams are moving beyond Quality Control (QC) and into Quality Assurance (QA).[1,2] Today's modern businesses are becoming more proactive and less reactive.[3]

The World Health Organization defines Quality Control (QC) as "the sum of all procedures undertaken to ensure the identity and purity of a particular pharmaceutical."[3] The purpose of QC is to ensure the safety and efficacy of a finished drug product before it is released to the public. Supporting quality systems need to detect whether items such as raw materials, components, containers, labeling and packaging fail to meet pre-existing specifications. The QC Department is responsible for conducting this work as well as testing the finished product to ensure it meets regulatory requirements. For pharmaceuticals, QC may involve analytical procedures ranging from simple substance screenings to complex pharmacopoeia monographs.

Quality control at its core is a reactive process. The pre-market checks and inspections do their best to assure phar-

| Quality Control vs. Quality Assurance ||
Quality Control	Quality Assurance
Product	Process
Reactive	Proactive
Corrective tool	Preventative tool
Completed by experts	Implemented by managers
Ensures and checks	Develops and defines
Failure detection	Failure prevention
Identify and correct defects	Prevents defects
Identification through inspections and peer review	Prevention with statistical and managerial tools

maceutical manufacturers of the standard of products being made and sold, but QC alone cannot guarantee that a high quality product will be consistently produced. Substantial manufacturing waste (time and materials as a result of process deviations) and post-market recalls are evidence of this. A better approach is needed as the FDA acknowledge in their 2006 Guidance for Industry, Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations stated, "Quality should be built into the product, and testing alone cannot be relied on to ensure product quality."[4]

Quality Assurance (QA) involves taking a proactive approach to ensure drug products are made in accordance with manufacturing standards and met their pre-defined product specifications. The aim is for quality and compliance to be achieved "right the first time" rather than depend on detecting problems. The aim is to continually improve manufacturing standards, eliminating errors along the way. Quality control still has a role to play, but with effective QA and reliable operational performance during the process, it becomes a component of the pharmaceutical quality system.[2]

The responsibilities of quality assurance include:

- Products intended for public are safe, effective, and appropriate as to dosage.
- Predetermined quality standards are upheld when choosing and accepting products from suppliers.
- Labeling and packaging meets regulatory requirements as to storage and usage.
- Recall process is standardized and prepared for defects in post-market products.
- Post-market communications are available for public concerns and questions.

The leading guidance on pharmaceutical quality management systems is ICH Q10 published in 2009 by the International Conference on Harmonisation (ICH). This Guide describes quality system management integrating Good Manufacturing Practice (GMP), based on science- and risk-based approaches.[1] Quality assurance is a part (along with quality control) of the broader concept of quality management. Pharmaceutical quality systems need to provide the necessary framework for implementing continual improvement and risk management in the drug manufacturing process.[4] This is also consistent with the concepts of Quality by Design (QbD).[5]

A holistic approach to quality assurance is needed. The internal control framework needs to cover governance, systems and processes, as well as distinct activities that encourage a supportive mindset and organizational behavior. Key aspects to consider include:

- Company Awareness – quality assurance is a part of normal business, an integral part of achieving long and short-term goals. Success depends on total commitment of management and staff.
- Product Knowledge – quality assurance must have complete documented product, system, and process knowledge. Product knowledge must include raw material and specific production audit, testing, and validation requirements.
- Facility Knowledge – quality teams should include personnel with expertise of equipment and access to educational resources to stay current with regulatory updates and process validation changes.
- Basic GMPs – ensure basic cGMP compliance is robust and sustained (in place, in use and effective). Never assume basic processes like deviation management, root cause analysis and Corrective and Preventive Action (CAPA) look after themselves. CGMP compliance is perishable and needs nurturing to support quality assurance.
- Networking – quality assurance teams should be proactive in networking with regulatory agencies and peers with similar product lines. Opportunities should be made available for education and current trends through conferences and regulatory resources.
- Risk Analyses and Decision Allowances – risk analyses should be based on good science and data. Decision making authority should be backed with expert process analyses and the ability to alter standard operating procedures.[6]

> " *The holistic approach to quality assurance needs to promote transparency in support of performance improvement.*

Pharmaceutical companies must ensure they do not fall down on the basics. A good example was discussed at the ISPE Proactive Compliance event. Management often use a single metric to track the effectiveness of CAPA management. The chosen metric can have unforeseen implications if it focuses on the corrective aspect of CAPA to return a process to normal operation. CAPA actually comprises two distinct activities as the name suggests. The first aspect focuses on investigating, understanding, and taking action to correct a problem. The second aspect focuses on defining and implementing action to prevent recurrence. Fundamental to both, in order to achieve successful quality performance improvement, is the identification of the real root cause of the problem being fixed and not to rely or accept cursory or superficial assessments based on assumptions. A separate

Do you calculate a Cost of Poor Quality at your site?
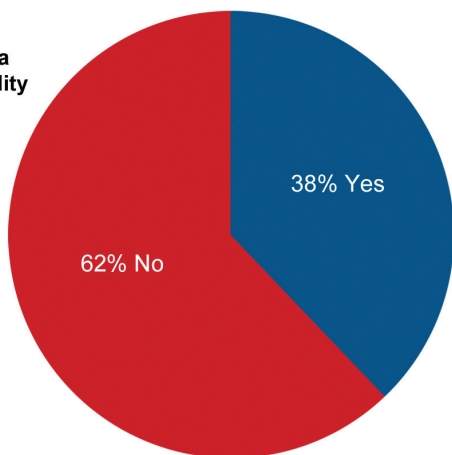
38% Yes

62% No

Figure 1. Calculating cost of poor quality at your site (ISPE/PDA Survey September 2011).

Have you evaluated the cost of improving quality vs. the cost of failure (recalls, rejections, low yield, downtime, etc.)?
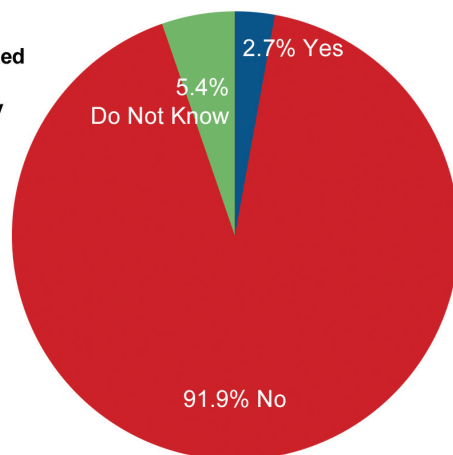
2.7% Yes

5.4% Do Not Know

91.9% No

Figure 2. Evaluating the cost of improving quality (ISPE/PDA Survey September 2011).

metric for each aspect of CAPA is therefore recommended which require equal management attention.

The holistic approach to quality assurance needs to promote transparency in support of performance improvement. Staff, wherever they work, need to feel safe in raising deviations and other concerns with their line management. An open and trusting relationship must be maintained so that production problems are raised as they occur for rapid resolution. A learning culture needs to replace a "mistakes-are-punished" or a "someone-is-to-blame" approach to quality issues. A Speak-Up program should be established to provide an alternative means for staff to raise concerns to an internal independent group. Such programs need to make provision that enable confidential disclosures to be made. It is vital to sustain trust and prevent any retaliation against those raising problems in good faith. It is better for organizations to deal promptly with issues raised than wait for a frustrated individual to feel their only option is to become a whistleblower.

Although companies are finding the value in moving toward the QA paradigm, reaching optimal quality assurance has its challenges. Quality systems in manufacturing sites are often hindered by cumbersome collections of documents requiring reactive rewrites with process or procedural changes. Manufacturers also face a lack of Subject Matter Experts (SMEs) with the necessary process and product understanding to support leading edge practices such as Quality by Design (QbD) and Quality Risk Management (QRM). Pharmaceutical manufacturing companies need to lead the manufacturing industry by commit-

ting to enhanced QA by eliminating inefficient processes and streamlining manufacturing operations.

In 2012, Richard Friedman, Associate Director of FDA's CDER's Compliance Office's Office of Product Quality, addressed the need for pharmaceutical companies to modernize the control process in which products are manufactured and better analyze the quality risks. This direction is supported by Generic Drug User Fee Program and the FDA Safety and Innovation Act. Friedman endorsed the intent of ICH Q10 which is optimal quality through knowledge management, change, and innovation.[7] Pharmaceutical quality management teams can modernize manufacturing by constructing their quality system on a holistic framework of key elements. Governing management, system processes, and a quality culture mindset become the basis of quality management, and therefore, quality assurance. Within this structure, elements such as QbD and QRM support each
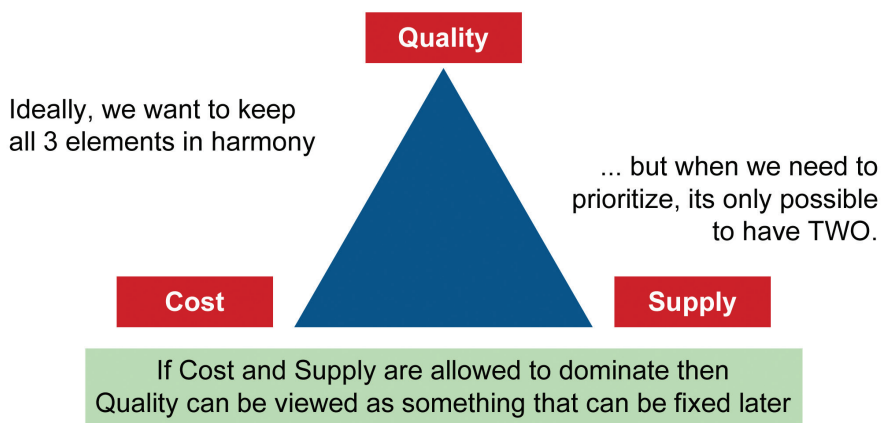
Quality

Ideally, we want to keep all 3 elements in harmony

... but when we need to prioritize, its only possible to have TWO.

Cost

Supply

If Cost and Supply are allowed to dominate then Quality can be viewed as something that can be fixed later

Figure 3. Ghost in the Machine – Culture.

What significant benefits have you achieved through the measurement of Cost of Poor Quality? (check all that apply)
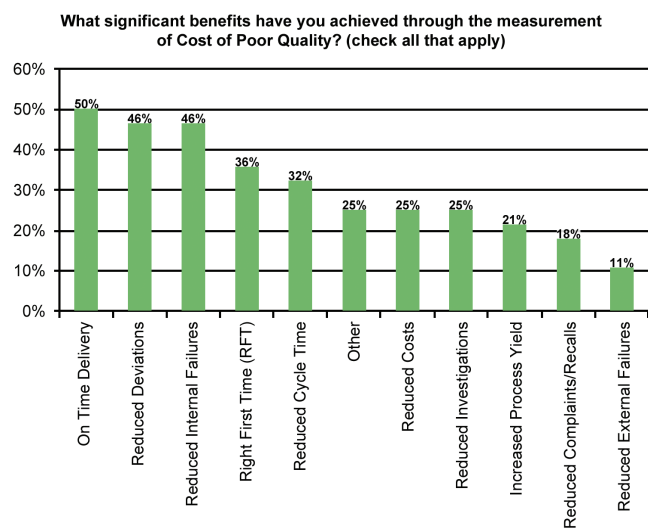

Figure 4. Significant benefits achieved through the measurement of cost of poor quality.

other. This facilitates sustained and continual improvement benefiting both patients and business stakeholders.

Quality can be better managed when it is recognized and understood that the control of variability and prevention of waste is imperative to achieve a cost effective business[8] - *Figure 1*. In 2011, an ISPE/PDA joint survey found that more than half of manufacturers had not calculated or evaluated the projected outcomes of the Cost of Poor Quality (CPQ) - *Figure 2*. Ideally, we strive to keep quality, cost, and supply in harmony, but when we need to prioritize, it is only possible to achieve two and quality must always be preserved - *Figure 3*. Quality management when structured with quality assurance using cost analyses as a business driver, reaps the cost benefits of a proactive approach - *Figure 4*.

A company must set the "tone from the top" when raising expectations of quality by implementing a systematic quality management approach. To move into quality assurance and therefore a more proactive approach to quality, senior managers must first understand the specific working principles of the site including its drivers, constraints, and manufacturing goals. Taking these points into account, management must then strategically prioritize cost targets, quality expectations, and their business scope.[2]

The U.S. Department of Justice has set out clear expectations for company executives senior management when it comes to cGMP compliance.[9] The following reflective questions give an indication of what is expected from company leaders.

- Do we have the right people (capability and attitude – employees, contractors, suppliers)?
- Do people have the right incentives to see, report and fix problems?

- Are people satisfied and engaged?
- Do policies and procedures acknowledge how real people work and what they are capable of?
- Do managers have personal visibility into what people are actually doing?
- Is there a supportive organisational culture in place?

Individuals can find themselves culpable for not taking these expectations seriously.

Management must clearly communicate what needs to be accomplished so that everyone understands what is expected. Part of this should include explaining what is not tolerated in terms of standards and behavior. The same expectations should be applied equally, including any supporting disciplinary processes, to all levels of the organization.

To achieve higher quality through QA, manufacturing companies, as well as suppliers and regulators must work together. FDA Commissioner Janet Woodcock recommends an investment in the mutual objective of "an agile, flexible pharmaceutical manufacturing sector that can reliably produce high quality medicines without extensive regulatory oversight."[10] Shared beliefs, values, attitudes, and behavior patterns are pieces of the jigsaw that must come together.

> **"** *Adopting a proactive approach to quality management is essential to achieve the step change in quality performance expected from our industry.*

Adopting a proactive approach to quality management is essential to achieve the step change in quality performance expected from our industry. The energy and motivation for quality comes from the top. Management must acknowledge the challenge of change this will involve in their organizations and stay vigilant. Everyone must play their part. A culture of quality will empower teams to continually improve and solve problems. We must remember that the person at the end of our supply chain is depending on us to provide safe and effective medicines.

*Disclamer: the views expressed are personal opinions and do not necessarily represent the views of GlaxoSmithKline.

References

1. Dubey, Neetu, Himanshu Gupta, R.K. Sharma, Nitin Dubey, and Nidhi Dubey, "Pharmaceutical Quality Manangement System: Current Concept," *Journal of Advanced Pharmacy Education and Research*, 2: 120-124, 2011.
2. Caldwell, Pete, Alex Sifniotis, and Edite Laka, "Quality Assurance in the Pharmaceutical Industry," Tefen Tribune: Life Science Issue, 2012.
3. World Health Organization, Medicines: Quality Control, http://www.who.int/medicines/areas/quality_safety/quality_assurance/control/en.
4. US Food and Drug Administration, Guidance for an Industry: Quality Systems Approach to Pharmaceutical cGMP Regulations, Rockville: US Department of Health and Human Services, 2006.
5. Khar, Dr. Roop Krishen, "Evolution of Quality Control in Pharmaceutical Technology," *Journal of Advanced Pharmaceutical Technology and Research,* 4 (4): 172, 2013.
6. Huxsoll, Jean F, "Quality Assurance for Biopharmaceuticals," Wiley-Interscience, 1994.
7. Shanley, Agnes, "FDA's Friedman's Challenge to Pharma Execs: Modernize!" *pharma QbD,* February, 2012.
8. Lynn, Stephen, "Product Manufacturing and Quality: Pharmaceutical Current Good Manufacturing Practices (CGMPs)," US FDA, 13 October 2013.
9. Maame Ewusi-Mensah Frimpong, (Deputy Assistant Attorney General for DOJ's Consumer Protection Branch), Pharmaceutical Compliance Congress, 29 January 2013.
10. Woodcock, Janet, "Driving Quality and Compliance throughout the Product Life Cycle in a Global Regulatory Environment," FDA/PDA Joint Conference, Keynote Speaker, 2013, Renaissance Washington DC Hotel, Washington, DC.

About the Author

Guy Wingate, PhD is currently Vice-President and Compliance Officer for Global Manufacturing and Supply at GlaxoSmithKline and has more than 20 years of experience working in the pharmaceutical industry. At GSK he has held several roles including overall responsibility for quality for one of GSK's largest manufacturing sites, responsibility for QA technology strategy, leading a major revision to the GSK corporate quality management system, and overall responsibility for computer compliance standards and implementation. Wingate has been involved with the GAMP COP for 21 years in various capacities; most recently he has chaired its governing body GAMP Council 2000-2010. He has led the Task Teams producing several ISPE guidance documents, including GAMP® 5 and the Science and Risk-based Approach for the Delivery of Facilities, Systems, and Equipment Guide. Wingate served on the ISPE International Board of Directors between 2008-2012. He is a Chartered Engineer and holds a BSc, MSc, and PhD from University of Durham in computing, advanced electronics, and engineering science respectively. He is widely published in journals and books, and regularly chairs and speaks at conferences in the US and Europe. He can be contacted by email: guy.as.wingate@gsk.com.

GlaxoSmithKline, C Block Main Office Harmine Rd., Barnard Castle, County Durham, United Kingdom DL 12 8DT.