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QMS Deficiencies: If our quality systems were good enough, inspectors wouldn't find deficiencies.

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In a recent report, the Medicine and Healthcare products Regulatory Agency (MHRA) stated, "Deficiencies relating to 'Quality Systems' are by far the most prevalent observed during inspections." We should ask ourselves why.

Introduction

Quality system elements have been the top 10 category of deficiencies found by in the U.K. by the MHRA for the last 10 years. In the U.S., the FDA believes that pharmaceutical quality system (PQS) element deficiencies are the major contributor to drug shortages.

More than 10 years ago, it is probable that neither the industry nor the regulators really appreciated the importance of a PQS or indeed what it looked like and what system elements made up the QMS. There was a huge reliance on just GMP compliance.

Now with the introduction of ICH Q 10 we all have a much better understanding of what a PQS is. So why do inspectors still find so many inspection deficiencies relating to the PQS? Surely it is the fundamental approach to everything we do to ensure patient safety, regulatory compliance and ultimately a successful business. After years of regulatory oversight of the pharmaceutical industry and years of applying a quality approach to the business we are in, it is worrying that we still see very serious deficiencies relating to the PQS.

MHRA Deficiency Database

The MHRA has been one of the few regulatory authorities to publish the statistics and classifications for the deficiencies that it finds during inspections. This is a great source of information and yet sadly does not appear to have had the desired effect of preventing further similar deficiencies. It is very clear that MHRA continues to have concerns about our quality systems.

The last figures we have are for year 2013, and it is sincerely hoped that the MHRA continues to provide us with this *invaluable, free lesson*. Interestingly, MHRA groups deficiencies into various main headings:

1. Quality Management
2. Production
3. Materials Management
4. Premises and Equipment
5. Quality Control
6. Validation
7. Regulatory Compliance
8. Personnel

This is probably a misleading breakdown. It implies that quality management is a separate system from the others. In fact, each of these items is a key element of a pharmaceutical quality system and they all relate to how quality is managed.

In other words, it is all about how the PQS is designed, operated, monitored and improved. For example, the way that personnel are recruited, managed, trained, educated, informed, assessed and developed is probably the most important element of the PQS and yet it is a separate category in the MHRA listings. Without the right motivated people in the right jobs, given the right information to do

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their jobs well – none of the other systems will work. All the systems are interlinked and all form part of the PQS.

An essential characteristic of a PQS therefore is that all elements work together. Indicators that this is not happening are high levels of deviations previously assigned to human error. Such errors occur in the vast majority of cases because the PQS elements are not well designed and managed.

The Major PQS Deficiencies

Essentially all deficiencies result from an ineffective PQS no matter what heading you give it. Even deficiencies listed under categories 2 – 8 are symptomatic of the quality system not working effectively or not being designed, reviewed and improved as required by regulators.

Table 1: Top 10 MHRA GMP deficiency categories during 2013.

1	Investigation of Anomalies
2	Quality Management
3	CAPA
4	Contamination: Chemical/Physical (or potential for)
5	Supplier and Contractor Audits
6	Change Control
7	Documentation Procedures/PSFs/TAs
8	Personnel Issues: Training
9	Design and Maintenance of Equipment
10	Documentation: Manufacturing
11	Finished Product Testing: Chemical

Table 2: Top 5 deficiencies identified by MHRA in 2013. *Specific examples found during MHRA inspections.*

#	Deficiency	Examples	Regulatory Expectations
1	Investigation of Anomalies (Deviations)	> An appropriate level of root cause analysis was not applied during the investigation of deviations. > No formal documentation of the product impact assessment and associated rationale for determining whether issues encountered were significant deviations or lower level incidents.	Deviation system must require all deviations to be classified or ranked based on risk to patient. Risk assessment must be documented. For those considered more serious, an effective impact assessment and root cause analysis must be performed and documented. Appropriate corrections should be implemented and corrective action should be taken to ensure the problem does not reoccur. Internal audits should look for evidence of recurrence and deviations should be trended for the same purpose.
2	Management of Quality	> There was no self-inspection program established for the current year. > There was no risk management procedure. > Significant quality incidents were not included in PQRs.	Senior management should ensure that the quality system includes all the necessary elements/systems that drive continuous improvement and risk-based thinking and should review them on a formal regular basis at a quality review meeting.
3	CAPA	> It was unclear how CAPA actions were linked to the root cause. > There was no process to ensure CAPA actions from any system, including regulatory inspections, were completed on time and in full. > There was no mechanism for measuring CAPA or demonstrating its effectiveness.	All elements of the quality system can give rise to opportunities for improvement. CAPAs are by definition improvements, provided that they are effective. Any failures, complaints, deviations and audit findings should be prioritized based on risk and fed into the CAPA system. CAPAs must be implemented in a defined time frame and the effectiveness of the CAPA system must be monitored by various systems, e.g. internal audits, PQRs, trending of deviations or other parameters, changes, CAPAs, etc.
4	Potential for Contamination	> There was no documented process for assessing the introduction of new molecules on the site. > White powder was noted on a roller compactor that had been in the engineering workshop for six months. > Unidentified white powder was noted on the production corridor floor and on a hand pallet truck.	Every company should have a documented approach to minimize contamination, including a requirement to raise a change request to introduce a new product or molecule, resulting in an impact and risk assessment. Effective design of facilities, equipment, and maintenance/cleaning programs should prevent product residue from causing a potential contamination of other products. Many elements of the quality system can contribute to contamination if not well designed and effective.
5	Supplier and Contractor Audits	> Audit report for a contract manufacturer was not available when site was added to approved supplier list. There was no contemporaneous evidence to base the approved manufacturer decision. > Audit reports for an API were high level. It was not apparent what had actually been audited. > Audit report for a supplier concluded the site was not suitable to supply an API due to GMP issues. API supplied had not been quarantined or rejected.	Supplier management system should not allow any supplier to be used without going through quality assessments. These assessments must be documented and available for inspectors to support the use of any supplier or contractor. If audits are required to form part of the assessment, the audit reports must be available and sufficiently detailed to support the use of the supplier. Any findings and recommendations made by the auditor should be addressed and acted upon.

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The Root Causes of PQS Deficiencies

If we come back to the question of why these deficiencies still exist after all these years, then the following causes must be considered:

1. Lack of understanding of what an effective quality system includes
2. Poor design and description of the quality system
3. No common understanding across the company of what the quality system consists of and how it works
4. No measures, or inappropriate measures, to indicate how well the quality system is working and driving the right behaviors
5. No regular formal senior management review of the quality system
6. No formal system in place to drive continuous improvement of the quality system, led by the senior management team
7. No formal system in place to drive continuous improvement of the products and processes
8. Inadequate resources provided to monitor and improve the quality system
9. A compliance culture rather than a quality culture
10. No effective internal audit program to identify weaknesses in the quality system

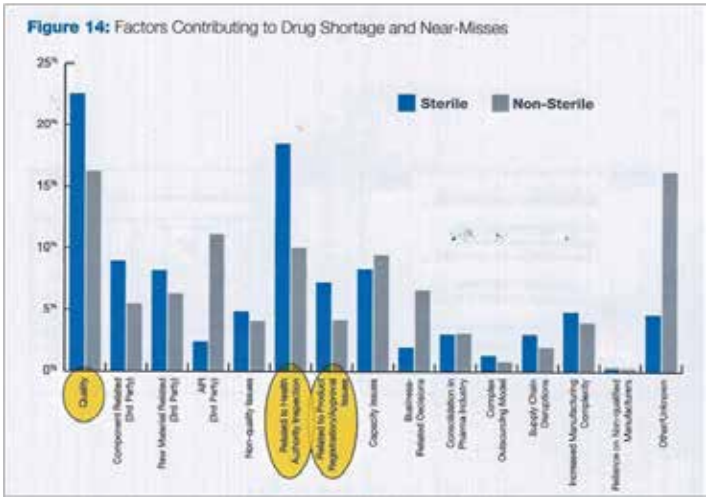
Perhaps these are the top 10 explanations as to why regulators still find GMP deficiencies, and why companies fail to meet current expectations. Essentially it indicates that most companies still have significant gaps in their pharmaceutical quality system and the individual components that make up the PQS.

The FDA Perspective

The findings from an analysis of warning letters from the FDA present a very similar picture. In addition, the FDA has determined that QMS deficiencies are also the single biggest contributing factor of drug shortages, especially sterile products.

This has been confirmed in an ISPE Report[1] from which Figure 1 is taken. This shows that non-quality issues are a very minor contributor to drug shortages.

As a consequence, the FDA has a very active project with the aim of requiring the industry to provide the agency with quality metrics on an ongoing basis. It has identified some metrics which are being discussed with industry, and wishes to extend them to include metrics about the performance of our manufacturing processes, e.g. process capability as well as the performance of the QMS.



So far the suggested metrics[2] are:

- Lot Acceptance Rate: 1 – Number of batches rejected
- Right First Time: 1 – Number of lots without a deviation
- Product Quality Complaint Rate: Number of specification failure complaints vs. number of lots released
- Invalidated Out-of-Specification (OOS) Rate: Number. of invalid tests vs. total number of tests performed
- Annual Product Review (APR) on Time Rate: Within 30 days of the due date vs. the number of products
- Management Engagement: Seniority of the APR sign off
- CAPA Rate: CAPA actions initiated from the APR vs. the total number of APRs generated

[1] Report on the ISPE Drug Shortages Survey, June 2013 (www.ispe.org/drug-shortages/2013junereport.pdf)

[2] These are abbreviated definitions. For the full definitions, see the FDA website (www.fda.gov).

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Other measures under consideration relate to process capability and quality culture, though the latter is clearly much more difficult to measure.

Conclusion

The cynical among us may say, “Ah yes. but regulators are always pushing the bar higher.” Perhaps it is a poor indictment of any company if it waits for regulators to force it to improve! Generally speaking, the regulations drive good business practice.

Continuous improvement, driven by the senior management team, is essential for any company to stay in business and of course it is a legal requirement in GMP and an essential component of a PQS!

Regulators want to see companies taking the initiative and in particular senior management driving the continuous quality improvement, which is good business sense anyway. That is a key difference between a quality culture and a compliance culture.

About the Author

Liz Allanson, MRPharmS, is a pharmacist by profession and has a special interest in quality management and leadership skills. She spent almost 19 years as a GMP inspector with the UK MHRA, primarily as a senior manager in the MHRA Medicines Inspectorate. Her last position with MHRA was managing the GMP inspection team.

Ms. Allanson is eligible to act as a Qualified Person and is a registered IRCA lead auditor. Her areas of expertise include:

- EU GMP pharmaceutical legislation and regulatory expectations, including requirements for investigational medicinal products
- GMP and GDP compliance
- Quality management systems
- Clinical trial manufacture/packaging and QP release
- Auditing and mock regulatory GMP inspections
- Supply chain management

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