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Review

Role Of Quality Management System (QMS) For Effective Regulatory Compliance

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Abstract

Regulatory compliance is an organization's adherence to laws, regulations, guidelines and specifications relevant to its business. Violations of regulatory compliance regulations often result in legal punishment, including federal fines. The International Organization for Standardisation (ISO) produces international standards such as ISO/IEC_27002. The International Electrotechnical Commission (IEC) produces international standards in the electrotechnology area. Compliance is about more than prevention. It's also about navigating opportunities. Regulatory compliance is not just about playing defence. It also offers an opportunity to consistently strengthen your organisation through strategic, proactive measures—such as best practices, employee training, internal controls, and benchmarking appropriate for your industry and size.

Keywords: Regulatory Compliance, ISO, IEC, Industry

INTRODUCTION

The changing regulatory environment

In a Science Board Meeting held in November 2001, FDA raised some concerns regarding the efficiency of the pharmaceutical industry. The factors contributing to this situation were identified as follows:

- Pharmaceuticals are complex, multivariate physicochemical systems that are

- Often treated (during development) as univariate systems (one-factor-at-a-time, trial- and-error experimentation)
- Physical properties of materials normally not well characterized
- Equipment selection based on tradition
- Process factors are not well understood

- Development is done under time crunch
- Post approval changes require regulatory oversight

It was said that a *higher efficiency* is required in order to provide high quality drugs to the market in a timely manner, to successfully take advantage of the new drug development opportunities offered by advances in chemistry and biology. In addition, one should also ensure the optimal utilization of public and private resources to meet the growing health care needs and, last but not least, to obtain global competitiveness for the pharmaceutical industry.

The consequences are that the status quo is no longer tenable and that the pharmaceutical manufacturing could be much better. Furthermore, it is claimed that traditional metrics hide poor performance, and that compliance infrastructures are not economic. Currently, utilization levels are judged to be down to 15 percent or less, and costs in terms of quality are in excess of 20 percent.

The agency's conclusions were that often processes are transferred that are neither fully understood nor capable of being so at commercial scales. Also, there is a lack of scientific basis for deeper process understanding. Further, the pharmaceutical manufacturers fall short in the ability of a process to be 'right the first time' (e.g. pro-active quality management, six sigma approach)

Under the umbrella of the GMP for the 21st century initiative, the FDA started an international co-operation to find answers to the current situation covering the following topics:

- A science based approach
- Risk management
- QSIT (Quality System Inspection Technique)
- PAT (Process Analytical Technology)

QSIT and PAT

The Quality System Inspection Technique moves the FDA from reviewing all documentation to a system- based inspection covering the following six subsystems:

- Quality system
- Facilities and equipment system
- Production system
- Packaging and labeling system
- Laboratory controls system
- Materials system

Scientific and technological advances in the area of process analytical chemistry, engineering, and multivariate data analysis offer new opportunities for improving the overall efficiencies of drug development, manufacturing and regulatory processes. Although for many years the pharmaceutical community has recognized the need for improvements in these areas, little progress has been made. Therefore FDA forced the development of PAT (Process Analytical Technology). PAT is a model to facilitate the discussion on of emerging regulatory science issues in pharmaceutical manufacturing. PAT provides an opportunity to move from the current "testing to document quality" paradigm to a "Continuous Quality Assurance" paradigm that can improve the ability to ensure quality that was "built-in" or was "by-design" – the ultimate realization of the true spirit of GMP. It is the expectation of the industry that these initiatives will result in improved product quality, reduced manufacturing cycle times, reduced laboratory testing burdens and costs.

QMS combining ISO and GMP

Overall, there is a clear tendency of authorities towards Quality Management Systems (QMS), as already outlined in some new guidelines, e.g. in ICH Q7a, Section 2.11 *"Each manufacturer should establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel"*.

Finally, ISO 9002 already stated in the introduction: *"It is emphasized that the quality system requirements specified in this International Standard are complementary – not alternative - to the technical (product) specified requirements"*. As early as 1997 a guideline on the integration of the GMP requirements with the QMS requirements, issued by CEFIC/APIC, was available for the API manufacturers.

Introduction to the old APIC version (excerpt)

Because the pharmaceutical industry has traditionally focused upon the application of Good Manufacturing Practice (GMP), it has been slow to consider the potential benefits to be gained by implementing an EN ISO 9001 Quality Management System (QMS). Over the last few years the global pharmaceutical market has undergone significant change, forcing pharmaceutical companies, more than ever before, to focus on customer needs and upon their own internal efficiency in order to continue to compete effectively. With this in mind CEFIC commissioned a working group of experts drawn from several major Active Pharmaceutical Ingredients (API) producers to prepare a practical, user-friendly guidance document integrating current GMP requirements into the EN-ISO 9001 QMS framework. To achieve this the working group have taken relevant features from the August 1996 CEFIC/EFPIA publication "Good

Manufacturing Practice for Active Ingredients Manufacturers" and combined these with the relevant complementary requirements of EN-ISO 9001 "Quality Systems: Model for quality assurance in design, development, production, installation and servicing". It was intended that these Guidelines would be applicable to all APIs. To facilitate understanding of this composite guidance document it is important for the reader to be aware of the following points:

- EN-ISO 9001 is a generic, business-focused standard that supports the effective management of quality to an internationally recognized level of best practice. It is flexible in that it specifies what is to be achieved, but allows each company freedom to determine, and justify, how these requirements are achieved. In contrast, GMP is an industry-specific standard prescribing what should be done to ensure product safety and efficacy. Thus, EN-ISO 9001 benefits the business by ensuring the quality of the management system, while GMP ensures that quality is built during the whole manufacturing and control process and that regulatory requirements are met.
- Although there is inevitably some overlap between the requirements of a QMS and GMP they are, in fact, highly complementary. This view is supported by a statement in the introduction to the PIC (Pharmaceutical Inspection Convention, now called PIC/S) GMP Guideline which refers to "... a correctly implemented system of Quality Assurance incorporating GMP ...", and by the wording of the introduction in ISO itself which points out that "..... this international standard is complementary - not alternative - to the technical (product) specified requirements".
- The interrelationship between EN-ISO 9001 and API GMP is illustrated in this guidance document by a matrix cross-referencing the main QMS elements and GMP requirements.
- To be effective the QMS should have the visible and ongoing support of top management.
- To fully benefit the company the QMS should involve all staff whose activities influence quality, have a clear and unambiguous continuous improvement focus, and incorporate relevant, realistic performance measures with emphasis on reducing failure costs, and satisfying (internal and external) customer needs.
- The quality manual occupies the highest level in the document hierarchy. It overviews and acts as a directory to the QMS, capturing the unique character of the company.
- An effective QMS has a minimum of paperwork, and should constantly question the need for the existing documents. In contrast, a bureaucratic and inefficient QMS will arise if the Standard is misinterpreted, and incorrectly applied.

Safety, health and the environment were not specifically addressed. However, it was widely acknowledged that implementation of a robust QMS provides a sound basis for the future development of such an Integrated Management System.

Changes of the relevant GMP/ISO requirements

In the meantime the GMP as well as the QMS requirements have changed. For this reason the 1998 APIC guideline needs to be updated.

Changes to the GMP requirements

API manufacturers no longer need to follow GMPs as defined in e.g. 21 CFR Part 210/211, or draft versions of API guidance documents. The new ICH guideline Q7a "Good Manufacturing Practice for Active Pharmaceutical Ingredients" has some fundamentally different GMP requirements, and specifically applies to the manufacture of APIs for use in drug (medicinal) products. The guide covers APIs manufactured by chemical synthesis, extraction, cell culture/fermentation, by recovery from natural sources, or by any combination of these processes.

Changes to the QMS requirements – ISO 9001:2000

The ISO 9001 series has changed fundamentally. The differences are outlined below.
ISO 9001:2000 is based (as is ISO 9004:2000) on the following eight quality management principles:

- Customer focus
- Leadership
- Involvement of people
- Process approach
- Systematic approach to management
- Continual improvement
- Factual approach to decision making
- Mutually beneficial supplier relationship

The fundamental difference between the ISO 9000:1994 series and the ISO 9000:2000 series is the change in scope from addressing an organization's "capability to design and supply conforming product (where this) needs to be demonstrated" to "ability to consistently provide product that meets customer

and applicable regulatory requirements, and aims to enhance customer satisfaction….".

The new standard emphasizes the involvement of "Top Management", (e.g. the Board) in the quality management process. In this context customer satisfaction and continual improvement are of particular concern. The new standard promotes the adoption of a process-approach. Processes convert inputs into outputs. They have first to be identified, then managed and linked to other processes. They form part of a system and can extend beyond the boundaries of the organization. Once a process is identified and appropriately defined, the following points should be checked:

- are responsibilities assigned (e.g. process owners nominated)?
- are the procedures implemented and maintained?
- is the process effective and providing the required results?

Relationship with ISO 9004:2000

ISO 9001:2000 and ISO 9004:2000 are two stand-alone documents which were designed to be a consistent pair of standards. ISO 9001:2000 defines the requirements which have to be fulfilled in order to accomplish compliance with customer needs and continual improvement of the Quality Management System. In addition, if considered necessary, this standard can be used to achieve third-party certification. ISO 9004:2000 develops the concept in a more extensive and intensive manner as a roadmap for organizations on their way to excellence with links to:

- The EFQM Business Excellence Model
- The Balanced Score Card Approach

Compatibility with other management systems

The standard has been made compatible with ISO 14001:1996 "Environmental management systems – Specification with guidance for use" and should assist users in implementing (and certifying) both quality and environmental systems. The common requirements in both standards (such as continual improvement of the processes, training, auditing and documentation) will facilitate auditing, and integration, if desired by an organization.

One can easily infer that the ISO 9001:2000 series are an excellent complementary fit to the GMP requirements, and additionally addresses the concerns of the authorities, e.g. as raised in FDA's GMP for 21^{st} century initiative mentioned earlier.

CONCLUSION

In the past, some organizations established QMS procedures and forms separately or on top of regular operations management procedures in order to pass audits and get a required certification. Many older QMS processes focused on generating the paper trail necessary for evidence in a checklist-based certification process. However, the new ISO 9001:2008 QMS standards require more. The new standards are process-based versus checklist-based and require that a company walk auditors through normal every day processes demonstrating mechanisms that enforce disciplines dictated by the QMS requirements—disciplines that identify, manage and control any risk of missing quality goals throughout the entire product realization process. Instead of treating a QMS as a side initiative required for compliance, organizations can take a new look at their existing business processes and enterprise systems to optimize not just QMS compliance, but optimize the entire performance of business operations. Perhaps filling gaps where necessary and integrating systems with risk management, process control and quality management in mind. The improved procedures and processes will not only provide compliance, but will also reduce cost, improve product quality, and ultimately improve customer satisfaction and the bottom line.

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