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## Review Article



## Covering Global Pharmaceutical Regulations in a Quality System

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### ABSTRACT

This article describes how to address compliance with a wide range of applicable regulations within a company's quality system. The focus is on the way regulatory intelligence can be obtained and subsequently be interpreted within the quality system. Roles and responsibilities of those involved are also discussed.

Regulatory agencies try to harmonise regulations regionally and to some extent globally, but that still requires a lot of work. To remain up-to-date with the Good Practices, i.e. remain in a continued state of compliance, one needs to be aware of the regulations, interpret their impact on the quality system and operations, and if necessary, then change, adapt and improve these. This process is a continuous improvement process cycle in Pharmaceutical Industries (1).

**Keywords:** Quality system, regulatory intelligence, QMS, SOP, data integrity (DI), SME.

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### 1. Introduction

Many pharmaceutical companies operate internationally, if not globally. Therewith comes the obligation to comply with the regulations in force in all these countries. As there is only limited regulatory harmonisation, this can be a daunting task. A company's quality system describes what regulations the firm intends to or must comply with and how this is achieved. The quality system is a "translation" of the regulatory requirements, i.e. the law, into a company's procedures and processes. The quality system has to comply with the current regulations and for that reason a company needs to have a system of regulatory intelligence in place, in order to know which regulations are in force or are expected to come into force. Regulatory Intelligence also needs to encompass guidelines or advice available that assist in interpreting the spirit and meaning of said regulations.

The quality system is subject to regulatory inspections and client audits, which will scrutinise the system for compliance. Minimising the regulatory risk of non-compliance is important, as regulators generally share information of the compliance status of a company with each other, and often also with the public.

#### *Understanding regulatory requirements*

A quality system must be appropriate for a company's present and planned range of products and markets, be of the right structure and contents for the specific organisation and of course be compliant with the applicable laws and regulations. Thus, there are no two quality systems that are the same; even quality systems for different sites within the same organisation usually have some differences due to organisational or operational differences. This article focuses on the regulatory compliance aspect of the quality system.

Clearly, the owner of the quality system is the quality unit, or more specifically, Quality Assurance (QA). That defines the ownership. But who has to abide by the quality system and who has to support it? That is everyone in the company who performs activities that fall under the relevant healthcare regulations. For the specific task of gathering information on regulations, guidances and best practices, generally referred to as Regulatory Intelligence (RI), companies have varying approaches. Certainly, the quality unit must have knowledge of the regulations and so must the Regulatory Affairs (RA) department. In addition, there should be perhaps more product, process or equipment specific regulatory knowledge in the operations department. This is best illustrated by an example:

Company A aseptically manufactures a drug product for parenteral use. They use Water for Injection (WFI) for that purpose in their manufacturing process. The product is then sold in the European Union and the USA. The **Table 1** WFI guidance information

Department	EU Regulations	US Regulations
Quality Assurance	EudraLex Vol 4 EMA reflection papers and Q&A	21 CFR 210 & 211
Quality Control Laboratories	European Pharmacopoeia	US Pharmacopoeia
Regulatory Affairs	Marketing Authorisation Application	New Drug Application
Utilities Department	Industry best practice for biofilm remediation and prevention of rouging	Industry best practice for biofilm remediation and prevention of rouging
Engineering Department	ISO standards	ASTM standards

departments are asked to provide input regarding relevant regulations and guidances. Following feedback from the departments, table 1 was prepared.

This example shall illustrate the importance of involving all interested parties in the Regulatory Intelligence activities. It also shows the wide range of standards, laws, guidances, etc. available or in force, and which must or should be adhered to.

As mentioned before, these need to be incorporated into the quality system. Using this example, the quality system may require WFI to be produced by distillation as the EU authorities did not permit the use of reverse osmosis until recently. The laboratory testing instructions will be designed to comply with both pharmacopoeias. The preventive maintenance instructions for the utilities team will be written based on industry best practice information and the engineering department will have design, build and commissioning instructions that conform to the respective industry standards, depending on the location of the facility. What can be gleaned from this short description is that companies will always strive to harmonise in order to simplify and thereby minimise cost.

## 2. Gathering Regulatory Intelligence

Of course, the above example (sending out a request for information) is not a sensible way for gathering RI. Instead, RI must be a formalised process that is effective in finding the relevant information (filtering out irrelevant information), finding it as soon as possible, disseminate it to the interested parties, and if necessary analyse and interpret the information. Some companies have dedicated teams for RI, whereas others may rely on individuals or a particular department for that purpose. It is not possible to provide guidance on the best option as it all depends on a variety of factors, not least the size and complexity of a company.

Irrespective of the organisational assignment for RI, the sources and resources for RI can be accessed by any company. These include:

- Regulatory agency websites
- Regulatory agency email updates or alerts
- Regulatory agency conferences or webinars
- Industry Association websites (e.g. Drug Information Association (DIA), International Society for Pharmaceutical Engineering (ISPE),

Parenteral Drug Association (PDA), Regulatory Affairs Professionals Society (RAPS))

- Industry Association email updates or alerts
- Industry Association conferences or webinars
- Publications (e.g. books, magazines, journals, white papers)
- Specialist Regulatory Intelligence providers' databases (e.g. Cortellis)
- Conferences or webinars
- Internet searches
- Personal contacts

There are thus a lot of resources available and many of these are free, or accessible for a reasonable annual fee. A company must evaluate, preferably as part of their RI strategy, which sources are of importance to them and who will need to have access to these.

As mentioned, some companies have a dedicated team of quality and regulatory affairs personnel who actively search for new regulations, guidances, industry best practices, etc. relevant to the specific operations of the company. To do so, the team may pay service providers who specialise in this activity. The advantage of using such subscription services is that one obtains English translations, or at least summaries, of regulations published in other languages. The team then collates the information, may annotate, group or otherwise enhance it before distributing to interested parties within the company (e.g. the quality unit, managers, etc.).

It is important to understand the nuances of each regulatory authority and take the appropriate steps to fully abide by each set of standards. Some agencies wish to see their regulations specifically stated in a company's quality system, whereas others are satisfied with a generic statement (e.g., "we comply with all applicable laws and regulations in the markets we operate in") about compliance.

In addition to a generic statement, companies should consider including a list of the regulations (e.g., 21 Code of Federal Regulations 210, 211, and 820; EudraLex Volume 4 Part II) in their quality manual or similar high-

level document. It may otherwise be unclear, which regulations the firm knowingly wishes to comply with. Including a list of regulations will help ensure transparency, especially in the case of audits or inspections (2, 3).

Obviously, for a company that operates in many countries, this can become quite an onerous thing to document. Here, a risk-based approach is recommended. There are some world-renowned regulatory agencies, some regulations that are widely accepted as global standards and some key industry best practices that are being recognised by the majority of agencies and industry partners. It is therefore not unusual to find in a quality system for example a mention of EU and US current Good Manufacturing Practice (cGMP) regulations together with the Good Automated Manufacturing Practice Guide Volume 5 (GAMP5).

Once a company has clarified, which regulations they intend to comply with, it is necessary to demonstrate how compliance with all the countries' regulations is assured and what documented evidence for this will be provided. Inspectors from regulatory agencies often prefer organisations demonstrate compliance through established processes and documented evidence. All too often, companies list within their standard operating procedures (SOPs) a series of regulations pertinent to the subject of the SOP (e.g., International Council for Harmonization [ICH] Q9 in a risk management SOP). Merely listing a regulation, however, doesn't demonstrate that relevant personnel have read, understood, and implemented it into the QMS. There must be a process by which dedicated persons or teams assess regulations for their applicability to the company's operations, and then implement these into the QMS. Documenting this process provides the necessary proof of compliance.

The intellectual assessment how a new or changed regulation affects the company, its quality system and operations, has to be made by the subject matter experts (SME). Although the quality unit will have a lot of expertise, they are not the SMEs for all and everything. Let us take the case of the recent guidance on data integrity (DI) from various agencies. Owners of automated systems (say the operations manager) together with an IT specialist need to examine the validation and the operation mode of that system for compliance with the DI guidance. The quality unit may be of assistance, but they are not the SMEs for the automated system. On the other hand, quality assurance needs to review the quality system to assure that it contains all the required DI elements. Thus, assuring continued compliance is a team effort! (4)

### 3. Harmonisation efforts

In principle, regulatory agencies try to harmonise regulations regionally or even globally. Therefore, if a company is in substantial compliance with say European Union and USA regulations, they are probably substantially compliant with many other regulations, bar some specific differences. A typical example of a significant harmonisation effort is the ongoing revision of Annex 1 to EudraLex Volume 4, where feedback was sought from many regulatory agencies from outside the

European Union. Despite the best harmonisation efforts, there are likely to remain some local peculiarities.

As mentioned, it is necessary to maintain compliance with current regulations and thus any regulatory change must be assessed for its impact on the QMS. This assessment may require a review of all documents in a QMS, unless the company maintains a matrix (e.g., in a spreadsheet or relational database) that shows which regulation translates into which documents (e.g., SOPs) within a given QMS. Such a correlation matrix has another important benefit: should you plan a change to a system, process, or document, you could easily verify if this is permissible under the regulations impacted by the change.

It is unlikely that such a matrix is 100% complete, covering all and every regulation from every country operated in. However, taking a detail-oriented, risk-based approach helps ensure the countries and regulations most critical to one's operations are covered.

This article focuses on pharmaceutical healthcare regulations, but of course, many companies have a range of products, including medical devices, food, Traditional Chinese Medicines, etc. In such cases it is usually recommended to create the above-mentioned relationship information matrix on a product type basis, rather than try and put it all into one single matrix. There are various reasons for this, not least the fact that terminology can vary tremendously (e.g. validation for a drug product is fundamentally different from validation for a medical device) and that the expectations (e.g. for documentation) also differ significantly.

Due to the advancement in Information technology, regulatory authorities from regulated countries throughout the globe started to accept data in electronic format either in eCTD (Electronic common technical document)/ Nees (Non eCTD electronic submission) (5).

The international protection of IPR assumes far greater importance today because of the huge amount of cross-border business. As such, the role of organisations, such as the World Intellectual Property Organization, becomes very important in order to seek harmony amongst national laws. The international treaties have formulated rules in relation to areas such as international filing, disclosure, and compulsory licensing. These treaties and conventions contribute to the process of harmonisation of IP laws (5).

Advancement in terms of quality of pharmaceutical products can be achieved through quality management systems that conform to international quality standards like those promulgated by key regulatory agencies (e.g. FDA, MHRA, WHO) and in terms of technology these can be achieved by improving local R & D capabilities and applying modern approaches to quality, as formulated e.g. in ICH Q8 and ICH Q11- QbD (Quality by Design) (5).

There is thus a concerted effort globally to harmonise pharmaceutical healthcare regulations as much as is possible, which in turn will benefit not only patients, but also the pharmaceutical industry (5).

### Agility

Some regulatory agencies change or issue new regulations at a fast pace (e.g. the Chinese regulatory agency, the China National Drug Administration (CNDA) has issued over a hundred documents in recent years), which requires constant monitoring and assessing for relevance to the company's quality system. Where these are identified as being applicable regulations, the quality system may need to be changed accordingly.

Quality systems are documented in a variety of documents, ranging from policies to Standard Operating Procedures (SOPs), to Work Instructions, Manuals, etc. - all of which could be impacted and need changing. The more complex the documentation structure, the more paper-based the system, the more complex and complicated it becomes to affect changes.

Really, in a 21st Century Company, the quality system and its management have to be agile or compliance is likely to get compromised. There are plenty of automated solutions available for managing quality systems in such a manner. Linking these with regulatory intelligence information is a logical step.

#### 4. Conclusion

Harmonisation efforts continue between regulatory agencies, but differences will remain. To remain current with the Good Practices, i.e. remain in a continued state of compliance, one needs to be aware of the regulations, interpret their impact on the quality system and operations, and if necessary, then change, adapt and improve these. This is all part of the never-ending continuous improvement cycle within the pharmaceutical industry.

At the same time, companies evolve, expand, merge, etc., all of this resulting in a change of circumstances that has to be reflected within the quality system. Therefore, aligning regulatory changes with a changing quality system is a continual necessity.

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#### Conflict of interest

The authors declare that there are no conflicts of interest.

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