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SHORT COMMUNICATION

Importance of quality risk management in pharmaceutical quality systems: Recent trends and harmonization

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Abstract In July 2013, the World Health Organization (WHO) of the United Nations finalized the Annex 2 of the new Technical Report 981 that is the WHO guideline on the implementation of a Quality Risk Management system. In general, alignment of the WHO requirements with the harmonized guidelines means consensus with the harmonized European, US and Asian regulations. In this short communication some aspects and the role of quality risk management (QRM) in the pharmaceutical quality systems (PQS) are discussed.

1. Introduction

Pharmaceutical Quality Assurance (QA), in general, is the complex entirety of all activities, arrangements and responsibilities required to ensure that the medicine reaching the patients is safe, effective and of standard quality. In the industrial practice, QA is a wide-ranging-concept covering all factors those individually or collectively influences the final quality of any medicinal product (ICH Q7A, 2000; EMEA, 2012; FDA, 2003; HC, 2011; SFDA, 2011).

Current Good Manufacturing Practice (cGMP) rules are the collection of recommendations that oblige the producers – by the force of law! – to take proactive steps in order to maintain consumers' safety. That means GMP is aimed primarily to reduce the risk inherent in any pharmaceutical production by assuring that the product is free from cross-contamination or any hazardous error of the production. Thus, cGMP is the part of QA activities in order to ensure that products are consistently produced and controlled to the quality standards and are appropriate to their intended use as required by the medicines regulatory authorities (MRAs) (see e.g. Mohammed-Ziegler, 2012). As it is said "the basic concepts of QA, GMP, and quality control are inter-relating" (HC, 2011). Obviously, a well-established, robust quality system is a fundamental expectancy of pharmaceutical authorities.

Pharmaceutical Manufacturers have to fulfill the GMP requirements of every country where their products are

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marketed. Certainly, countries have their own national MRAs those are responsible for setting the regulations, controlling the pharmaceutical producers (including inspections) and issuing certificates, such as marketing authorizations and certificates of acceptance. Since the many different national rules became cumbersome in the international market, thus the need aroused already in the '90s to harmonize. Therefore, the International Conference on Harmonization (ICH) started a hard process to harmonize the pharmaceutical regulations of the European Union, the United States and Japan with the participation of both industrial and regulatory organizations. Much effort has been concentrated until the harmonized tripartite GMP guideline was issued in 2000 (ICH Q7A, 2000) as a collection of recommendations.

2. State of the art and the role of World Health Organization

At the end of the '90s the technical/technological development of the industrial production evoked the change of the regulations that resulted in a shift in the quality concept. As a result, ICH issued the "A New Vision for Ensuring Product Quality" that addressed a "harmonized pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science" (see Mohammed-Ziegler and Medgyesi, 2012). The latest harmonized guidelines were written on the "Quality Risk Management" (ICH Q9, 2005), "Pharmaceutical Quality System" (ICH Q10, 2008), "Pharmaceutical Development" (ICH Q8(R2), 2009), and "Development and Manufacture of Drug Substances" (ICH Q11, 2012).

In 2011 the US Food and Drug Administration (FDA) has issued the guidance on process validation, updating its 1987 document to incorporate advances in manufacturing technology and thinking. These recommendations span the three stages covered by process validation, namely process design, process qualification and continued process verification.

In the recent years, numerous guidelines have been revised according to the need for technical development of the industry and the global pursuit to harmonize the different national GMP rules around the world. The current trends of changes in the GMP arena show that requirements are becoming more consistent globally as illustrated by the examples in Table 1. In spite of the continuous harmonization efforts, manufacturers have to be aware of the differences as e.g. the differences of the Indian and European GMP regulations for API production were just recently discussed in detail (Drug Regulations, 2013). This extensive comparison shows that the ICH Q7A-based EU GMP Part 2 rules are more comprehensive and detailed in many areas than the Indian GMP regulations.

The World Health Organization (WHO) as the global authority of health matters, sets norms and standards internationally and, as such, has been an observer from the beginning of the work of ICH. Thus, the new WHO guideline facilitates the expansion of the harmonized quality concept by adopting the corresponding harmonized regulations around the world. A draft guideline on quality risk management (QRM) had already been issued in 2010, and after various stages of commenting it was revised several times until the present, final format was reached during the summer in 2013. The aim of the WHO guidelines is to assist the development and implementation of effective QRM, covering activities such as research and development, sourcing of materials, manufacturing, packaging, testing, storage and distribution. Annex 2 (WHO, 2013) is directed to both, manufacturers and MRAs.

3. Quality risk management

ICH Q10 describes two enablers of the PQS (ICH, 2008):

(1) Knowledge management: It is "a systematic approach to acquiring, analyzing, storing and disseminating information related to products, processes and components." In general, experience in the development using scientific approaches provides knowledge about product and process understanding. This understanding forms the base of keeping the production under control.
(2) QRM: "is the overall and continuing process of appropriately managing risks to product quality throughout the product's lifecycle in order to optimize its benefit–risk balance. It is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product" as defined by Annex 2 (WHO, 2013). In the practice, QRM is a systematic process consisting of risk identification, risk assessment, risk mitigation, risk avoidance/reduction and communication. Although, the WHO guide allows the application of QRM both proactively and retrospectively, the proactive QRM ensures the opportunity to take efficient preliminary actions in case of need.

The importance of QRM became more pronounced when FDA published the new regulation on process validation (FDA, 2011). The essence is that quality has to be built in the product already from the stage of design and therefore, technological decisions have to be established based on true scientific justification through the course of quality risk analysis. All attributes and parameters concerning production should be evaluated in terms of their roles in the process and impact on the product or in-process material, and reevaluated every time when new information becomes available. "Thus, risk assessment conducted prior to initial commercial validation batches can highlight the areas where particular focus and data are needed to demonstrate the desired high level of assurance of commercial process robustness" (Mohammed-Ziegler and Medgyesi, 2012). In agreement with both ICH Q10 guide and FDA's process validation guide, WHO states that "the level of effort, formality and documentation of the QRM should be commensurate with the level of risk".

The new guideline (WHO, 2013) depicts the WHO approach to QRM based on the model described in ICH Q9 earlier, as illustrated in Fig. 1.

Quality risk management can be useful for both MRAs and manufacturers. MRAs can use QRM to optimize (a) choice of manufacturing sites to be inspected, (b) inspection frequency and areas to concentrate more effort, and (c) to find the best allocation of resources. In case of pharma producers, the application of QRM can be advantageous throughout the whole lifecycle of any pharmaceutical product. Thus, "it should be an integral element of PQS" as it is emphasized in the guideline (WHO, 2013).

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Table 1 Selected examples of recent changes in national GMP regulations.

Authority	Document(s)	Date	Goal	References
EU/EMEA	EU GMP chapter 1.	31st January, 2013 (effective)	The general concept of ICH Q10 and the lifecycle approach were incorporated	EMEA (2012)
Canada/Canada Healthy	GMP (GMP) for active pharmaceutical ingredients (GUI-0104)	8th May, 2013 (published)	To implement GMP requirements for APIs according to ICH Q7A	HC (2013)
Mexico/ COFEPRIS	GMP of active pharmaceutical ingredients	25th June, 2013 (published)	To make the country's requirements to be comparable to those issued by the EU	COFEPRIS (2013)
China/CFDA	Good quality control standards for drugs	1st July, 2013 (published)	To become consistent with the WHO GMP (new GMP rules since 1st March 2011)	CFDA (2013)
Australia/TGA	e.g. Residual solvents, bioanalytical method validation	1st June 2013 (effective)	Some European and ICH guidelines were adopted	TGA (2013)

(a) Development stage (or Stage 1 in FDA, 2011): Application of QRM is cardinal during the development of medicinal products (see e.g. Mohammed-Ziegler and Medgyesi, 2012) in order to develop the finished pharmaceutical product (FPP) according to the quality target product profile (QTPP), i.e. the complex entirety of all predetermined characteristics those form the basis of drug product formulation and process development. That means the QRM process is intended to support the acquisition of sufficient product and process knowledge to assess risk associated with the commercial production of the medicinal product. Thus, it is obvious for the practitioner that the two enablers of PQS, i.e. QRM and knowledge management (ICH Q10, 2008) are in strong connection with each other. Consequently, results of QRM support the product development and the establishment of control strategy, in a well-documented manner. It can be noted that WHO also consider bioavailability as an aspect of risk above safety, efficacy and quality of FPP (WHO, 2013).

(b) Transfer activities (or Stage 2): The process of knowledge transfer (e.g. scale up) and the whole product development history can be facilitated by QRM. It also helps to communicate with all relevant parties involved in the QRM, since methodology of QRM is based on teamwork.

(c) Commercial production (Stage 3): Since QRM serves with a systematic analysis on the product and its production process, it is expected to ensure the best scientific rational for any of the improvement. QRM principles can be used to determine the scope of qualification. They can also be used to determine the optional schedule for maintenance, monitoring, calibration and requalification. In agreement with the principles of QRM, these guidelines recommend that process validation embraces the product life-cycle concept. Any change related to the manufacturing process can be handled based on the details of QRM within the frame of the change management system and, thus, criticality of the change and decisions on follow up activities can also be decided on the same basis.

In general, the benefits of QRM are (i) it helps to reduce the overall cost since it supports more qualified decision making in the planning stage; (ii) it promotes quality, through increased efficiency and knowledge transfer with strong potential to reduce catch-up work that is done to mediate the effects of poor quality; (iii) it is an iterative and continuous process where risk is either mitigated or recognized prior to becoming a problem and reviewed in a predictive manner for the future; (iv) it provides a mechanism for risk communication and exposure to management; (v) provides framework to better understand processes: what is critical and why; (vi) it provides rationale for not spending time on low risk activities, process events, or systems rather focusing resources and time on the things that are really important.

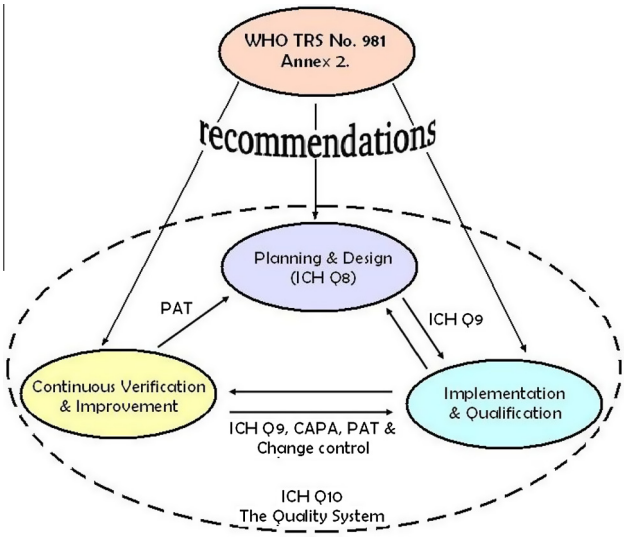

Figure 1 Recommendations of WHO TRS No. 981 Annex 2. Within a comprehensive pharmaceutical quality system (extended based on Amer, 2010).

The importance of a complying documentation system and a well-structured archive is underlined. One of the reasons is that companies are required to communicate with MRAs, as well, both in the form of applications and inspections. The essence of the guide (WHO, 2013) is summarized: "QRM activities are focused on the product/process development and product manufacturing, ultimately to ensure a robust, safe and effective FPP."

4. Conclusions

The changing attitude of guidances and authorities, and the competitive economical environment of the pharmaceutical industry requires the continuous improvement of the pharmaceutical quality system of manufacturers. All aspects of the production that may influence the quality of the final product, and in turn the risk of the patient being inherent in medicinal products, have to be controlled in an extremely complex manner. QRM activities are usually, but not always, undertaken by a matrix of interdisciplinary teams. When teams are formed they should include experts from the appropriate areas (quality unit, business development, engineering, regulatory affairs, production operations, sales, marketing etc.) in addition to individuals who are knowledgeable about the QRM process. Risk assessment is expected to be conducted prior to initial commercial batches in order to highlight the areas where special focus and data are needed to demonstrate the desired high level of assurance of commercial process robustness. Consequently, technological decisions must be established based on true scientific, risk-based justification to maximize benefits from innovation and continual improvement.

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