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A risk management ontology for Quality-by-Design based on a new development approach according GAMP 5.0

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ABSTRACT

A new approach to the development of a risk management ontology is presented. This method meets the requirements of a pharmaceutical Quality by Design approach, good manufacturing practice and good automated manufacturing practice. The need for a risk management ontology for a pharmaceutical environment is demonstrated, and the term "ontology" is generally defined and described with regard to the knowledge domain of quality risk management.

To fulfill software development requirements defined by good manufacturing practice regulations and good automated manufacturing practice 5.0 for the novel development approach, we used a V-model as a process model, which is discussed in detail. The development steps for the new risk management ontology, such as requirement specification, conceptualization, formalization, implementation and validation approach, are elaborated.

1. Introduction

In recent years a paradigm shift has taken place in pharmaceutical drug-product and manufacturing-process development. The so-called "Quality by Design" (QbD) approach described in the ICH guidelines ICH Q8(R2) "pharmaceutical development" (ICH, 2009), ICH Q9 "quality risk management" (ICH, 2005) and ICH Q10 "pharmaceutical quality system" (ICH, 2008) aims to replace empirical methods in drug and process development by a science- and risk-based approach. In addition to a deeper scientific understanding of products and processes, risk management and knowledge management are considered critical for the implementation of this new paradigm.

During a pharmaceutical development and risk management process, significant amounts of information and data are generated. However, they have to be handled, managed, re-used and shared over the entire lifecycle of a drug product. The use of knowledge management during the entire product lifecycle is emphasized by the ICH Q10 guidelines (ICH, 2008), defining it as a "systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes and components." Holm, Olla, Moura, and Warhaut (2006) defined the general objective of knowledge management as "getting the right information to the right people at the right time" such that the information can be used more effectively. Thus, knowledge management – in addition to risk management – is a key instrument helping pharmaceutical product and process developers and manufactures to implement QbD according to the ICH Q8, Q9 and Q10 guidelines. A possible integrative approach, including knowledge management as a distinct element of QbD, is illustrated in Fig. 1. However, the ICH Q10 guidelines neither recommend nor describe any knowledge management methods or tools for its implementation.

In contrast to knowledge management, risk management accompanying the entire pharmaceutical product lifecycle is considered state-of-the-art since the ICH Q9 guidelines "quality risk management" was published in 2005 (ICH, 2005). ICH Q9 defines risk management as a "systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle." Moreover, the related medical device industry uses a similar risk management process described in ISO 14971:2007 (ISO, 2007). Currently, the typical results of a risk assessment/risk control process are paper-based documents or databases, i.e., the knowledge gained is captured in paper-based documents or stored in isolated databases. As a result, the knowledge cannot be automatically shared by various users of the product throughout its life cycle. Communication and reuse (and to a certain extent re-generation) of the knowledge is therefore time-consuming and inefficient. Furthermore, the knowledge

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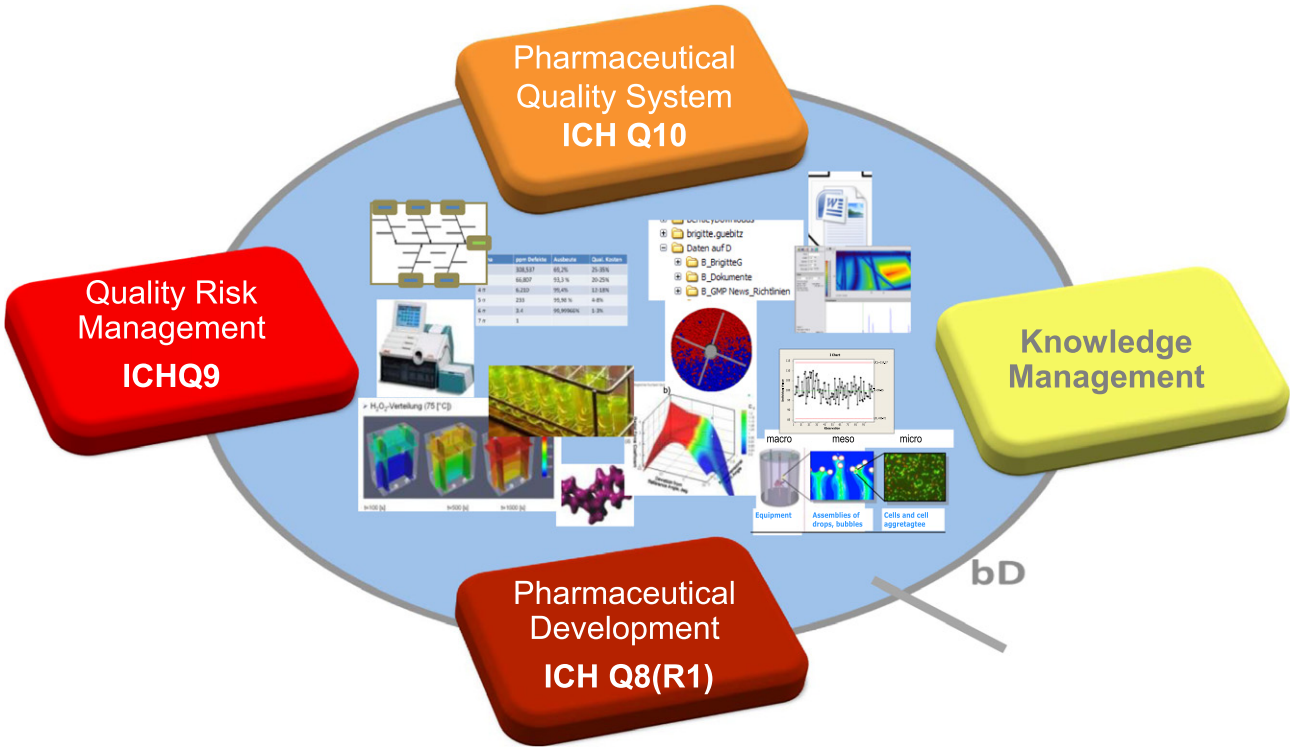

Fig. 1. Knowledge management as a key step in QbD.

cannot be analyzed and updated automatically, and as a result, a comparison with the experience gained later in the process is often extensive and error-prone. Thus, from a knowledge-management point of view, current risk management is data-rich yet knowledge-poor. This is illustrated in Fig. 2, which partly depicts the so-called knowledge staircase (North, 2002). As can be seen, using conventional risk management tools companies typically operate at the data level. However, by using ontology-based methods as knowledge-management tools one can reach the level of knowledge also for the risk management process. This idea is shown in Fig. 2 by the up-pointing arrow.

For that purpose, several ontologies for risk analysis and other pharmaceutical applications were developed and published over the past years. Examples include an ontology approach to support failure mode and effect analyses (FMEA) by Ebrahimipour, Rezaie, and Shokravi (2010) and Dittmann (2007), a computer support system for the management of regulatory compliance of pharmaceutical processes (Sesen, Suresh, Bañares-Alcántara, & Venkatasubramanian, 2009) and organizational risk ontology approaches by NASA (NASA, 2004). These risk-oriented ontologies allow domain experts to share information, respectively knowledge, gained during risk-analysis and risk-control processes. However, most of these ontologies only focus on one single risk-assessment tool and do not consider the implementation of an overall risk-management process. In addition, a systematic development methodology, e.g., according to the pharmaceutical industry standard "good automated manufacturing practice (GAMP) 5.0" (ISPE, 2008) is currently absent. According to GAMP 5.0, ontologies – as customized applications – are high-risk software tools (category 5 Software by GAMP 5.0) and, therefore, have to be thoroughly specified and tested. For the use of ontologies in a product-related pharmaceutical environment, GAMP 5.0 requires a detailed and systematic development approach.

Therefore, in this study a new development strategy for ontologies using a V-model according to GAMP 5.0 is described. All relevant steps of the specification are discussed in detail, and an overview of the subsequent testing phases (i.e., the validation steps) is given.

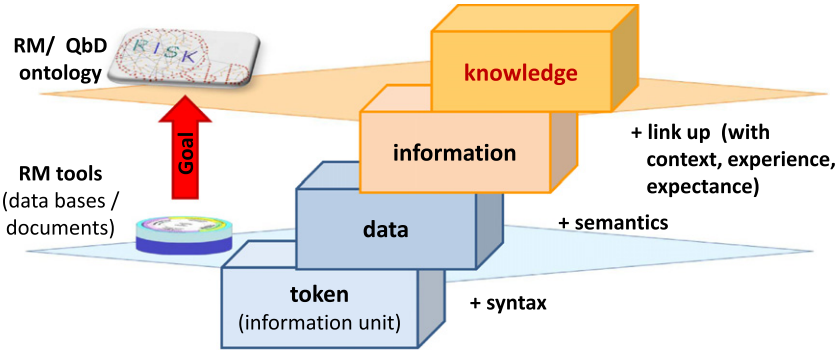

Fig. 2. Knowledge staircase for quality risk management process.