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Use of mechanistic simulations as a quantitative risk-ranking tool within the quality by design framework

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ABSTRACT

The purpose of this study is to evaluate the use of computer simulations for generating quantitative knowledge as a basis for risk ranking and mechanistic process understanding, as required by ICH Q9 on quality risk management systems. In this specific publication, the main focus is the demonstration of a risk assessment workflow, including a computer simulation for the generation of mechanistic understanding of active tablet coating in a pan coater. Process parameter screening studies are statistically planned under consideration of impacts on a potentially critical quality attribute, i.e., coating mass uniformity. Based on computer simulation data the process failure mode and effects analysis of the risk factors is performed. This results in a quantitative criticality assessment of process parameters and the risk priority evaluation of failure modes. The factor for a quantitative reassessment of the criticality and risk priority is the coefficient of variation, which represents the coating mass uniformity. The major conclusion drawn from this work is a successful demonstration of the integration of computer simulation in the risk management workflow leading to an objective and quantitative risk assessment.

1. Introduction

Quality by design (QbD) has by now become a well-known and widely accepted science- and risk-based regulatory approach that focuses on safety, efficacy and quality throughout the product's life cycle. It is increasingly used in the pharmaceutical industry to implement the vision of cost-efficient, market-oriented and high-quality products for patients (Aksu et al., 2012; European Medicines Agency, 2009; Kessel, 2011). Within the QbD framework risk-based approaches for quality assurance play an important role. Applying the risk-based approach via quality risk management (QRM) leads to a continuous improvement of process performance and product quality (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2008). Furthermore an effective application of QRM throughout the product's life cycle offers increased flexibility and reduced risk of product failure, as described in the International Conference on Harmonization (ICH) Q9 document (World Health Organization, 2010). Since this document was published, the regulatory requirements for assessing, controlling, reviewing, and communicating risks have become an integral part of the pharmaceutical quality system (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2005), supported by the implementation of decision loops to facilitate risk control (International Organization for Standardization, 2007).

Clearly, the effectiveness of the qualitative specification and the quantitative estimation of risks strongly depend on the underlying data and experience of individuals involved in the process. According to this fact, QRM initially identifies risks linked to the potentially critical quality attributes (CQAs), which characterize the products' quality (International Organization for Standardization, 2009a). These potentially CQAs (e.g., content uniformity of dosage units) are defined as "quantifiable and potentially critical characteristics" if a negative influence on the intended product's efficacy, quality and patient safety may occur (European Medicines Agency, 2009).

Understanding of the CQAs and the associated risks of failure is thus a critical part of the QbD approach. However, tools available for the risk assessment process are, to a large extent, based on qualitative decisions involving experts in the field (e.g., via FMEA or related tools), and a quantitatively exact framework is missing (Miláet al., 2012; Zimmermann and Hentschel, 2011). Therefore, in this publication we attempt to present a more quantitative

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approach, based on mechanistic modeling and simulations. As an example process, the coating of tablets was chosen. Specifically, an active coating process (i.e., the coating contains an API) was considered. Among other dosage forms, the ICH Q6A guideline describes the quality attributes (QAs) of solid oral dosage forms, such as tablets with active coating. One QA is the uniformity of dosage units, which can either be represented by the mass of the dosage form or the content of the drug substance in the dosage form (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1999). In our work, the focus is the potentially CQA "content uniformity of drug substance in the active coating", which is represented by the coating mass uniformity or inter-tablet coating variability.

Typically, experimental methods (mostly involving lab-scale equipment) have been used to study process influences on product quality and QAs. However, such studies are time-consuming and hard to perform on production-scale equipment (coating studies in full-scale coaters are highly demanding). In contrast, novel modeling and simulation approaches make it possible to investigate the impact of process conditions on product quality based on first principles and (which is a major advantage) at any desirable scale with any equipment type (Suzzi et al., 2012, 2010; Toschkoff and Khinast, 2013; Toschkoff et al., 2012).

Thus, in a quantitative risk assessment process, mechanistic simulations can play an important role: Such an "improved" risk assessment process would involve first the identification of failure modes based on an initial risk assessment. Second, a quantitative criticality assessment through risk priority evaluation would occur, both of which can be based on simulations. Lastly, product and process characterization could (at least partially) be guided by simulations. Thus, the gained mechanistic understanding may also support the process parameter (PP) definition and the screening studies within the QRM framework.

This is a new approach as demonstrated in Fig. 1. Although the ICH Q11 document already mentions the application of modeling and simulation for QRM during the development of manufacturing processes, model-based simulations have so far not been used to support the QRM process in a quantitative manner (European Medicines Agency, 2011; International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2004).

In this work we intend to support a quantitative risk assessment process by ensuring objectivity through the application of high-fidelity computer simulations (Fig. 1). The stepwise approach integrates computer simulation in DoE-based process parameter screening studies and in the verification of quantitative risk assessment. This stepwise approach was demonstrated by analyzing a tablet active-film coating process performed in a pan coater representing a common unit operation in the pharmaceutical industry.

2. Material and methods

2.1. The coating process

Most commonly, coated tablets are produced via drum coating, during which tablet cores are placed in a continuously rotating drum and sprayed from above. Due to the rotation, the tablets periodically enter and leave the spray zones of each spray nozzle. Concurrently, the coating layer is dried by evaporating the solvent with heated air (Cole et al., 1995). Perfect inter-tablet coating variability is achieved, if every tablet enters the spray zone for the same amount of time (Chen et al., 2010; Dubey et al., 2011; Toschkoff et al., 2012). Since this is not the case in a realistic process, perfect coating uniformity is never achieved. A minimization of the inter-tablet coating variability is, however, an important goal of process development nowadays (Tobiska and Kleinebudde, 2003).

Due to this fact, experiment- and simulation-based investigations focused on the coating and tablet mixing operations in various coating devices. For example, an experimental study by Porter et al. (1997) studied the coating uniformity, percent loss on drying and coating process efficiency to optimize the drug release profile based on DoE principles, including drying inlet air temperature, fluid spray rate, atomizing air pressure, pan speed and number of spray guns. In the work of Kalbag and Wassgren (2009) and Kalbag et al. (2008) the impact of tablet residence time within the spray zone on inter-tablet coating variability was studied as a function of the PPs pan speed, fill level and coating time. Furthermore, a computational study by Dubey et al. (2011) focused on the design of spray pattern amongst others. Toschkoff et al. (2012) identified the inlet air temperature, air flow rate, pan speed, spray nozzle position and spray nozzle direction as PPs with significant impact on spray loss, using numerical computational fluid dynamics (CFD) modeling. The sensitivity of the relative standard deviation (RSD) of the content uniformity to the variation of various critical coating PPs was evaluated by Chen et al. (2010). Just et al. (2013a) evaluated the PPs fill level, pan speed, spray rate, spray time and spray pressure for lab and pilot scale. One of the important conclusions was that the increase of the spray nozzle number in the pan coater leads to a significant impact on coating uniformity (Just et al., 2013a). Among others, these scientific findings provide the basis for the cause and effect analysis in this study.

2.2. Identification of process parameters

First, an initial identification of direct or indirect causes for non-uniformity of the tablet coating mass (Fig. 2) was performed. PPs for tablet mixing and coating, such as air flow, spray pattern, pan speed and fill level, as well as equipment design parameters, such as the spray nozzle position, angle and distance to the tablet bed were considered (Fig. 2).

This provides the basis for the assessment of potential failure modes via a quantitative ranking of the severity, the likelihood of occurrence and their detectability, described in the next section.

2.3. Initial risk assessment via PFMEA

2.3.1. Process failure mode and effects analysis (PFMEA)

Since its introduction as a risk assessment tool into pharmaceutical quality systems, many different approaches and standards have been published (International Electrotechnical Commission, 2006; International Organization for Standardization, 2009b; Liu et al., 2013; Stamatis, 2003). In general, a PFMEA uses the risk priority number (RPN) to classify the criticality of failure modes and the need of corrective actions. It is calculated by multiplying the assigned values for severity (S), occurrence (O) and detectability (D). For each class, scores are given by a panel of experts. Severity represents the effect of a failure that occurs during the process on the product quality or patient safety. It is classified as a numerical value according to the impact of the negative consequences. The occurrence characterizes the frequency of appearance of a failure. The detectability shows if the failure is easy to identify (Stamatis, 2003). For each of the three risk factors, the levels and their requirements are defined in a risk assessment catalog (Table 1). In this study we assigned odd numbers from 1 to 9, with five levels for each risk factor (International Organization for Standardization, 2009a).