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Application of ICH Q9 Quality Risk Management Tools for Advanced Development of Hot Melt Coated Multiparticulate Systems

Elena Stocker [1], Karin Becker [1], Siddhi Hate [2], Roland Hohl [3], Wolfgang Schiemenz [4], Stephan Sacher [3], Andreas Zimmer [1], Sharareh Salar-Behzadi [3, *]

[1] Department of Pharmaceutical Technology, Institute of Pharmaceutical Sciences, University of Graz, Universitätsplatz 1, Graz 8010, Austria
[2] Department of Industrial and Physical Pharmacy, Purdue University, Heine (Robert E.) Pharmacy Bldg, 575 W Stadium Ave, West Lafayette, Indiana 47907
[3] Research Center Pharmaceutical Engineering (RCPE) GmbH, Inffeldgasse 13, Graz 8010, Austria
[4] Hermes Arzneimittel GmbH, Großhesselohe, Germany

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ABSTRACT

This study aimed to apply quality risk management based on the The International Conference on Harmonisation guideline Q9 for the early development stage of hot melt coated multiparticulate systems for oral administration. N-acetylcysteine crystals were coated with a formulation composing tripalmitin and polysorbate 65. The critical quality attributes (CQAs) were initially prioritized using failure mode and effects analysis. The CQAs of the coated material were defined as particle size, taste-masking efficiency, and immediate release profile. The hot melt coated process was characterized via a flowchart, based on the identified potential critical process parameters (CPPs) and their impact on the CQAs. These CPPs were prioritized using a process failure mode, effects, and criticality analysis and their critical impact on the CQAs was experimentally confirmed using a statistical design of experiments. Spray rate, atomization air pressure, and air flow rate were identified as CPPs. Coating amount and content of polysorbate 65 in the coating formulation were identified as critical material attributes. A hazard and critical control points analysis was applied to define control strategies at the critical process points. A fault tree analysis evaluated causes for potential process failures. We successfully demonstrated that a standardized quality risk management approach optimizes the product development sustainability and supports the regulatory aspects.

Introduction

In 2004, the U.S. Food and Drug Administration published its final report on pharmaceutical quality and guidance for the industry on process analytical technologies, introducing a new regulatory framework for development of pharmaceutical manufacturing with enhanced product quality.[1-3] The ambition was to increase process capability, product development, and manufacturing efficiency, and to reduce product variability by improving product and process design, scientific understanding, and control strategies.[4] For this reason, the U.S. Food and Drug Administration encourages the application of Quality by Design (QbD) as a systematic holistic scientific and risk-based approach in drug product development, manufacturing, and regulation by identifying critical product characteristics and applying tools such as quality risk management (QRM).[4-7] With the International Conference on Harmonisation Q9 guidance and the International Organization for Standardization (ISO) standards such as ISO 14971, ISO 31000, International Electrotechnical Commission 31010, ISO 73, and IS/TR 31004, a selective and prospective QRM was provided for pharmaceutical research and development, production, and clinical testing.[8-13] Furthermore, the ISO/International Electrotechnical Commission Guide 51 defines risk as a combination of severity of harm and the associated probability of its occurrence and provides a guideline to reduce risk to a tolerable level.[14] The design and development of a robust drug product requires serious consideration of the physical (e.g., particle size distribution, polymorphism, and melting point), chemical (e.g., pKa, solubility, and stability), and biological (e.g., partition coefficient, bioavailability, and permeability) characteristics of a drug substance and of the selected excipients as well as their potential interactions.[4] These characteristics of the input materials (drug, excipients, intermediates) are defined as material attributes (MAs) and have a potential impact on the quality of the intermediate or finished drug

Elena Stocker and Karin Becker contributed equally as first author.

* *Correspondence to:* Sharareh Salar-Behzadi (Telephone: +43-316-873-30948; Fax: +43-316-873-1030948).
E-mail address: sharareh.salar-behzadi@tugraz.at (S. Salar-Behzadi).

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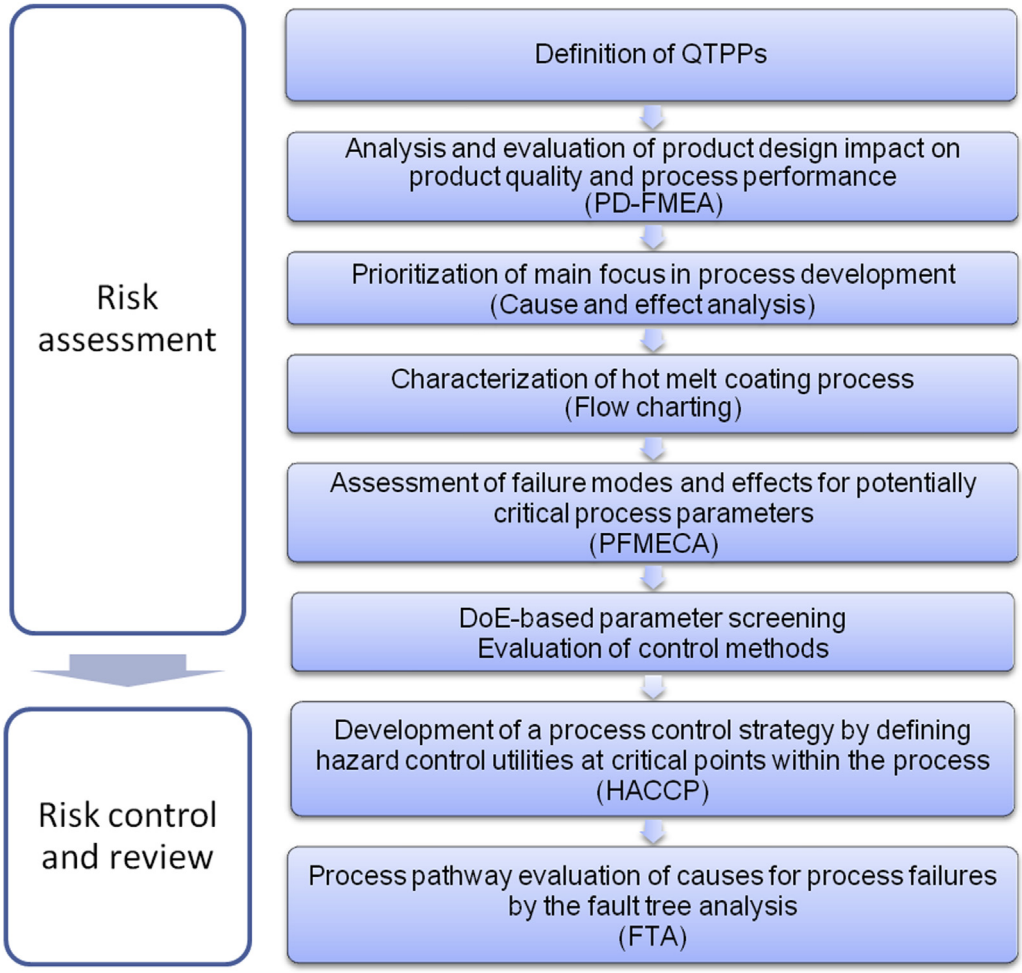

Figure 1. Step-by-step description of the QRM workflow including risk assessment, control, and review of the development of HMC process.

product.[4,15] The quality target product profile (QTPP) summarizes all quality attributes (QAs) of the output materials or drug products that should be achieved to ensure the desired quality by taking into account safety and efficacy of the drug product.[4,16] Further information included in the QTPP is the route of administration, the dosage form and strength, the container closure system, the pharmacokinetic characteristics, and the stability of the drug product.[4]

Critical quality attributes (CQAs) have been defined as the physical, chemical, biological, or microbiological properties or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product quality.[4,7] Risk assessment and scientific knowledge help to prioritize the critical material attributes (CMAs) posing a high risk to product quality, to identify the CQAs and the critical process parameters (CPPs) and to link CMAs and CPPs to CQAs.[4] Viable tools for this linkage and the identification of CPPs in pharmaceutical unit operations are the standard QRM tools, for example, the failure mode effects analysis (FMEA), cause and effect analysis (Ishikawa fish bone diagram), fault tree analysis (FTA), or hazard analysis and critical control points (HACCP).[13,17] Control charts, Pareto charts, or design of experiments (DoE) are mentioned in The International Conference on Harmonisation Q9 guideline as supporting statistical tools for a systematical operating approach within a predefined processing space based on prior knowledge.[13] Several pharmaceutical studies have been published using QbD and QRM to provide a risk-based and proactive approach for the development of robust formulations and the optimization of pharmaceutical processing.[18-22] Most of these studies applied FMEA, Ishikawa fish bone diagrams, or other tools such as qualitative initial risk-based matrix analysis in combination with statistical design to identify CPPs and CQAs and optimize various pharmaceutical unit operations.[18-22] Moreover, a biopharmaceutics risk assessment roadmap has been introduced as a powerful patient-centric approach for optimizing product development and performance. In this approach, therapy-driven target drug delivery profiles are used as a framework to achieve the desired therapeutic outcome, by considering the clinical relevance in the early formulation development stage and using biopharmaceutical tools to identify the potential challenges of product optimization for patient benefit.[23]

In the last years, applying *in silico* techniques has gained major attraction in the industry and academia for estimation of pharmacokinetics, pharmacodynamics, and toxicity parameters of compounds and formulations of interest.[23,24] Moreover, several theoretical mechanistic process modeling techniques such as computational fluid dynamics, direct numerical simulations, or the discrete element method have been developed to significantly reduce the number of required experiments.[25] For example, Stocker et al. and Adam et al. successfully integrated a discrete element method simulation within the framework of QbD and QRM and improved the scientific process understanding of a tablet coating and a blending unit