



CPPM for Effective Multivariate Risk Modeling for Life Cycle Management

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Regulatory initiatives such as ICH Q8, Q9, Q10, and effective process and product life cycle management (LCM) highlight the need for a science-based causal and mechanistic understanding of all up- and downstream processes to ensure the development and manufacture of a safe and effective product. This requires new levels of process and product knowledge, the ability to master the variability of relevant sources, and understand relationships between the process and product, as well as knowledge of all associated risks and their effect on product quality (Figure 1).

An adequate and universally applicable method is needed, therefore, to integrate available data, knowledge, and expertise and provide:

- Science-based modeling and process behavior simulation and its effect on product quality
- Multivariate quantitative quality risk management (QRM) that considers propagation of associated risks along the process and their effects on product quality risk

The causal process and product mapping (CPPM) approach provides these capabilities and offers a unique combination of scientific data, expertise, and multivariate quantitative risk assessment. The generality of the approach lends itself well to QRM applications at any life cycle stage for any development and manufacturing processes, providing model-based proactive solutions for LCM.

CPPM Methodology Background

A system's behavior is determined primarily by cause-and-effect interactions between its elements.⁴ System dynamics (SD) is a methodology³ first developed by Jay Forrester in 1950s¹ to help model and manage complex processes by mathematically documenting the factors and interactions that influence a system. Using that same approach, we built CPPM models for quality risk management in pharmaceutical manufacturing. This approach

leverages some of Forrester's core principles about gathering the complex process and product knowledge required to build an effective model and documenting it in a social/collaborative environment—in this case, a mixture of scientists and engineers who were specific subject matter experts (SME).

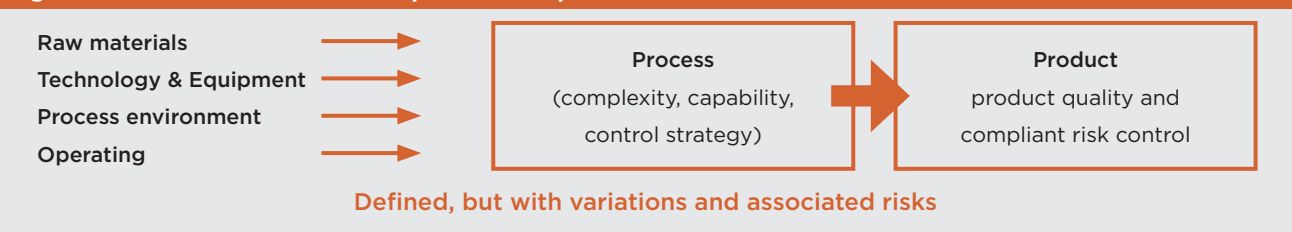
Using SD to document SME knowledge around the portion of the process in which they are experts, then linking these domains can provide a holistic model of the entire process. This can then be used to help the team build a testable model of their knowledge, which can validate their collective understanding. The approach helps overcome:

- Individual differences in perception and knowledge
- Practical limitations in identifying complex interconnections and thinking in causal networks
- Difficulties in processing multivariate individual experiences in a group

SD helps elicit the hidden assumptions that each SME holds by integrating them into more transparent and causal representation. This enhances understanding, consistency, and knowledge of data in addition to its implementation in the model-building process. It's important to note that the strategy should be considered complimentary to traditional integrated data-management strategies.² While the actual data around the processes is paramount, it's simply impossible to cover all possible variations—hence the need for the CPPM approach.

In summary, the CPPM methodology enables modelling and simulation of complex process behavior through comprehensive understanding of multivariate relationships, process and product variability, and associated risks. The approach requires a precise definition of the system boundary to be modeled; this will allow systemic process steering on operational, tactical, and strategic levels.⁷

Figure 1: Schematic illustration of process and product focus



The CPPM approach can be accomplished with a variety of software packages. We chose Vensim⁵ as it specializes in SD methodology⁶ and delivers a graphical interface that makes it easy to visualize the process and interact with the SMEs.

CPPM Models

CPPM allows scientific process and product modeling while capturing multivariate cause-and-effect relationships (including interaction feedbacks) between process parameters (PPs), material attributes (MAs), and product quality attributes (QAs). The approach also considers relevant context, conditions, and environment, such as prior knowledge and experience, data, process, and operation. The CPPM model represents complex process pathways and functions, enabling organizations to generate consistent (and common) understanding of cause-and-effect process and product relationships.

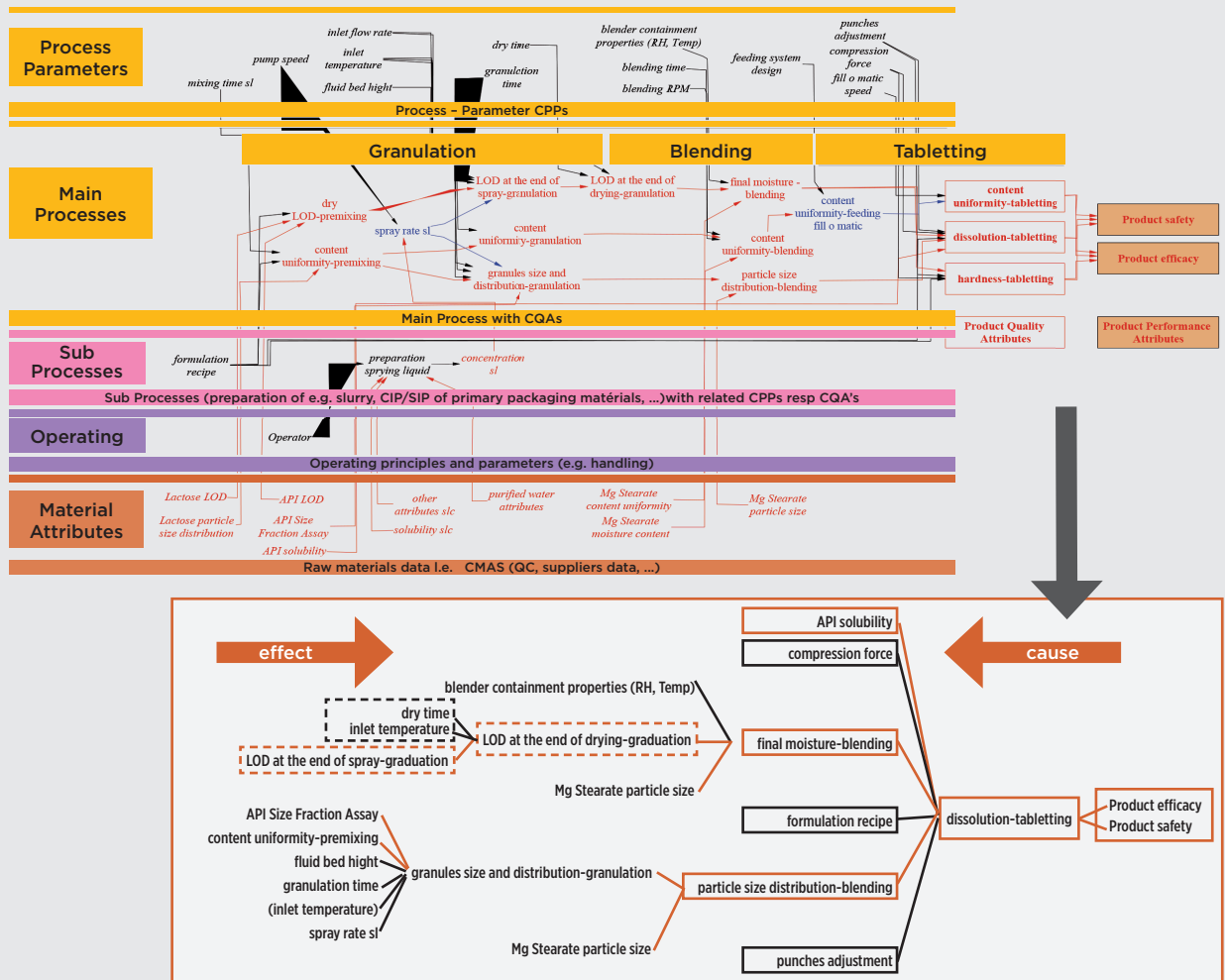
Each captured PP, MA, operation activity, and product QA is represented in the CPPM model as an individual variable. All causal relations, sketched as

graphical connections, are automatically captured as unambiguous allocated variable relations. A generic template for the approach was adopted to ensure a structured representation and understanding of the process and product.

A practical CPPM application can be demonstrated by a case study on a simplified solid manufacturing process. The qualitative CPPM model-building process begins by capturing all relevant PPs, MAs, and parameters that describe operation and product QAs and their causal relations. For any variable—such as the finished tablet dissolution QA—the automatically generated cause-and-effect tree captures the causal relations of process and product (Figure 2), showing us in an easily understandable way the process pathways at each step and along the entire process.

The finished tablet dissolution cause-and-effect tree, for example, identifies which PPs (e.g., compression force) MAs (e.g., API solubility), and intermediate product attributes (e.g., final moisture-blending) affect its attributes. Deeper tree levels manifest further product and process attributes: Blended material moisture is affected by Loss on Drying (LOD)

Figure 2: CPPM model of simplified solid manufacturing process and cause-and-effect tree with focus on finished tablet dissolution



of dried granules, which are in turn affected by drying process parameters (dry time, inlet temperature) and LOD at the end of the granulation phase. The effect of any PP, MA, and operation parameter on any product QA could be analyzed in similar way.

Cause-and-effect trees could be generated for any model variable, producing appropriate level depth in both directions, offering a deep understanding of causal process and product relationships, and enabling a multivariate cause-and-effect analysis with focus on process performance and product quality. This capability provides a justifiable simplification by modeling the real system while mapping “what is well known,” understanding “what is unknown,” and exploring “how to get it better known.”

The qualitative CPPM model represents a paradigm change of the causal description of the process and product to identify PPs, MAs, and operation parameters that might affect process performance and product quality. From this point of view, qualitative CPPM model leverages and improves individual and collective process understanding, the qualitative CPPM enhances the scientific understanding of data model design and the meaning of gathered data.

The model-based solution approach requires determination of quantitative simulation results, i.e., it calls for approved data and model-building expertise to produce a valid applied model. A quantitative CPPM model is created by quantifying the input parameters and functional process interactions of a qualitative CPPM. The quantification is based on mechanistic process knowledge, experimental/multivariate analysis data, and expert estimation. Consequently, the quantitative CPPM delivers simulations that can analyze the effect of process variations on product quality attributes across an entire process.

In a pharmaceutical development tablet formulation project that included experimental data and process modeling information in the CPPM model, the design of knowledge space for process development was effected in a proactive manner. As a result, CPPM helped provide greater process understanding and reduced the effort and resources needed (i.e., number of development and scale-up batches, costs, time). The ability to perform adaptive parameterization ensured the alignment required for tech transfer (scale-up and site harmonization) as teams worked collaboratively on the model. In addition, the model-based approach provided both knowledge transparency and greater opportunities to “recycle” knowledge so that design decisions were improved.

Any model-based approach requires proof of the validity of the model. Validation of a CPPM model is supported by Vensim techniques and is carried out in following four steps:

1. Structural fit (verification of the cause-and-effects relations based on data and expertise)
Causal analysis by means of the cause-and-effect trees
2. Behavior correctness (dynamic and logical behavior are verified, based on data and expertise)
Simulation of dynamic behavior (parameter adjustment, reality check)

3. Plausibility and consistency (proof of completeness and consistency, based on data and expertise)
Simulation on change, sensitivity simulations
4. Validity for model-based process and product development (precise adjustment of simulation results with experimental values)
Nonlinear (and other) model adaptations; model optimization (calibration, policy)

The validity of the executed CPPM model assures its compliant application.

A special case of CPPM quantification is provided by using risk assessment data and determining risk propagation along the process. As a result, a risk model could be carried out and applied for multivariate quantitative QRM applicable to any life cycle phase. The design journey of this approach and its practical applications are described in the next section.

CPPM-Based Risk Model for Multivariate Quantitative QRM

Quantitative risk determination requires causal understanding of variation-inducing and hazard-eliciting risk as well as knowledge of the mechanism of risk propagation across the entire process. The scientific content of CPPM cause-and-effect relations and the capabilities of Vensim software raised the idea to build a risk model applicable for a multivariate quantitative quality risk management.

A risk-focused quantification of PPs, MAs, and operation parameters, as well as functional process and product interactions can turn a qualitative CPPM model into a quantitative risk model. This could help determine the multivariate quantitative effect of risks associated with process variations on risks associated with product quality at each process step, and indicate propagation along the process on risks associated with the final product quality attributes.

The Vensim software capabilities open up the possibility of determining sensitivity and ranking the effect of risks associated with variations of PPs, MAs and operating parameters on risk of variations of product QAs.

In addition, the risk model-based QRM approach must comply with ICH Q 9 QRM process.⁸ It must also implement failure mode effects analysis (FMEA) and data scoring from risk assessment results. Figure 3 shows how the idea of risk model-based multivariate quantified QRM was compiled and put into practice.

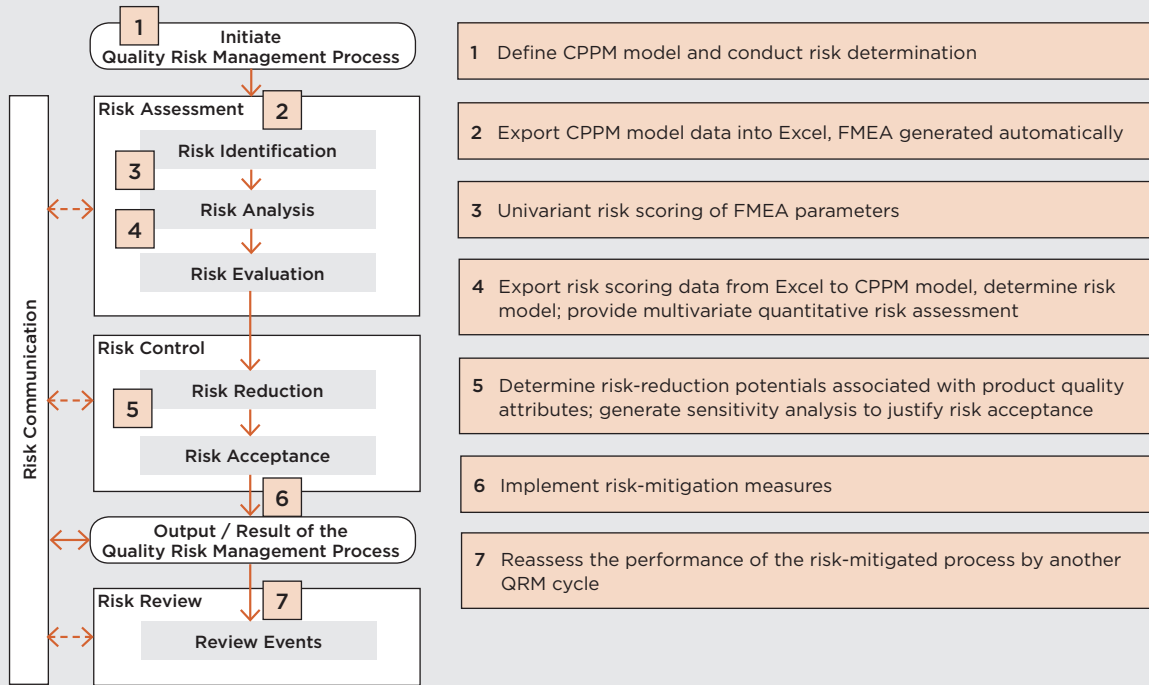
The risk model should be able to manage complexity and the inherently multivariate nature of process and product and associated risk assessment.

Quantifying the risks of process input parameters will apply common risk definitions, with capability to customize them to be compliant with the implemented QRM system. The risk propagation algorithm and simulation technique will follow process interactions characteristics.

Risk potential number

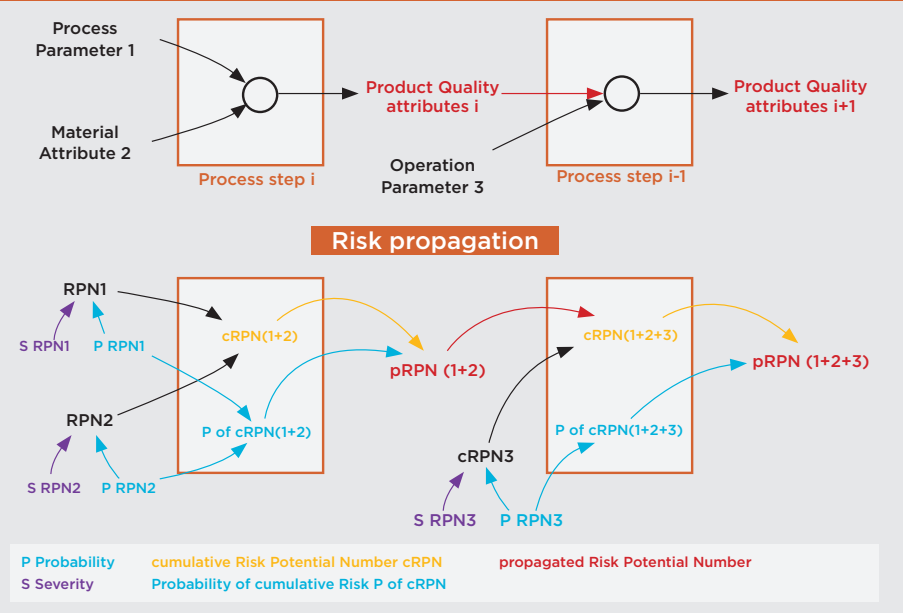
The basic causal effect of any process input parameter at any process step on intermediate product QAs is expressed by its risk potential number

Figure 3: Process flow of the risk model-based multivariate quantified QRM in alignment with QRM process taken from ICH Q9



Source: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonized Tripartite Guideline. "Quality Risk Management: Q9." Step 4 version, 9 November 2005.

Figure 4: Qualitative CPPM Model and corresponding risk propagation calculation



For simplicity, detectability has been omitted

(RPN) value. Process input parameter variations are expressed by variations of its RPN.

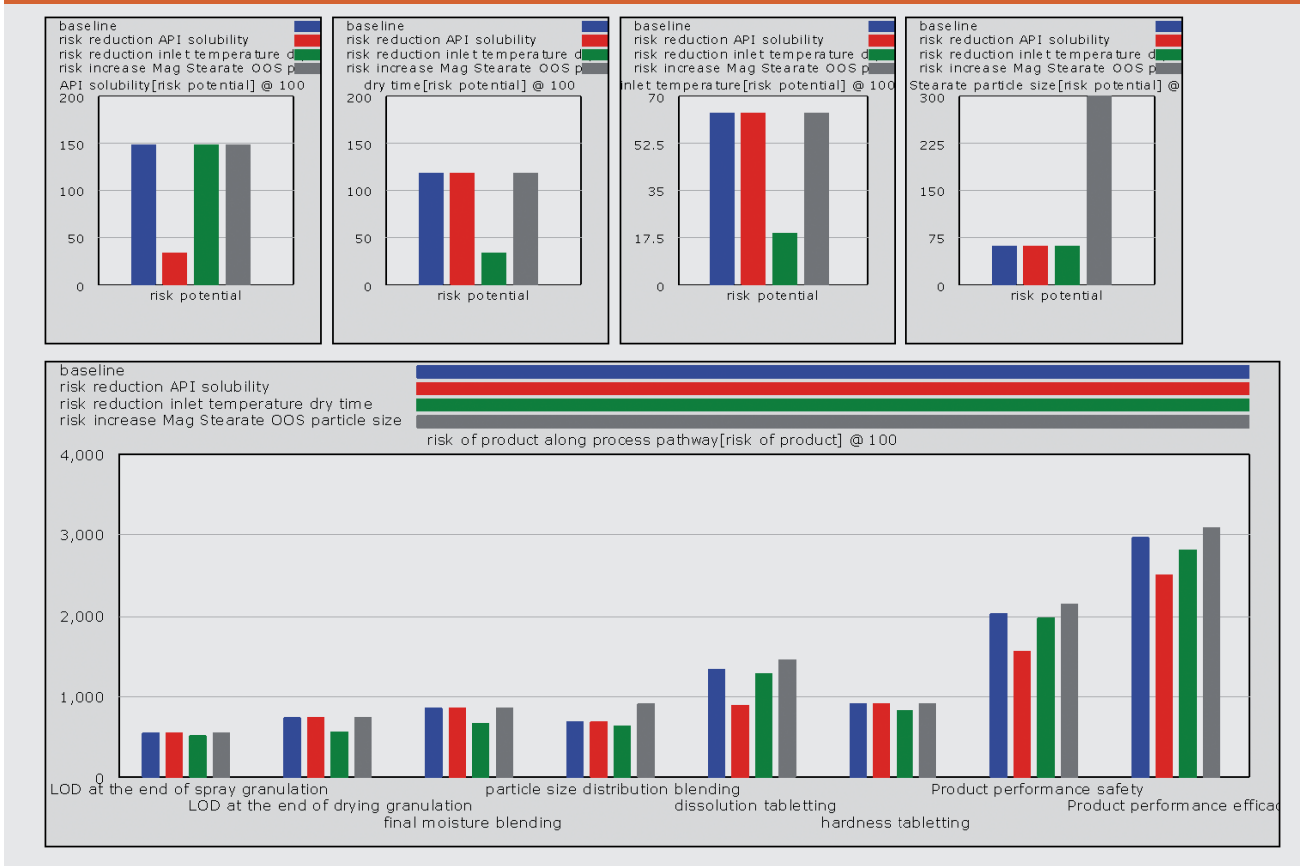
$$RPN = \text{Severity } S \times \text{Probability } P \times \text{Detectability } D$$

Severity S = severity of impact of process input parameter variations on product quality attributes

Probability P = probability of occurrence of process input parameter variations
Detectability D = capability to detect and monitor these variations

All of the above values could be assigned with a customized risk rating matrix, e.g., from one to 10. Implementing the FMEA procedure (i.e., using risk assessment RPN data as a model input parameter) makes the approach universally applicable and easily leverages current QRM toward a multivariate quantitative QRM.

Figure 5: Illustration of effect of risk reduction of Process Parameters on risks of product QAs along process pathway



Calculation of risk propagation

Risk propagation captures multiple input parameter risk effects (PPs, MAs, operation [handling]) on risks associated with product QAs for each process step as well as along the process pathway (Figure 4).

cRPN = cumulative risk potential of propagated risk

cRPN: algorithm is simple or weighted sum of risk potential of considered risks; in principle the algorithm must follow process step characteristics

P of cRPN = probability of propagated risk occurrence

P of cRPN: algorithm applies standard formula from probability theory (values between 0 and 1)

Propagated risk potential (pRPN) = cRPN × P of cRPN

The pRPN is determined for each consecutive step and relevant intermediate product QAs without any limitations on the number or type of risk parameters (i.e., without any constraint on the process complexity). Determination of pRPN sensitivity could be provided under selective consideration of the probabilities population (e.g., Monte Carlo).

The simulation techniques provide a way to determine the impact of any process input parameter variation on the variation of any QAs. Further, the optimization policy (i.e., Monte Carlo and payoff definition) offers the

unique ability to determine the impact ranking (criticality) of individual variations of particular (i.e., one-to-many) process input parameters on arbitrarily selected product QAs. This provides highly effective risk mitigation and defines a more effective process control strategy for more robust process design.

Provided that the RPN determination and risk propagation algorithm represent process input parameters and process step behavior accurately, the simulated risk-focused process behavior could approach actual process behavior correctness, plausibility, and consistency. Applying available data in combination with expertise could provide an appropriate verification of the risk model. Executed applications confirmed the correctness and practicality of this approach. Consequently, a multivariate quantitative risk model-based QRM can be applied to determine process control strategy, execution of investigational analysis for troubleshooting and optimization of the process performance.

To unfold the risk model details for multivariate quantitative QRM, we will continue with the solid manufacturing process case study, following the QRM process flow in Figure 3.

1. Define CPPM model and conduct risk determination (see “CPPM Models”)

2. Export CPPM model data into Excel, FMEA generated automatically:

Qualitative CPPM data (i.e., model variable with description and information of causal linkages) will be exported automatically into a customized Excel file and allocated into appropriate structured FMEA templates (macros).

3. Univariate FMEA parameter risk scoring: The univariate risk scoring of RPN for PPs, MAs, and operation parameters (model input parameter) will be executed following FMEA procedure.

4. Export risk scoring data from Excel to CPPM model, determine risk model, provide multivariate quantitative risk assessment: RPN data will be imported automatically back to the CPPM model with unambiguous allocation to the considered model variable. Risk model quantification is finalized by determination of risk-associated functional process interactions and risk propagation. The result is a risk model ready for multivariate quantitative determination of risk propagation along the process pathway. The simulation with primary determined RPN value is captured in Figure 5 as baseline.

Another important risk assessment is evaluation of the most critical input parameters. For this, the simulation optimization policy determines their impact ranking. This could be executed for multiple inputs on one or more outputs.

Returning to the finished tablet dissolution product attribute, which was used to illustrate cause-and-effect relations, we first ranked the impact of all PPs, MAs, and operating parameters on dissolution of finished tablet (Table A).

Risk potential values indicate the primary determined risk RPN score.

A payoff is a single number that summarizes a simulation (result valuation). In this application it defines relative risk score of impact of parameters on dissolution. The corresponding ranking indicates the priority of risk mitigation. This lets us understand that variation of the API solubility and formulation recipe affects the dissolution of tablets

Table A: Impact ranking of PPs, MAs, and operating parameters on finished tablet dissolution

Policy focus: Product Attribute "dissolution-tabletting"		
Sorted Parameter Sensitivities = Ranking of impact		
Parameters are changed by ± 20%, if 0 by ± 0.2	Ranking	Payoff
API solubility[risk potential]=150	1	12120
formulation recipe[risk potential]=63	2	3436
compression force[risk potential]=96	3	1939
binder solubility sl[risk potential]=96	4	1357
inlet temperature[risk potential]=64	5	1164
pump speed[risk potential]=72	6	1018
granulation time[risk potential]=56	7	792
mixing time sl[risk potential]=75	8	758
Lactose particle size distribution[risk potential]=72	9	727
Mag Stearate particle size[risk potential]=64	10	646
fluid bed height[risk potential]=64	11	646
dry time[risk potential]=120	12	485
etc.		

most, followed by compression force on tablet press, and granulation process PPs.

5. Determine risk-reduction potentials associated with product quality attributes; generate sensitivity analysis to justify risk acceptance:

Achieved risk assessment results could be used to define the risk-mitigation focus and provide adequate simulations of the risk-reduction assessment. Subsequently, the effect of any PP, MA, and operation parameter variations (expressed by their RPNs) on any product QA variations (determined by their pRPNs) could be determined. Figure 5 shows three sample risk control simulations.

The first focuses on determining risk reduction of product attributes, assuming improved API solubility. The second zooms in on the granulation process. Earlier, we explored the effect of variations in

Figure 6: Impact of variation of O2 sparging on variation of dissolve oxygen DO and of harvest CQAs

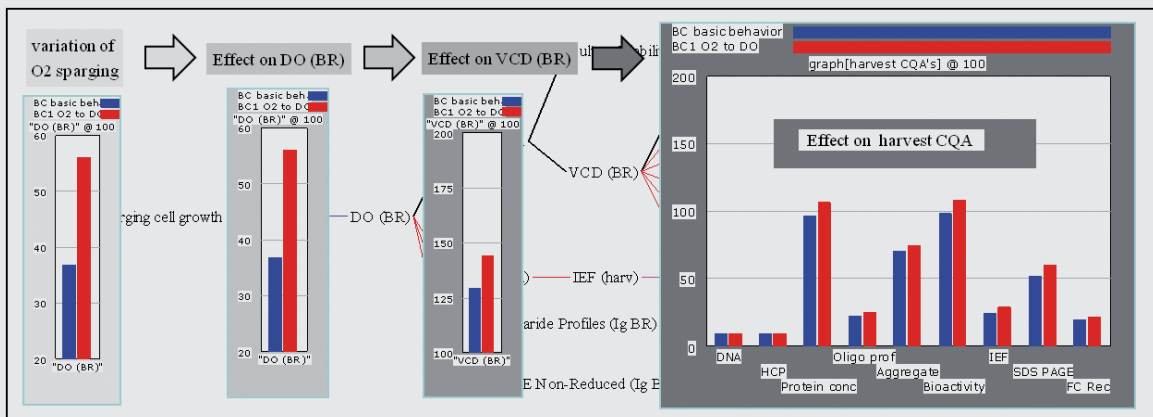
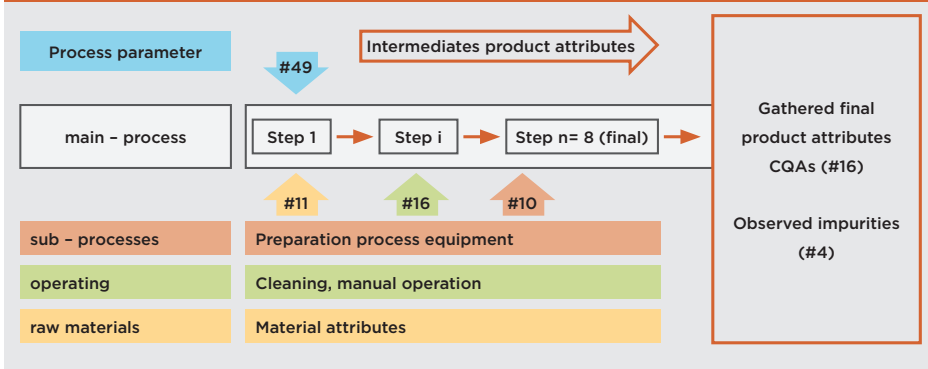


Figure 7: Illustration of structure and complexity of the risk model


Practical Applications

Example 1: Multivariate criticality analysis of the bioreactor process

The goal of the project was to support the evaluation of the potential causes that may have resulted in an observed shift in certain product quality attributes. For this purpose, the risk model was established and a focused multivariate quantified risk analysis was executed. The process diagnosis (ranking the impact of possible causes), for example, indicated that O₂ sparging

PP was one of the significant causes. The subsequent simulation showed the effect of O₂ sparging variation on dissolved oxygen and intermediate product attributes (e.g., viable cell density), and consequently on harvest critical product attributes (CQAs), measured by variation of risk potential respective of propagated risk (Figure 6).

This risk model-based investigational analysis supported concurrent evaluation and development. The captured complexity includes approximately 11 seed CQAs, 37 PPs, 16 MAs, and 80 process interactions. The responsible SMEs had actively contributed to the risk model design, provided the risk quantification, and verified the quantitative risk model. The efficiency of the model-building and simulation processes, content and suitability of achieved results, and leverage of collective knowledge confirmed the practicality, applicability, and benefit of this approach (Figure 8, number 4).

Example 2: Multivariate investigational analysis to improve process robustness

The purpose of the project was to support the investigational analysis of the causes of observed shift in certain product quality attributes and to improve robustness (i.e., reduce impact of variations induced by variation of biological raw material attributes on the considered product attribute) in a manufacturing process with high complexity (variation of MAs, multiple process steps, number of PPs, diverse technologies). At the beginning of the project the SMEs had different perceptions and knowledge about the cause-and-effect interactions of process and product. For this reason—and to support ongoing improvement—the company decided to use CPPM and to apply the multivariate quantitative risk assessment by means of risk model.

As a goal, the risk model should provide an enhanced scientific understanding of cause-and-effect interactions of process and product and include a deep-dive multivariate risk analysis to evaluate the potential causes that may have resulted in observed shift in the product quality attribute being considered. For this purpose, the risk model had been established with special focus on inherent chemical and microbiological processes that affect the considered product quality attribute.

The structure and complexity of the manufacturing process risk model is illustrated in Figure 7. The cause-and-effect relations represented in the

dry time and inlet temperature on dried granule LOD on finished tablet dissolution and associated product efficacy. In the third case, risk control focuses on determining risk increase in product QAs as a consequence of out-of-specification deviation of material attribute. As the sequence of product QAs follows the process pathway, the bar graphs illustrate how the risk is propagated and how the risk potential of product QAs change in comparison with the baseline.

The structural fit of the risk model and the plausibility and consistency of the simulation demonstrate the capability to generate a realistic multivariate determination of risk associated with variations within an entire process and to provide unprecedented multivariate understanding of risk-based process behavior and its effect on product quality. Consequently, analyzing simulation results can provide an adequate justification of risk acceptance.

- Implement risk-mitigation measures:** The multivariate quantitative understanding of the effect of risk mitigation measures on risk associated with product quality enables to provide an effective and efficient implementation.
- Reassess the performance of the risk-mitigated process by another QRM cycle:** Based on results, the risk model could be adapted as needed and prepared for next QRM cycle.

The applied software technique enables the risk model assess any combination of multiple input parameters (PPs, operating and material attributes) and focus on any combination of multiple output parameters (product QAs). Consequently, the risk model tool is applicable for a wide range of situations relevant to multivariate quantitative QRM for LCM.

In similar way, a rash of practical CPPM applications and risk model-based multivariate QRM was executed (Figure 8). The short extract of following two practical applications may indicate the capability of CPPM approach to handle even high process complexity and demonstrate the benefit of risk model-based multivariate quantitative QRM and its implementation for investigational analysis and process development and optimization.

Figure 8: Overview of practical applications of CPPM and Risk model approach with life cycle stage allocation

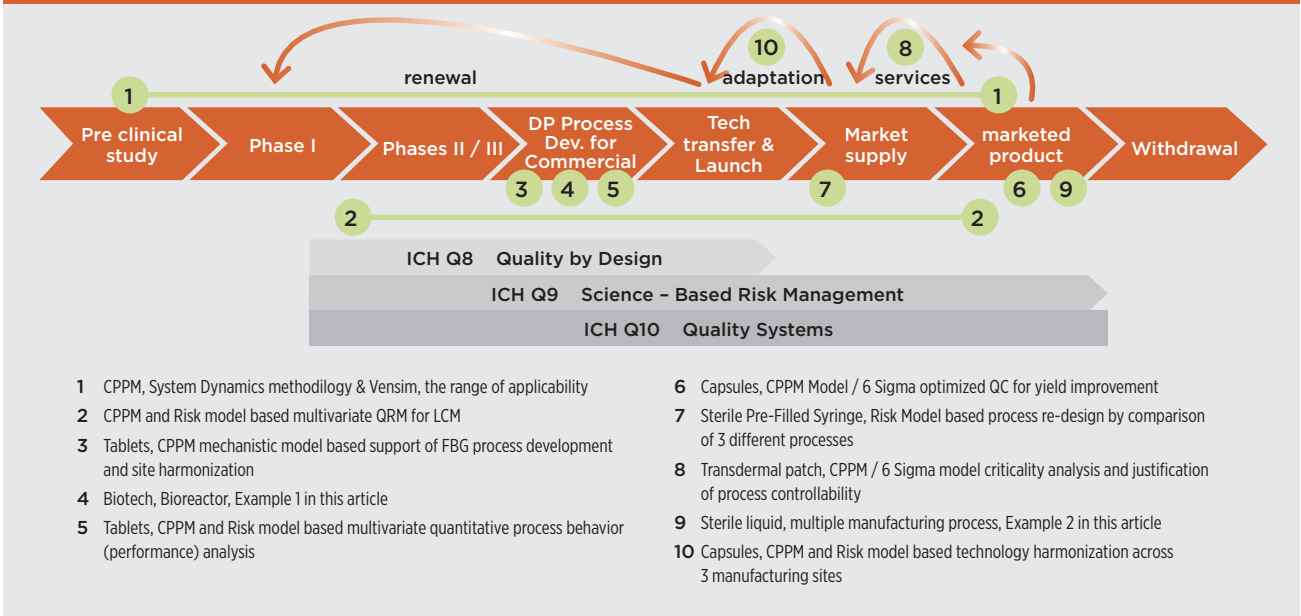
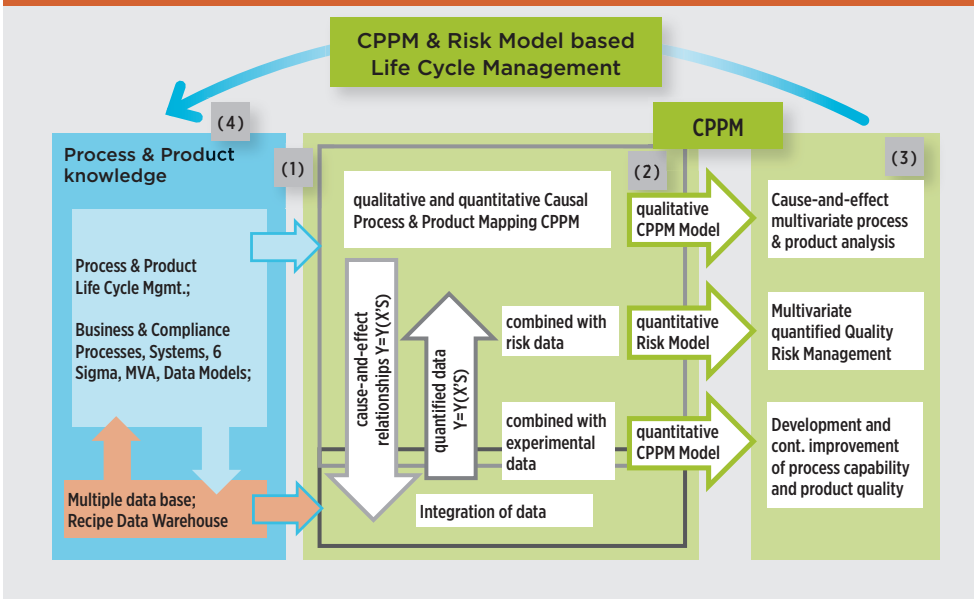


Figure 9: Overview of the CPPM and risk model-based LCM



process behavior, while the sensitivity analysis captured the risk impact of any process parameter variations and their combination on variation of product quality attributes. Consequently, appropriate practical operating measures for each manufacturing process were stipulated in order to support concurrent investigational and process improvement processes. This enhanced the meaning of the simulation results and the alignment of the experiments' conceptual approaches. Comparing results achieved through concurrent experiments with simulation results confirmed the application validity of the risk model.

The contribution of responsible SMEs and operation managers in the risk model building process led to a significant alignment and leverage of process understanding and knowledge, and resulted in sustained process robustness improvement: During the last 2-year period, product attributes were within specifications and no batch was rejected (Figure 8, example 9).

model captured and calculated approximately 20 interactions per process step. Another interesting aspect was the existence of feedback interactions between the critical product quality attribute CQAs (each process step averaged about seven CQA interactions).

To understand the complexity of the process from an operation and risk mitigation perspective, the ranking (criticality) of individual impact of variations of particular process parameters on arbitrarily determined product QAs was established. Simulation results determined the risk potential of intermediate critical product attribute CQAs at each process step as well as of final product. These results allowed a better understanding of the

Overview of executed practical applications

These examples demonstrate the flexibility and wide applicability range of CPPM and risk model approaches.

As these practical applications show, the CPPM and risk model generate new levels of process and product knowledge and can provide an enhanced LCM. This includes:

- Identifying critical PPs and critical MAs to justify criticality of each process step
- Defining multivariate establishment of the process with predefined impact on product quality and risk control
- Ranking the impact (criticality) of process parameters variations on product QAs to determine risk mitigation and optimize process control strategy
- Providing proactive analysis and determine process design improvements
- Comparing performance of manufacturing processes at different manufacturing sites
- Determining and understanding the mechanisms of intrinsic (e.g., equipment, process) and extrinsic (e.g., operating) risks and their impact on risk of intermediates and final product QAs

Summary and Conclusions

Figure 9 illustrates CPPM and risk model-based LCM:

1. Expertise and data input from deployed processes and systems
2. Creation of the CPPM and risk models
3. Determination of new expertise and knowledge
4. Feedback and implementation into deployed processes and systems

CPPM applications confirm its capability to handle the complexity of the considered system (processes, procedures, data integration) in a universally applicable way. Simulation capabilities, augmented with sensitivity simulations and solution-focused optimizations support process development, strengthen troubleshooting, and enhance continuous process capability and product quality improvement. The execution practice verifies the trouble-free and flexible implementation of the CPPM approach, with transparent and simple interpretation of the results. The integration of the data, validity of the CPPM model, compatibility of the risk model with state-of-the-art and approved QRM procedures and tools, and the capability of applied Vensim software ensure an a priori compliant and high-performing support for LCM.

The results of executed practical applications of the CPPM models and risk model-based multivariate quantitative QRM confirm the unique capability of this novel, innovative, and advanced approach for LCM.

Finally, CPPM implementation increases collaborative process understanding, speeds up knowledge management process, and emphasizes the power of systems thinking for managing process and product complexity. ■

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