Integration of Risk Management into existing pharmaceutical Quality Systems

Masterarbeit

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Mag. Dr. rer. nat. Siegfried Adam

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(Siegfried Adam)

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API	Active Pharmaceutical Ingredient
CAPA	Corrective Action and Preventative Action
DoE	Design of Experiments
ERM	Enterprise Risk Management
FDA	Food and Drug Administration
FMEA	Failure Modes and Effects Analysis
FTA	Fault Tree Analysis
GMP	Good Manufacturing Practice
HACCP	Hazard Analysis and Critical Control Point
ICH	International Conference on Harmonization
QA	Quality Assurance
QbD	Quality by Design
QC	Quality Control
QRM	Quality Risk Management
RPN	Risk Priority Number
SOP	Standard Operating Procedures

1 Introduction

Risk-based approaches including risk management are applied in many areas of business, e.g., automotive, oil and aerospace industries, finance, and insurance. Although there are some examples of the use of quality risk management in the pharmaceutical industry, they are rather limited and do not represent the full possible contributions that risk management has to offer[1]. Recently, the economic and regulatory environment of the pharmaceutical industry has started to change and calls for implementation of a sound science and risk-based approach towards product development, commercial manufacturing and business operations in general. Due to stringent regulatory demands and the steadily increasing economic pressure pharmaceutical companies strive to find new strategies to improve efficacy and efficiency of their products and associated manufacturing and business processes. It has become clear that new approaches towards pharmaceutical quality systems and the integration of quality risk management as an integral part of an effective quality management system will facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities[2]. The industry must apply comprehensive risk management and innovative approaches to product life cycle not only to enhance patient safety but also to improve business outcomes, and hence, it is critical to understand and employ appropriate risk management approaches and their associated tools that would be acceptable to regulatory agencies[3].

In the following chapters a brief overview of the current status of the pharmaceutical industry is provided to demonstrate the need for transformation and hence, the primary goal of this work is presented.

1.1 Status quo of the pharmaceutical industry

The pharmaceutical industry is currently undergoing a tremendous change in the way medicinal products are developed and manufactured, affecting the whole life cycle of such products, starting from the very first proof of a potential pharmacological effect of a new entity, to the development of new formulations and their associated manufacturing processes, the filing and regulatory approval of a new product, and finally, the variations of already approved products, e.g. to include additional therapeutic indications into the existing product dossier. The overall goal is to make these life cycle processes more effective, predictive and efficient, with regard to (i) shorter time-to-market for new medicinal products to make the most out of the available patent-protected time as possible, (ii) lean manufacturing processes with predictable quality outcomes to save time and resources for product release and (iii) straight communication activities with regulatory authorities to overcome delays in market launches and product variations.

The need for change emerged from the current (economic) situation of the pharmaceutical industry and is manifold. For instance, the industry's growth rate has decreased from double to single digit growth, with the revenue growth rate slowing down from 15% in 1999 to 3-6% between 2010 and 2015[4]. Consequent decrease in sales mainly results from block-

[1] ICH (2005), p. 1.
[2] ICH (2008), p. 1.
[3] Baseman et al. (2013), p. 7.
[4] KPMG (2011), p. 7.

buster products' patent expiration (i.e. the "patent cliff") and the competition by generic products makes up a loss of more than 1 billion Dollars between 2011 and 2016[5]; e.g., the four largest drug selling companies have lost patent protection in 2012: GSK (Advair), Pfizer (Lipitor), AstraZeneca (Nexium) and BMS and Sanofi (Plavix).

Low quality and productivity output by R&D and empty development pipelines during the past few years will not be able to fill this gap with new top selling products: over the past decade number of applications for new medical entities to the US Food and Drug Administration (FDA) has averaged 24 per year; however, only 23 applications were filed in 2010, the second lowest number in a decade and all this despite the fact that pharmaceutical companies steadily increase their expenditures for R&D[6] and seek to merge with other companies in order to get access to additional product pipelines. Summing up, rising R&D costs come along with a steadily decline in approvals of new products.

Furthermore, many pharmaceutical companies did not place much emphasis on pharmaceutical production and its problems; hence the amount of waste as a result of mistakes in manufacturing was reported to be as high as 50% of the batch sizes manufactured[7]. Additionally, a stringent regulatory oversight in order to promote safety and efficacy of pharmaceutical products led to increased effort of companies to file manufacturing supplements associated with soaring costs[7]. This combination of dramatically dropping sales and steadily rising costs created a more than challenging environment for the pharmaceutical industry.

Beside these R&D and productivity related problems of the pharmaceutical sector, at the same time, national authorities are creating a more stringent regulatory environment and higher quality standards in order to better control drug manufacturing processes and to assure safe and effective pharmaceutical products. Hence, this led to a huge increase in workload with regard to approval processes[7] for authorities and the industry. Furthermore, the regulatory framework only allows changes to existing products and associated processes, so called variations, when providing excessive amount of data. Hence, this comes along with enormous costs and resources to be spent. This of course resulted in an inflexible environment that did not encourage changes and therefore prohibited real innovations in the field of products and processes with regard to development, product quality and manufacturing costs.

Table 1 shows an overview of major risks in the pharmaceutical sector. According to this survey, problems caused by new or existing regulations represent the biggest threat to pharmaceutical companies. However, beside these compliance risks, other aspects are business risks by their nature (e.g., human capital risks, financing risks or market risks).

[5] Fischer et al. (2010), p. 283.
[6] EP Vantage (2010)
[7] Rathore et al. (2009), p. 26.

Table 1: Major risks in the pharmaceutical sector[8]

Risk	Percentage of companies who rated the risk as very high
Regulatory risks (e.g., problems caused by new or existing regulations)	67%
Human capital risks (e.g., skills shortages, succession issues, loss of key personnel)	42%
Financing risk	41%
Political risk (e.g., danger of a change of government)	38%
Reputational risk (e.g., events that undermine public trust in products or brand)	37%
Foreign exchange risk (e.g., risk that exchange rates may vary)	37%
IT risk (e.g., loss of data, outage of data centre)	37%
Market risk (e.g., risk that the market value of assets will fall)	29%
Country risk (e.g., problems of operating in a particular location)	28%
Credit risk (e.g., risk of bad debt)	27%
Terrorism	13%
Crime and physical security	11%
Natural hazard risk (e.g., hurricanes, earthquakes, etc.)	9%

Hence, it is clear that the pharmaceutical industry, like every other industrial sector, is exposed to various threads that are internal or external by their nature. Other industries have already implemented effective approaches to identify, mitigate and review those risks. Recently, it has become clear even in the pharmaceutical sector that an adequate risk management system is not only required by regulatory stakeholders but may also result in a competitive advantage when appropriately implemented.

1.2 Aim of this work

Taking the above described status quo of the pharmaceutical industry into account, it is obvious that new models for drug discovery, development, post-approval activities and general product management are needed. However, this requires a radical advancement from traditional approaches of the pharmaceutical sector.

In the past, there was no need for traditional quality assurance and production systems to efficiently use resources due to their nearly inexhaustible availability. High financial returns caused by blockbuster products put the pharmaceutical companies in a position to simply discard produced batches in the case of a quality issue than to perform sound root cause analysis and to improve existing products and processes. To a lesser extent, the regulatory environment was also responsible for this situation, as any changes made to the production

[8] KPMG International (2009), p. 4.

or control of an approved product would require costly and time-consuming post-approval regulatory procedures.

Hence, to be prepared for future challenges, more predictive and proactive strategies towards product and process development, quality assurance and quality control, product life-cycle management and business operations in general are required. Risk management can be seen of one major aspect of these approaches with the goal to facilitate innovation and continuous improvement.

Due to internal and external requirements posed by different stakeholders as discussed above, the need to implement and continually improve risk-based approaches with regard to different quality systems has recently become imminent. Besides steadily increasing regulatory requirements, especially the existing business environment requires a fundamental change in the way products are developed and managed over their whole life cycle. A major approach towards a more proactive way towards pharmaceutical business is the consideration of risk-based strategies with regard to product-quality related activities. Therefore, the overall goal of this master thesis is to describe a possible approach towards enhancement of an existing pharmaceutical quality system with relevant elements of quality risk management by the means of a partial integration of risk management system elements.

As risk management should be an integral part of pharmaceutical quality management, as also set forth by relevant guidance documents[9,10], and therefore has to be acknowledged in an organisation's quality policy and quality system, the framework for pharmaceutical quality management is an appropriate starting point for risk management integration. Using already existing system elements that are obligatory in the pharmaceutical industry as departure is a very efficient and effective way to realise a quality risk management system. At this point it has to be emphasised that risk management heavily relies on the input from various quality systems and vice versa. Therefore, pharmaceutical quality and quality management will be briefly characterised in the following chapters. The basic meaning of quality and pharmaceutical quality is discussed and an introduction to quality systems in general by the means of ISO 9001 is provided and special requirements of the pharmaceutical industry are elaborated. Hence, a detailed description of the pharmaceutical quality system is deemed necessary as it builds the basis for further risk management integration activities.

Afterwards, an introduction to risk management is provided with a special focus on existing standards and the purpose of risk management within the pharmaceutical industry. In these sections, general risk management processes are reviewed and a basic risk-based approach for the pharmaceutical industry is introduced. A brief overview of risk management approaches in other industries is provided and general tools that are heavily used in existing pharmaceutical risk management processes are described.

The main chapters of this master thesis then describe the actual integration of risk management into selected quality systems. The chosen quality systems represent major aspects of the pharmaceutical quality assurance system and their enhancement with regard to risk management can be well used as primer for further integration activities. A focus is set on general integration activities and a specific integration strategy for the pharmaceutical industry is deduced.

Finally, a potential analysis of the newly integrated systems is provided as a starting point for the implementation of further risk-based approaches. Here, special emphasis is not only put on the further integration into existing quality systems, but on integration activities on

[9] European Commission (2013), p. 8.
[10] ICH (2005), p. 1.

the overall company level. A holistic enterprise risk management system is suggested in order to overcome future threads of changing business and regulatory environment. A company-wide integrated risk-based approach aims at facilitating decision making on the top-management level as correlations between individual risks that may appear in different areas of business, different product lines, or different organisational units become visible and thus controllable.

2 Quality management and pharmaceutical quality systems

2.1 Quality and the management of quality

Risk management activities often rely on already implemented management systems, and actually, in the pharmaceutical industry the presence of a sound quality management is indispensable for being in compliance with regulatory requirements, and hence, it is realised in every pharmaceutical organisation. The author of this work sees quality management as an important primer and necessary prerequisite of risk-based approaches within the pharmaceutical industry. Thus, this section will provide a brief background on quality and the management of quality. The characteristics, implementation, use and improvement of quality management systems in different industrial sectors with a special focus on the pharmaceutical industries are discussed. The aim is to provide a basic understanding of the pharmaceutical quality environment and its associated tasks as a requisite for the integration of quality risk management elements.

The general need for improved product quality emerged in the 1980s, as it came apparent that the US was economically logging behind some other countries, e.g., Japan, in the area of product quality, although many of the tools and methods that were used to identify and solve quality problems date back decades earlier[11].

To elaborate the meaning of quality management to the different industries and especially to the pharmaceutical sector, it is crucial to considerably understand the meaning of quality. There are numerous definitions of the term "quality". According to Juran[12] two are of critical importance to manage quality:

(1) Quality relates to those features of products that are needed to meet customer requirements and therefore provide customer satisfaction. Hence, instruments are required to perceive customer needs, to translate them into distinctive product characteristics and to assure that customers stay satisfied. However, it is not always easy to find out about customer requirements as they are various, may differ depending on different target groups and are very often even not know in every detail by the customers themselves. Taking as an example a pharmaceutical product into account, e.g., a tablet against headache, the patient wants the medicine to cure his/her pain; that's obviously a definitive product requirement and the tablet can be regarded to be a high quality product if the headache will relief after a certain time after intake. The customer then will be satisfied. However, there are additional requirements, unknown by the customer, that have to be fulfilled, e.g., coming from the regulatory environment, e.g., certain levels of toxic by-products or impurities are not to be exceeded in order not to jeopardise patient's safety.

(2) Quality means freedom from deficiencies, for instance, freedom from errors that would result in field failures, customer dissatisfaction or customer claims. In this sense, quality is related to costs, and higher quality usually costs less. E.g., a tablet against headache breaking when it is pressed out of the blister would usually result in a customer complaint.

According to Janet Woodcock (Director of the Centre for Drug Evaluation and Research of the US Food and Drug Administration) pharmaceutical quality means that a product is

[11] Mazumder et al. (2011), p. 366.
[12] Juran (1999), p. 2.1.

free of contamination and reproducibly delivers the therapeutic benefit promised in the label to the customer[13].

Quality management is the process of identifying and administering the activities necessary to achieve the organisation's quality objectives. According to ISO 9000 quality management is the sum total of all activities to assure, control and improve the quality of the quality management system itself and the product or service provided, taking into account cost effectiveness and the relevant organisational structures[14]. According to Juran[15], quality management consists of the following three universal processes: quality planning, quality testing/quality control and quality improvement (Table 2).

Table 2: Three universal processes of quality management[15]

Quality planning	**Quality testing/control**	**Quality improvement**
Establish quality goals. Identify who the customers are. Determine the needs of the customers. Develop product features that respond to customers' needs. Develop processes able to produce product features. Establish process controls; transfer the plans to the operating forces.	Evaluate actual performance. Compare actual performance with quality goals. Act on the difference.	Prove the need. Establish the infrastructure. Identify the improvement projects. Establish project teams. Provide the teams with resources, training and motivation to diagnose the causes and stimulate remedies. Establish controls to hold the gains.

These universal elements of quality planning, quality testing/control and quality improvement are at the heart of quality management and can be applied to the general design of virtually any quality system, irrespective of the industry affected. In fact, these processes do not only relate to the development, production and improvement of a product or service of a company; they also focus on the efficacy and efficiency of the quality management system itself, with its associated processes, methods, responsibilities and so on. Hence, they relate to the PDCA- or Deming-circle in order to continuously improve the quality of (organisational) processes and their associated products or delivered services[16]. These elements are frequently-used building blocks of quality management that are required to define and translate top management's quality policy and targets into operative actions. Quality planning is not only responsible for defining customer required product features and setting up appropriate quality requirements. Moreover it is responsible to plan the quality management system itself.

[13] Woodcock (2004), p. 1.
[14] ISO 9000 (2005)
[15] Juran (1986), p. 2.
[16] Schmitt et al. (2007), p. 35.

According to ISO 9000 a quality management system is used to define and realise a quality policy and its associated quality targets[17]. A system is defined as a collection of components organised to fulfil a specific function or set of functions[18]. Ringfencing the system is required to separate it from the environment, as the environment can still interact with the system but cannot be controlled by the system[19]. A quality management system is defined as a structured and documented management system describing the policies, objectives, principles, organisational authority, responsibilities, accountability, and implementation plan of an organisation for ensuring quality in its work processes, products and services[18]. A quality system provides the framework for planning, implementing and assessing the work performed by a company and for carrying out required quality assurance and quality control activities. Figure 1 depicts the main building blocks of a quality management system.

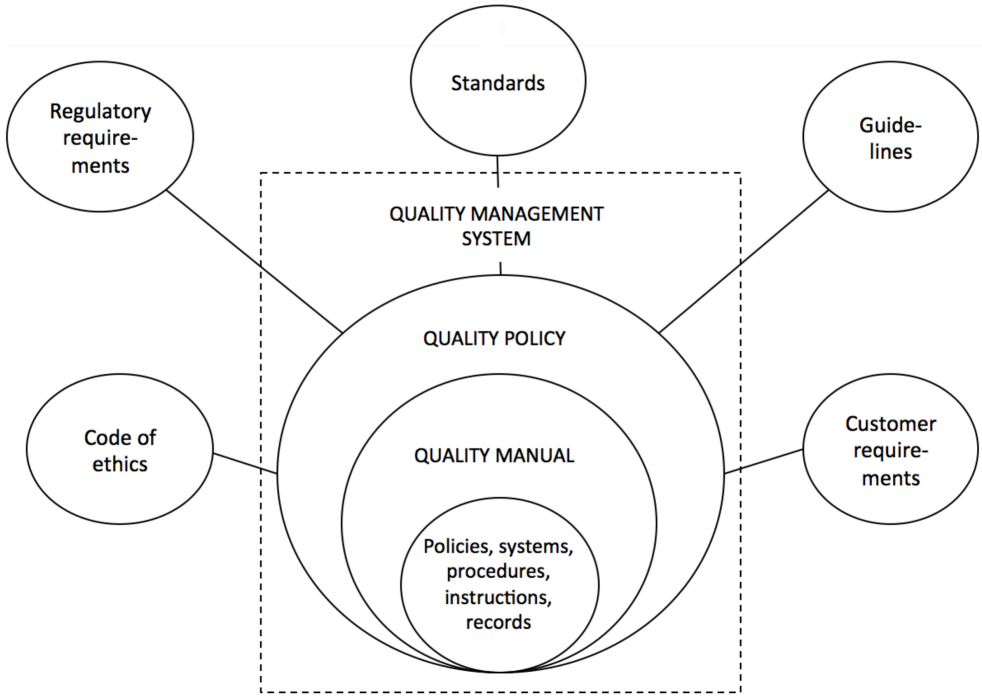

Figure 1: Main building blocks of a quality management system[20]

It is the responsibility of senior management to set up a quality policy that sets forth quality principles and targets and defines basic aspects of the company's quality management approach. The quality policy is written down in the quality management manual. Furthermore, the manual describes all relevant quality related activities that are performed within the company in order to realise the quality targets. Obviously, there is a clear link between the corporate and quality goals and policies.

[17] ISO 9000 (2005)
[18] Nally et al. (2007), p. 218.
[19] Haberfellner et al. (2012), p. 35.
[20] UNDOC (2009), p. 5.

It is important to point out that requirements for risk management are often defined in the companies' quality policy[21]. Risk management can be regarded as a proactive approach towards assuring quality of processes and products. Hence, quality risk management with its processes should be clearly defined in the quality manual and should be an integrated part of quality management.

In the line of quality planning, relevant quality elements are designed[21]. Quality elements are distinctive parts of the quality system and may be, for instance, quality procedures or processes. Quality procedures can be regarded as standard operating procedures (SOPs) that describe specific quality related activities in a standardised way.

As can be seen in Figure 1 external aspects may influence the system, e.g., regulatory requirements set forth by the state government or standards, e.g. ISO 9001, which can be regarded as guidelines, however, are often subject of contracts between a company and its suppliers and customers.

ISO 9000 series introduced eight quality management principles that can be used by senior management as a framework to guide their organisations in the establishment of a quality system and towards improved performance[22]: (1) Focus on customers: as an organisation is heavily dependent on its customers, it should understand customer needs, meet their requirements and make an effort to exceed their expectations. (2) Leadership: It is up to the senior management to streamline activities of the organisation towards quality targets. An appropriate internal environment should be created and maintained so that employees can become fully involved in achieving the organisation's objectives. (3) Involvement of people: It is important to involve employees from all levels of the organisation in order to get them motivated, committed and involved within the organisation. (4) Process approach: It is necessary to systematically define activities that are relevant to obtain the required results. For all activities responsibilities, required input, methods and output to be obtained have to be defined. (5) System approach to management: Relationships and interdependencies between the individual processes of a system have to be understood with the ability to focus effort on the key processes. (6) Continual improvement: With the definition of goals to guide and measures to track continual improvement, where continual improvement of products, processes and systems is an objective for every employee within the organisation. (7) Factual approach to decision making: Available data and information are an indispensable requisite for effective decisions. (8): Mutually beneficial supplier relationships: this would enhance the ability of the organisation and its suppliers to create value.

Another important universal process of quality management as defined previously in this chapter is quality testing/control. In the line of quality testing, the actual performance of the product or service and the quality system are compared with the quality goals set forth in quality planning. Quality management systems have to be reviewed periodically with regard to their efficacy and efficiency. This can be realised, for instance, by performing internal audits. During audits processes are checked for conformity to the relevant standards as defined in the company's quality policy. In order to evaluate their actual performance quality testing of raw materials, intermediates and final products or services against documented standards (specifications) are performed. Quality control encompasses proactive, monitoring and corrective actions in the line of product realisation to fulfil product requirements[23].

[21] Benes et al. (2012), p. 106.
[22] ISO Central Secretariat (2012), p. 2.
[23] Benes et al. (2012), p. 116.

Finally, quality improvement seeks to increase efficacy and efficiency of quality management processes, manufacturing processes and their associated products and services. As an example, quality improvement could be a result of a corrective action triggered by a quality defect or may originate from innovation and continual improvement processes (see Figure 2).

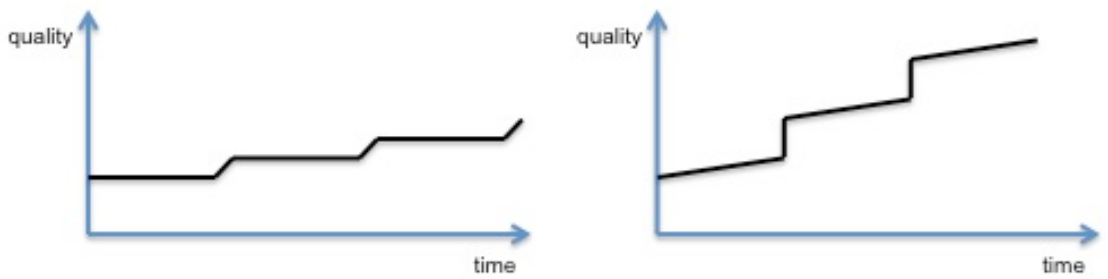

Figure 2: Quality improvement through continuous improvement (left) and through a combination of innovation and continuous improvement (right) [24].

2.2 Quality management systems

As outlined earlier in this chapter, quality management systems provide the organisational structure, processes and resources needed to implement quality management. Figure 3 depicts the development of different approaches with regard to quality over time. Quality management systems evolved from quality control and quality assurance and are the precursors to total quality management (TQM). Quality control stood at the beginning of providing products that fit customers' expectations. However, at this stage only the finished product was tested against proven specifications. The production unit did not feel responsible for resulting quality issues. After a certain level of quality was reached (e.g., a defect rate of x%) even better quality levels beyond this rate came at a high price (e.g., intensified controls, need to rework). Quality control can be seen as one part of quality management. The establishment of quality assurance is the next step towards quality management. In contrast to quality control that is focused on process outputs only, quality assurance provides a proactive approach towards quality by establishing, monitoring and improvement of processes that are fit for purpose. Quality assurance is one part of quality management as it provides the operative framework for quality management, e.g., quality assurance is responsible for supplier qualification or deviation management. Hence, processes with a reproducible and stable output let to a constant high quality product. Finally it is the philosophy of total quality management that product quality depends on the overall quality of the whole company including all departments and all stakeholders, internal and external ones. In the following chapters we will see that pharmaceutical quality management comes very close towards the common understanding of total quality management. Along with environmental management, occupational safety management and risk management systems, quality management can be further developed to a comprehensive integrated management system. It has to be emphasised that the different quality systems according to Figure 3 coexist all over the world, depending on the different requirements with regard to quality that have to be fulfilled.

[24] Benes et al. (2012), p. 138.

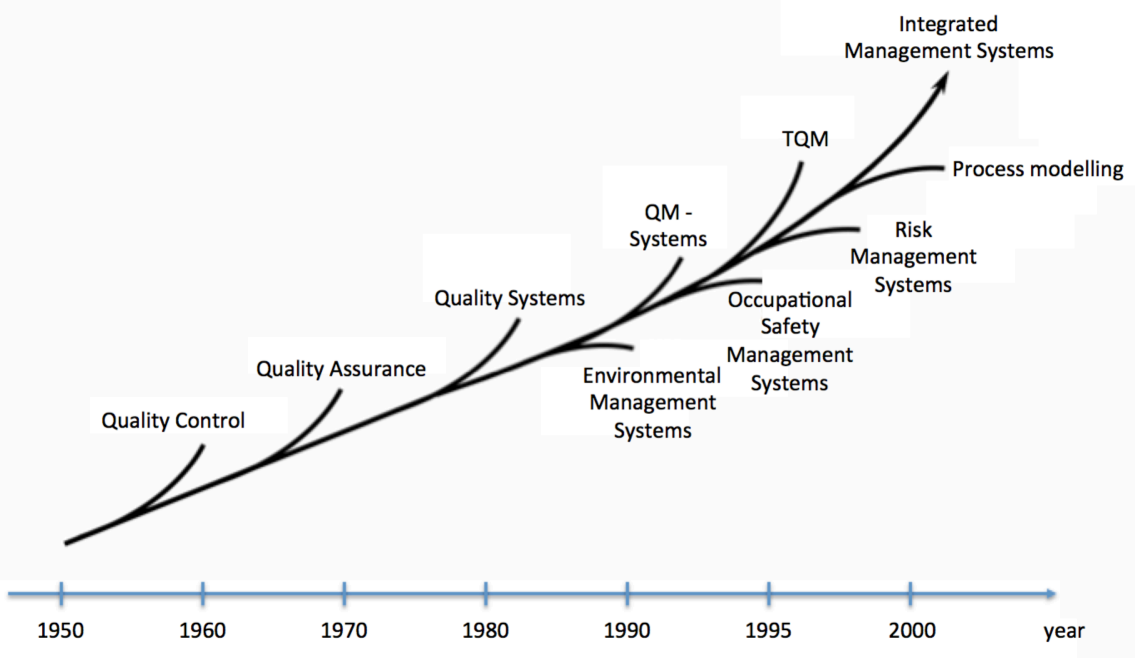

Figure 3: Evolvement of quality management and related management systems over time[25].

The international standard EN ISO 9001:2008 provides minimum requirements for organisations that wish to implement a quality management system[26]. The purpose of this standard is to guarantee that a company has a system ensuring the delivery of a product or service in conformance with quality requirements and that the system is being operated effectively.

According to ISO 9000 following elements build up a quality management system[27]:

- A structural organisation including responsibilities
- Procedures and processes to ensure conformity with the relevant standard
- Documented and realised working instructions
- Resources for quality management system realisation

ISO 9001 uses a process approach that means that organisations have to identify and manage their processes that make up their quality management systems[28]. A process can be defined as a repeatable sequence of activities with measurable inputs, value adding activities and measureable outputs, where each process has an owner who adds value to the input and is responsible for the output[29]. Four different main processes are required by ISO 9001: (1) management responsibility, (2) management of resources, (3) product realisation and (4) measurement, analysis and improvement.

An important tool of ISO series is the PDCA-cycle developed by Deming[30]. However, it is also propagated in abbreviated form in other management standards. Based on already

[25] Benes et al. (2012), p. 280.
[26] Austrian Standards Institute (2008)
[27] ISO 9000 (2005)
[28] Wagner et al. (2008), p. 5.
[29] Nally et al. (2007), p. 218.
[30] Deming (1993), p. 132.

implemented processes a systematically continual improvement can be realised. Hence, all processes of an organisation should be designed according to the PDCA-cycle. The four steps in a PDCA-cycle are: (1) Plan: Definition of targets and processes necessary to achieve these targets. (2) Do: Implementation of the planed processes. Furthermore, during this step data is collected to perform analysis in the subsequent step. (3) Check: Actual results are compared to planned targets. If deviations occurred then measures would have to be taken in the following step: (4) Act: Root causes for deviations are analysed and corrective actions are initiated.

In the following, the main chapters of ISO 9001 are represented, as pharmaceutical quality management systems are basically similarly structured (numbering according to the ISO standard):

(4) Quality Management System

- (4.1) General Requirements
- (4.2) Documentation Requirements

(5) Management Responsibility

- (5.1) Management Commitment
- (5.2) Customer Focus
- (5.3) Quality Policy
- (5.4) Planning
- (5.5) Responsibility and Authority
- (5.6) Management Review

(6) Resource Management

- (6.1) Provision of Resources
- (6.2) Human Resources
- (6.3) Infrastructure
- (6.4) Work Environment

(7) Product Realisation

- (7.1) Planning of Product Realisation
- (7.2) Customer Related-Processes
- (7.3) Design and Development
- (7.4) Purchasing
- (7.5) Production and Service Provision
- (7.6) Control of Monitoring and Measuring Devices

(8) Measurement, Analysis and Improvement

- (8.1) General
- (8.2) Monitoring and Measurement
- (8.3) Control of Nonconforming Product
- (8.4) Analysis of Data

(8.5) Improvement

A comprehensive quality management system will encompass all processes supporting development, manufacturing and stakeholder relationship and includes the standards, policies and procedures to measure those processes with regard to performance and continual improvement[31].

2.3 Pharmaceutical quality management

Within the pharmaceutical manufacturing environment the various functions related to quality management are critical and there is a need to clearly understand the difference between quality management, quality assurance and quality control. An efficient quality management in the pharmaceutical environment results from the correct interfacing of these three elements including risk management as an additional integrative dimension (Figure 4).

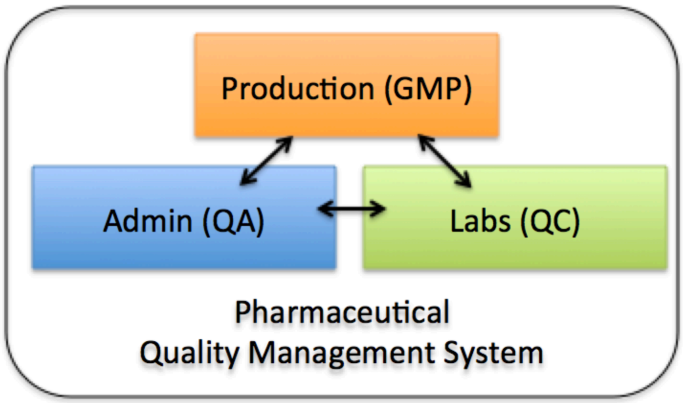

Figure 4: The relationship between pharmaceutical quality management, quality assurance (QA), Good Manufacturing Practice (GMP) and quality control (QC) [32]

Pharmaceutical quality elements as seen in Figure 4 have a hierarchical relationship: Quality management providing the overall policy of the organisation towards quality acts as the framework and comes above everything else. Quality management contains quality assurance as a proactive approach, which takes care that quality is achieved. GMP is part of quality assurance and deals, among others, with the risks that cannot be tested and builds quality into the products. Finally, quality control is part of GMP and is focused on testing of the environment and facilities as well as the testing of the raw materials, intermediates and final products in accordance with predefined standards[33].

According to the WHO good manufacturing practices[34] in the pharmaceutical sector quality management is usually defined as the aspect of management function that determines and implements the quality policy, i.e. the overall intention and direction of an organisation

[31] Arling et al. (2008), p. 239.
[32] Sarker (2008), p. 19.
[33] McCormick (2002), p. 30.
[34] World Health Organization (2011), p. 103.

towards quality, formally expressed and authorised by top management. Similar to ISO 9001 the attainment of the quality objective is the responsibility of senior management and requires the participation and commitment by staff in many different departments at all levels within the company[35]. However, a company's quality management also integrates specific groups or stakeholders outside the company, e.g., suppliers and regulators. Thus, pharmaceutical quality management is getting close towards total quality management. Beside this, the basic elements of pharmaceutical quality management are[36]:

- A quality system acting as an appropriate infrastructure, including the organisational structure, procedures, processes and resources
- Systematic actions necessary to assure adequate confidence that the medicinal product will fit its purpose. The totality of these actions is termed quality assurance.

Before moving on to the discussion of quality assurance and GMP a brief definition of pharmaceutical quality is provided. One possible explanation has already been given in the introduction, where it was stated that a high quality pharmaceutical product is free of contamination and reproducibly delivers the therapeutic effect promised in the label to the customer. Though this crisp interpretation gets to the heart of requirements on pharmaceutical quality, a more elaborative explanation is required. In fact the pharmaceutical quality parameters are defined in product specifications that are part of marketing authorisations reviewed by the competent authorities. Products have to fulfil requirements with regard to identity, strength, purity and bioavailability. McCormick defines these aspects as follows[37]:

- Identity means that the product must comply with the information given on the product label with regard to the (active) substances contained in the formulation. That means that no mix-ups must occur.
- Strength refers to the quantity of ingredients claimed on the label within applicable limits of the specifications as determined by chemical testing or with regard to a biological standard.
- A dosage form can be regarded as pure in the case raw materials used or a drug in a dosage form is free from undesirable chemical, biological or physical entities as set forth in the relevant specification.
- Finally, bioavailability requirements assure that upon administration, the product provides the active ingredient for the intended therapeutic availability.

Quality assurance now encompasses those processes and activities, performed to assure that a pharmaceutical product consistently fulfils its requirements and is fit for its intended use. In the pharmaceutical industry this means the activities that result in the assurance of the product's identity, strength, purity and bioavailability as defined above[38]. Recently, more advanced approaches towards quality assurance have evolved, i.e., to include quality systems[39] and risk management[40] approaches. The pharmaceutical industry is increasingly interested to adopt such approaches as they allow the manufacturers to apply new quality management principles in order to more effectively and efficiently assure product quality and better allow harmonisation with international regulatory quality system requirements.

[35] European Commission (2013), p. 2.
[36] World Health Organization (2011), p. 103.
[37] McCormick (2002), p. 26.
[38] Siegel et al. (2008), p. 202.
[39] ICH (2008)
[40] ICH (2005)

Good manufacturing practices (GMP) is defined in the EU guidelines[41] as that part of quality management which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorisation. Hence, GMP is both concerned with manufacturing and quality control.
The EU guidelines define further the basic requirements of GMP as listed in Table 3. It is clear that risk management activities would have to take into account these relevant aspects. Moreover, it has to be emphasised that GMP is part of quality assurance as described above and hence, GMP can be regarded as a preventive framework that assures that manufacturing operations are performed in a correct manner. Therefore, unlike quality control, GMP measures performed can affect the quality of any operation[42] and GMP activities act as general strategies to mitigate the risks associated with the manufacturing of medicinal products.

Table 3: Basic requirements of GMP[41]

(1)	All manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with their specifications;
(2)	Critical steps of manufacturing processes and significant changes to the process are validated;
(3)	All necessary facilities for GMP are provided (e.g., qualified and trained personnel, premises and space, suitable equipment);
(4)	Instructions and procedures are written in an instructional form;
(5)	Procedures are carried out correctly and operators are trained to do so;
(6)	Records have to be made during manufacture which demonstrate that all steps required by the defined procedures were appropriately realised and that the quantity and quality of the product was as expected;
(7)	Significant deviations are recorded and investigated including elucidation of root causes and implementation of corrective and preventive actions;
(8)	Manufacturing records enabling a complete batch history have to be retained;
(9)	The distribution of products should minimise any risk to their quality taking account of Good Distribution Practice;
(10)	A system for batch recall is in place;
(11)	Product complaints are investigated and measures are taken to prevent the reoccurrence of reason for complaint.

It has to be pointed out that GMP rules are a central part of pharmaceutical quality management, although they don't contain specific guidance on approaches towards pharmaceutical manufacturing but a general framework. The idea behind this is to transfer the responsibility for the quality of the pharmaceutical product from the authorities to the manufacturers. Table 4 provides an overview of different GMP guidelines with regard to their validity in different regions and countries.

[41] European Commission (2013), p. 4.
[42] Siegel et al. (2008), p. 202.

Table 4: Overview of different national and international GMP-guidelines[43]

Title	Relevance
	International
WHO GMP-Guideline	Worldwide recommendation (guideline); basis for several national guidelines
PIC/S-Guideline	Guideline for member states of PIC/S (association of national authorities with regard to harmonisation of GMP-guidelines)
ICH Q7	Guideline of the International Conference on Harmonisation
	Europe
EC Regulations	Directly applicable European standards (no need for national transposition)
EC Directives	Have to be transposed to national law
Guidelines, Note for applicants, recommendations	Implementation not explicitly required; however guidelines can be regarded as expert opinions
	Austria
Federal law	Arzneimittelgesetz (AMG)
Decree	Arzneimittelbetriebsordnung (AMBO) detailing AMG
	USA
Regulation	Code of Federal Regulation (CFR) contains in part 21 requirements of cGMP (current good manufacturing practices)

Finally, the last building block of a comprehensive pharmaceutical quality management system is quality control that acts as an integral part of Good Manufacturing Practice, and is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials or products are not released until their quality has been judged satisfactory[44]. Table 5 summarises resources and tasks of quality control. Obviously, risk-based approaches would have to take these tasks, e.g., as strategies for risk control, into account.

Table 5: Resources, tasks and related objects of pharmaceutical quality control[45]

Resources	Tasks	Objects
Adequate facilities	Sampling	Starting materials
Trained personnel	Inspecting	Packaging materials
Approved procedures	Testing	Intermediates
Approved specifications	Monitoring	Bulk products
	Releasing/rejecting	Finished products
		Environmental conditions

[43] Fischer et al. (2010), p. 152.
[44] European Commission (2013), p. 5.
[45] McCormick (2002), p. 30.

A modern approach towards a pharmaceutical quality system is described in the ICH Q10 guideline "Pharmaceutical Quality System"[46]. This guideline is not intended to define new legal requirements that amend GMP regulations but describes a model for a pharmaceutical quality system that can be implemented to facilitate innovation and continual improvement with the intention to establish and strengthen a link between all elements of the pharmaceutical product's life cycle. Moreover, it is the intention of ICH Q10 to complement and integrate existing GMP-regulations and ICH Q8 (Pharmaceutical Development) and Q9 (Quality Risk Management) guidelines. Among others, ISO quality management system guidelines form the basis for ICH Q10 and Table 6 shows a comparison of the requirements of ISO 9001 and ICH Q10, respectively.

Table 6: Comparison between ISO 9001 and ICH Q10 requirements[47]

ICH Q10	ISO 9001:2008
1 Pharmaceutical Quality System	**4 Quality Management System**
1.1 Introduction	
1.2 Scope	**1 Scope**
1.3 Relationship of ICH Q10 to Regional GMP Requirements, ISO Standards and ICH Q7	
1.4 Relationship of ICH Q10 to Regulatory Approaches	
1.5 ICH Q10 Objectives 1.5.1 Achieve Product Realisation 1.5.2 Establish and Maintain a State of Control 1.5.3 Facilitate Continual Improvement	**6 Resource Management** 7.1 Planning of Product Realisation 7.2 Customer-related Processes 7.3 Development 7.4 Purchasing 7.5 Production and Service Provision **8 Measurement, Analysis and Improvement**
1.6 Enablers: Knowledge Management and Quality Risk Management	
1.7 Design and Content Considerations	0.1 General
1.8 Quality Manual	4.2 Documentation Requirements
2 Management Responsibility	**5 Management Responsibility**
2.1 Management Commitment	5.1 Management Commitment
2.2 Quality Policy	5.3 Quality Policy
2.3 Quality Planning	5.4 Planning
2.4 Resource Management	**6 Resource Management**
2.5 Internal Communication	5.5 Responsibility, Authority and Communication
2.6 Management Review	5.6 Management Review
2.7 Management of Outsourced Activities and Purchased Materials	7.4 Purchasing (partly)
2.8 Management of Change in Product Ownership	

[46] ICH (2008)
[47] Leitgeb (2011), p. 26.

ICH Q10	ISO 9001:2008
3 Continual Improvement of Process Performance and Product Quality	
3.1 Lifecycle Stage Goals	**7 Product Realisation (partly)**
3.2 Pharmaceutical Quality System Elements	**8 Measurement, analysis and improvement (partly)**
4 Continual Improvement of the Pharmaceutical Quality System	
4.1 Management Review of the Pharmaceutical Quality System	5.6 Management Review
4.2 Monitoring of Internal and External Factors Impacting the Pharmaceutical Quality System	8.4 Analysis of Data (partly)
4.3 Outcomes of the Management Review and Monitoring	8.5 Improvement

As can be seen in Table 6 ISO 9001 and ICH Q10 guide correspond well in the main parts of their requirements. Both standards define requirements for a quality system. Whereas ICH Q10 prescribes three main objectives with regard to a pharmaceutical quality system, i.e. achieving product realisation, establishing and maintaining a state of control and facilitating continual improvement, ISO postulates similar requirements with regard to resource management, product realisation and measurement, analysis and improvement. With regard to management responsibility, the requirements of both documents are analogue. Further ICH Q10 requirements correspond well with ISO 9001 approaches. ICH Q10 has two chapters with regard to continual improvement, one for improvement of the quality of products and performance of processes and another chapter for continual improvement of the pharmaceutical quality system itself. Corresponding contents can be found in ISO 9001 mainly in the chapter "measurement, analysis and improvement".

In the following section a closer look on the quality system approach of the ICH Q10 guideline is provided as it can be regarded as integrating link between standard pharmaceutical quality management and risk management.

One of the main aspects of ICH Q10 is that it promotes the integration of all relevant parts of a pharmaceutical product's lifecycle, i.e., (1) pharmaceutical development with regard to the development of drug substances, formulations, associated manufacturing processes and analytical methods, (2) tech transfer, e.g., upscaling of processes from lab or pilot scale to full scale, (3) commercial manufacturing with the application of regional GMP-requirements and finally (4) product discontinuation with the focus on retention of documentation and samples. One of the main reasons for this integration is that data and information that have been generated in a certain lifecycle stage can be efficiently used in other stages. This concept is, for instance, also promoted by ICH Q8[48] guideline "Pharmaceutical Development", that states *"A more systematic approach to development (also defined as quality by design) can include, for example, incorporation of prior knowledge, results of studies using design of experiments, use of quality risk management (see ICH Q10) throughout the lifecycle of the product…Product and process understanding can be updated with knowledge gained over the product lifecycle."*

[48] ICH (2008), p. 9.

As outlined in Table 6 implementation of a pharmaceutical quality system according to ICH Q10 should result in the achievement of three main outputs. First, the goal is to implement and maintain a quality system that results in products able to meet the needs of patients and other stakeholders. Second, focus is put on the realisation of effective monitoring and control systems to assure the on-going quality of the products, processes and the quality management itself. Third, a quality system concept according to ICH Q10 promotes continual improvement of products, processes and the quality system itself. ICH Q10 states in detail that quality risk management can be useful to identify the relevant monitoring and control systems and further to prioritise areas for continual improvement. Moreover, quality risk management is identified as an enabler and as an integral part to an effective quality system. According to ICH Q10, it can provide a proactive approach to identifying, evaluating and controlling potential risks to pharmaceutical quality.
Besides the requirement of regional GMP guidelines to introduce specific quality system elements, ICH Q10 specifically promotes four elements:

- Monitoring system for process performance and product quality
- System for corrective action and preventive action (CAPA)
- Change management system
- Management review with regard to product quality and process performance.

For each of these elements ICH Q10 requires the use of sound quality risk management approaches. With regard to the process performance and product quality monitoring system quality risk management should be used to establish a control strategy, i.e. which parameters of the input materials, the manufacturing process and the finished products have to be tested because of their potential high risk with regard to final product quality and patient requirements. A CAPA-system requires investigations of root causes, where "*the level of effort, formality and documentation of the investigation should be commensurate with the level of risk, in line with ICH Q9"*[49]. In the case of change management, quality risk management can be useful to evaluate proposed changes with regard to their effect on product quality and process performance.
Figure 5 shows a graphical representation of the model of a pharmaceutical quality system according to ICH Q10. It can be easily seen that the pharmaceutical quality system encompasses all stages of the lifecycle of a product, from development and tech transfer to commercial manufacturing and product discontinuation. GMP is an important element of the quality system. The importance of management responsibilities is outlined and the four important elements of a quality system according to ICH Q10 are listed. Knowledge management and quality risk management are intended to promote the quality system approach.

[49] ICH (2005), p. 2.

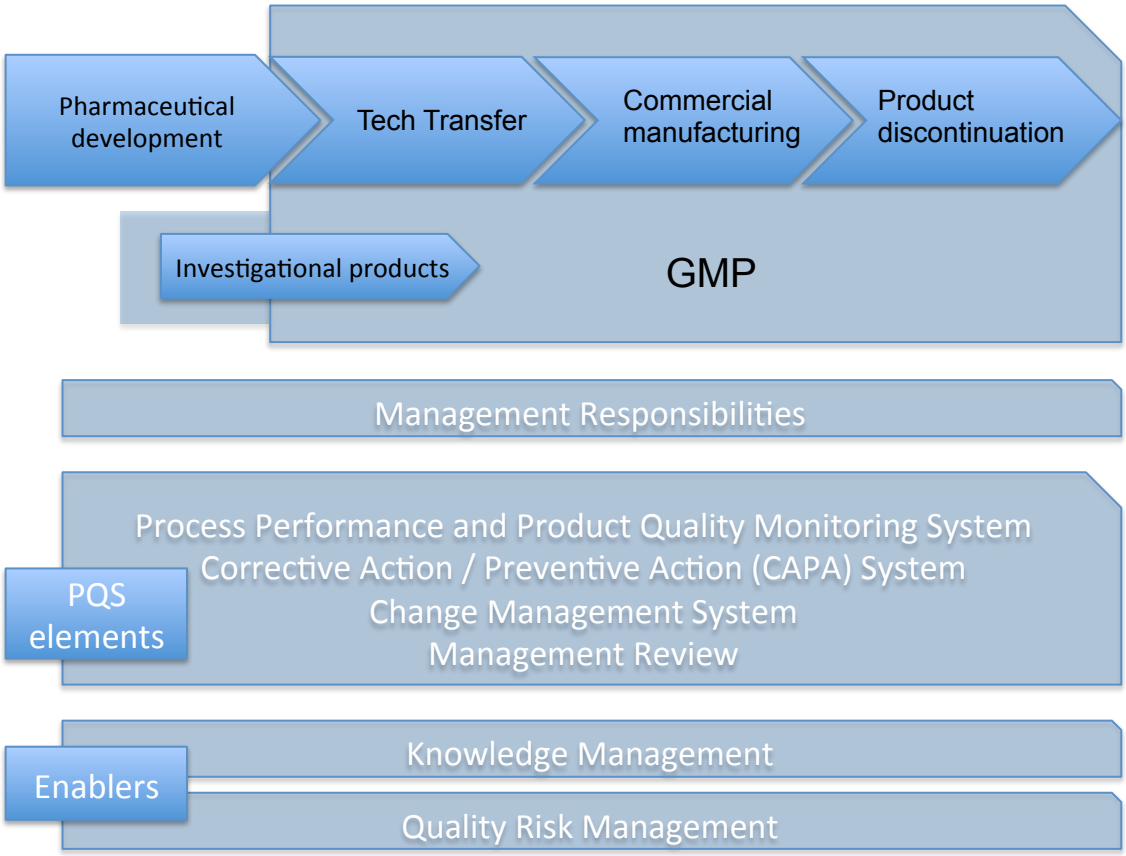

Figure 5: Realisation of a pharmaceutical quality system according to ICH Q10[50]

Although the main requirements for pharmaceutical quality systems and GMP-production are basically the same, additional requirements may arise with regard to the manufacturing of special medicinal products, e.g., parenterals, antibiotics or highly potent active pharmaceutical ingredients. As the recommendation for integrating quality risk management in existing quality systems will be based on quality systems deployed in the solid oral dosage form industry (e.g., tablets), Figure 6 gives a brief overview of a typical manufacturing process for an solid oral dosage form.

[50] ICH (2008), p. 17.

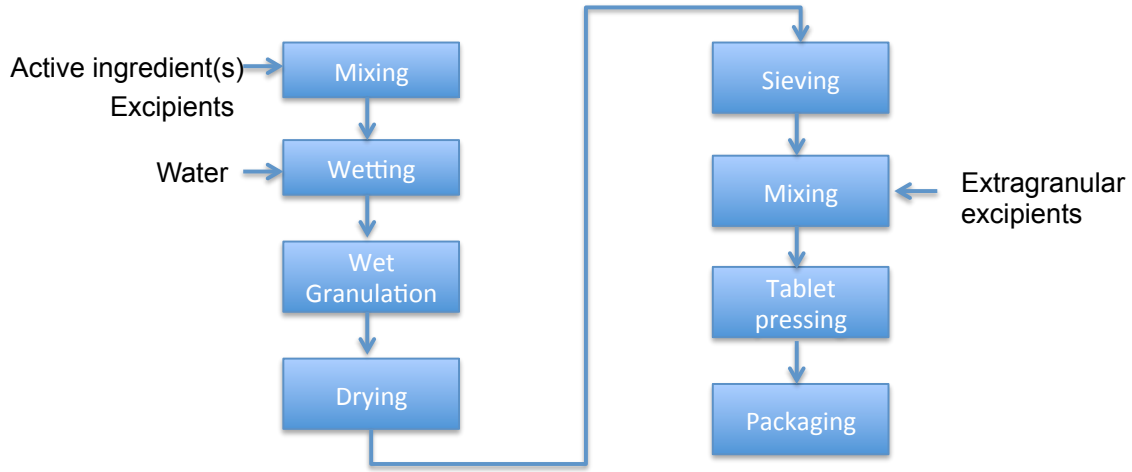

Figure 6: Typical process to manufacture a solid oral dosage form (e.g., a tablet)

A typical manufacturing process starts with the mixing of active ingredients and excipients (e.g., fillers, diluents). Before tableting can take place, granulation may be required as pre-treatment. Often wet granulation (besides dry granulation) is used to (1) improve flow characteristics of the powder by increasing particle size, (2) improve compression characteristics, (3) prevent segregation, as granulated particles cannot separate anymore and (4) to reduce dust during manufacturing[51], leading to a decreased risk of cross contamination. Drying can be performed by a separate unit operation or wet granulation and drying are realised within the same equipment. Sieving is then carried out to reduce the amount of agglomerated granulate. Sieving might also be part of the management of foreign particles and should prevent the contamination of the product, e.g., with spills. In a next step, some additional extragranular excipients may be added (e.g., disintegrants, flavours, colours) and finally, tablet pressing is performed. Pressed tablets are then filled or blistered into primary packaging.

Table 7 provides a choice of different quality systems elements used in pharmaceutical production. In the later sections, the focus will be put on some of these elements with regard to the integration of quality risk management.

Table 7: Quality system elements in the line of pharmaceutical manufacturing as basis for the integration of quality risk management[52,53]

Quality system group	Quality systems required by GMP
Facilities and equipment	Equipment qualification
	Facility qualification
	Equipment maintenance
	Equipment and facility cleaning
	Equipment calibration
Production	Process validation

[51] Armstrong (2007), p. 3657.
[52] Fischer et al. (2010), p. 183.
[53] Nally et al. (2007), p. 218.

Quality system group	Quality systems required by GMP
	Manufacturing operations
	Batch record execution and review
	Product sampling
	Reprocessing and rework
Packaging and labelling	Packaging operations
	(see manufacturing operations)
Materials	Raw materials and packaging materials
	Receipt, inspection, release, storage
Quality control	Sample management
	Test methods and specifications
	Method validation
	Instrument qualification, calibration and maintenance
	Reference standards management
	Reagents and solutions management
	Failure investigation
	Contract laboratories management
Quality assurance	Documentation management
	Standard operating procedures, protocols, records, forms, log books
	Training
	Change control
	Product quality review (annual product review)
	Internal and external auditing
	Complaint management
	Batch record review and product release
	Supplier qualification
	Product stability program
	Computerised system validation
	Recalls

It has to be emphasised that most of the quality system elements pointed out above involve more than one department of a pharmaceutical manufacturing company and hence, it is of upmost importance that policies, master plans or umbrella standard operating procedures are in place with regard to an integrative function with respect to all the departments and internal parties involved[54].

[54] Nally et al. (2007), p. 219.

3 Risk management and specifics of the pharmaceutical industry

3.1 Introduction and historical overview

During the last decades it has become of upmost importance for companies as well as for public institutions and governments to consider and take actions upon a variety of risks appearing internally and externally[55]. The global financial crisis, a drastically changing marketing environment coming along with specific demands from internal and external stakeholders and a number of sever natural disasters are just some reasons why organisations need to be prepared for disturbances[56]. Today, many organisations heavily rely on the global marketplace, and sourcing from other countries as well as having global customers has become more common[55]. In combination with higher demands and expectations from various internal and external stakeholders risk management approaches become more and more important in organisations[57]. It is clear that in the light of scarce internal resources, organisations are unable to give every potential risk that may jeopardise (or benefit) its economic, social or environmental targets the same attention. Hence, potential hazards have to be prioritised and measures to deal with them have to be planned, realised and controlled. This is one of the major aspects of risk management approaches. In fact, significant hazards and operational uncertainties are present in every manufacturing organisation and an integrated approach that takes into account operations, employees, assets and the management approach, is necessary to discover the risks and to develop methods for managing them[58].

In the following section a brief overview on the history of risk including important milestones in the development of risk management is provided.

The term risk probably originates from the Italian verb "risicare" which means "to dare"[59]. However, the history of risk management can be traced back to early times of mankind as for the first time a king or a chieftain decided to fortify walls, make alliances with other tribes or store food for times of scarce supplies[60]. For example, at around 3000 BC a tribe in the Euphrates and Tigris – valley known as the *Aspiu* were known to have served as (risk analysis) consultants for people that were to make difficult, uncertain or risky decisions[61].

In the 15th and 16th century shipping companies in Europe started to insure against piracy attacks, plunderings and fire[62] and thus mitigate the risk of financial losses. In 1792, Laplace set the basis of modern quantitative analysis, a prerequisite for many types of risk management, by calculating the probability of death with and without smallpox vaccination[63]. In the 18th century, the mathematician Thomas Bayes notably contributed to the further development of probability and statistics by postulating Bayes' theorem, which expresses how a subjective degree of believe should rationally change to account for evidence[64]. Hence, the development of probability theory and statistics allowed quantifying risk in a meaning-

[55] Bustad et al. (2013), p. 16.
[56] Jüttner et al. (2011), p. 246
[57] Hopkin (2012), p. 5.
[58] Islam (2012), p. 258.
[59] Aghili (2010)
[60] Hubbard (2009), p. 22.
[61] Corvello et al. (1985), p. 103.
[62] Klügl (2013)
[63] Dhillon (2003), p. 24.
[64] Bellhouse (2004), p. 3.

ful way[65]. From the 18th to the 20th century risk management was mainly exemplified in insurance, banking, financial markets and partly in government agencies dealing with public health, however, there were no attempts of retailers or manufacturers to use similar approaches to assess and manage risks in their processes, introduction of new products or acquisitions[65].
Though risk management began to be studied after World War II in a more intensified way, several sources date the origin of modern risk management in the late 1950s and early 1960s[66,67,68]. Since the early 1970s, especially financial risk management gained more importance[67]. By the way, risk management was long associated with market insurance only with the aim to protect individuals and companies from various financial losses associated with accidents. International requirements for risk management were first defined in the 1990s, and financial institutions developed internal risk management models to protect themselves from unanticipated risks. Governance of risk management became essential, integrated risk management was introduced and first risk manager positions were created[67]. However, until the end of the 20th century, risk management was not in the standard repertoire of most organisations[65].
An important step towards the further development of financial risk management was the introduction of the US Sarbanes-Oxley Act (SOX) in the year 2002 that requires the certification of annual and quarterly financial reports by the chief executive and chief financial officer of all companies with US securities registrations, with criminal penalties for knowingly making false certifications[69]. The Third Basel Accord (Basel III), that supersedes Basel I and Basel II, respectively, that is to be introduced from 2013, contains standards for banking laws and regulations and is aimed to establish sound risk and capital management requirements to ensure each bank holds reserves sufficient to guard against its risk exposure given its lending and investment practices[69].
Risk management standard ISO 31000 was introduced in 2009, providing principles and generic guidelines on risk management that can be applied throughout the life of an organisation, and to a wide range of activities, including strategies and decisions, operations, processes, functions, projects, products, services and assets[70].

Today, there are a number of reasons why an organisation would establish a risk-based approach within an associated risk management framework. One major objective of risk management is to assure compliance with various rules and regulations set up either by the company itself or by the government[71] (either with regard to financial or operative risk-based approaches). By identification and assessment of financial and/or operative risks the outcome information can be used to assist decision-making and hence, by supportive risk management, financial and organisational operations will be more efficient with regard to ease and speed by which objectives are obtained and more effective, i.e. delivery of required objectives[72].

[65] Hubbard (2009), p. 22.
[66] Crockford (1982), p. 170.
[67] Dionne (2013), p. 1.
[68] Williams et al. (1995)
[69] Collier (2009), p. 9.
[70] ISO 31000 (2009)
[71] Bustad et al. (2012), p. 16.
[72] Hopkin (2010), p. 47.

3.2 General aspects about risk

When dealing with the concepts about risk one quickly finds that the word *risk* is a rich source of considerable confusion, even among those people who are specialised in this topic. Hence, there is no single valid definition of *risk* and *risk management*. On the contrary, multiple definitions have evolved in multiple professions, when analysts and managers are using the word *risk* to mean some very different things[73]. This section reviews recent risk management literature and provides an overview of the different existing and valid meanings of the term *risk* and *risk management*. Subsequently a standard definition of risk that will be further used in this work is given.

According to the Dictionary of Contemporary English risk is defined as *the possibility that something bad, unpleasant, or dangerous may happen*[74].

Most risk management publications define risk as an event that occurs with a certain probability in combination with a consequence in the case of occurrence[75]. According to this definition risk may be outlined as: risk = frequency (events/time) x severity or magnitude (consequence/event)[76]. ICH Q9 guideline defines risk as the combination of the probability of occurrence of harm and the severity of that harm[77]. However, ICH Q9 states that it is difficult to achieve a shared understanding of the term risk among different stakeholders as each stakeholder might perceive different potential harms, place a different probability on each harm and attribute different severities to each harm.

In statistics risk can be defined as the expected value of a loss function[78].

In the traditional view, risk is always seen as a potential loss or failure; however, a more modern view of risk also includes the chance of opportunity in addition to the chance of loss[79]. ISO 31000 and the associated document ISO Guide 73 give the following definition: risk is the effect of uncertainty on objectives of an organisation, i.e. a deviation from the expected[80]. Therefore, the definition of ISO 31000 includes negative as well as positive effects of potential hazards on objectives. As this definition links risks to objectives, it can easily be applied when the objectives of an organisation are clear and fully stated[81]. Taking the ISO-definition into account, the term *uncertainty* has to be properly defined, since uncertainty is the source of risk[82]. According to Knight, an economist of the early 20th century, who wrote a fundamental thesis on risk titled "Risk, Uncertainty and Profit", a quantifiable and an immeasurable uncertainty have to be differentiated[83]. Hence, Knight made a distinction between risk and uncertainty, where risk is something measurable, while uncertainty is not quantifiable and the probabilities of the possible outcomes are not known[84]. Hubbard[73] distinguishes between *uncertainty* and *strict uncertainty*, where uncertainty can be measured (contrary to Knight's use of the term) by the assignment of probabilities to various outcomes. In the case of strict uncertainty possible outcomes are identified, but no probabilities could be assigned to them.

[73] Hubbard (2009), p. 8.
[74] Longman (2003), p. 1421.
[75] McNeil et al. (2005), p. 19.
[76] Islam et al. (2012), p. 258.
[77] ICH (2005), p. 1.
[78] Hines et al. (1990)
[79] Kirchsteiger (2002), p. 235.
[80] ISO 31000 (2009), p. 1.
[81] The Association of Insurance and Risk Managers et al. (2010), p. 2.
[82] Peters (1999), p. 1.
[83] Knight (1921), p. 11.
[84] Colicchia et al. (2012), p. 404.

Islam identified several commonalities in most of the definitions of risk[85]: In many definitions risk has a dual meaning, i.e. the probability that a potential hazard will be realised and the probability of the harm itself. Furthermore, risk is often associated with some kind of loss. Moreover, risk is often regarded subjective and risk is seen as a threat to organisations that might affect the manner in which business processes are carried out.

There are different types of risk that an organisation may face, including market risks, quality risks, credit risks, health and safety risks, environmental risks, fire risks, IT risks, technical risks and so on[86]. Risk is perceived differently with regard to gender, age and (organisational) culture, e.g., more experienced managers are more risk averse than younger ones[87]. Generally speaking, risk perception is about different ratings of hazards with regard to their effect and probability and why some people rate a specific risk as significant while others don't[88]. For instance, people have different risk perceptions when they rate the risk to themselves, to their family, to their company or to people in general[89]. Another aspect, that affects risk perception is the degree of control, a person might have over a rated hazard, where control is an important aspect in account for risk denial[89].

In order to clarify the use of the term *risk* in this work, the author will follow the definition of the ICH Q9 guideline that is close to the ISO 31000 definition.

3.3 Risk management

The Harvard Business Review dated 1956 was one of the first journals dealing namely with the term *risk management*[90,91]. Basically, risk management is aimed to assess and control the level of risk associated with a specific hazard and to mitigate risk effects and thus it became a major aspect of an organisation's activities with regard to reach overall goals effectively and efficiently[92]. When managing risks, an organisation identifies, analyses and evaluates whether a certain risk should be modified by risk treatment in order to satisfy given risk criteria[93].

ISO 31000 was the first standard on risk management with worldwide acceptance and applicability[94]. ISO 31000 provides a generic guideline for the set-up, implementation and maintenance of risk-based approaches throughout an organisation. In order to make risk management effective, ISO 31000 recommends that *organisations develop, implement and continuously improve a framework whose purpose is to integrate the process for managing risk into the organisation's overall governance, strategy and planning, management, reporting processes, policies, values and culture*[93]. According to Purdy ISO 31000 has four objectives: (1) Creation of a commonly used risk terminology; (2) Establishment of performance criteria that have to be adopted by organisations; (3) Provision of a framework on how to perform the risk management pro-

[85] Islam (2008), p. 258.
[86] Sadgrove (2005), p. 7.
[87] MacCrimmon (1986), p. 20.
[88] Agerberg et al. (2012), p. 12.
[89] Sjöberg (2000), p. 3.
[90] Gallangher (1956), p. 45.
[91] Islam (2012), p. 259.
[92] Labodova (2004), p. 571.
[93] ISO 31000 (2009), p. v.
[94] Bayerisches Staatsministerium (2011), p. 31.

cess in practice, from the identification to the treatment process; (4) Provision of guidelines on how to implement the risk management process in different organisations[95].

This section provides a sound background on the risk management process based on ISO 31000.

The implementation of risk management according to ISO 31000 starts with the set-up of a management framework that establishes the basis for risk management throughout the organisation. This framework consists of some important components as shown in Figure 7.

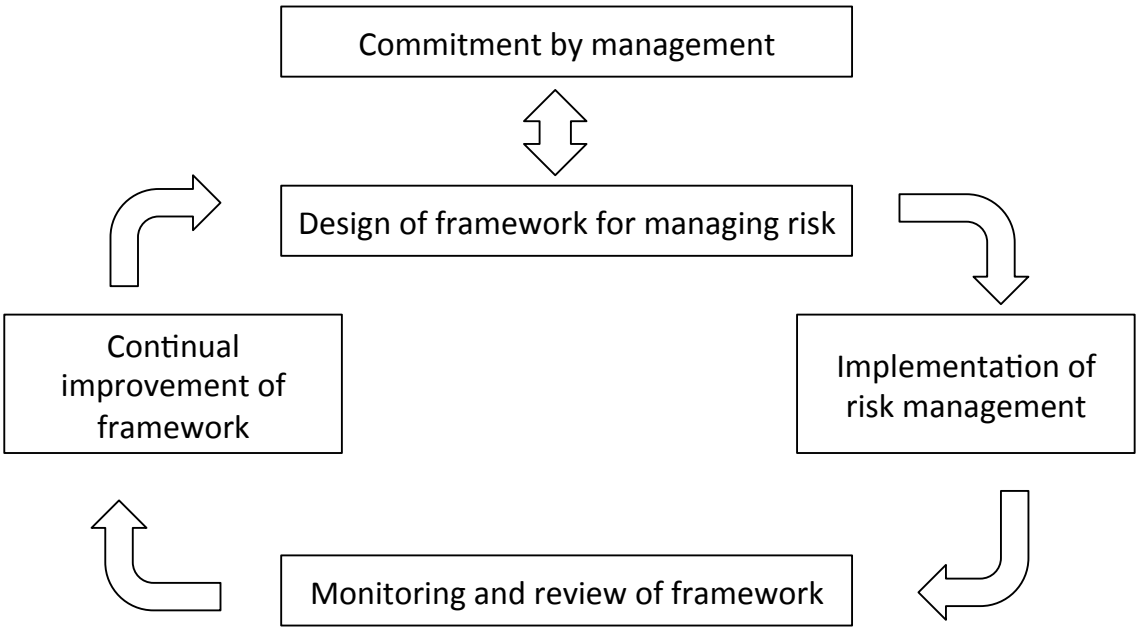

Figure 7: Framework for risk management according to ISO 31000[96]

Management commitment is inevitable when introducing a risk management system, as senior management is responsible to define the risk policy and assign appropriate resources. According to ISO 31000 management is also responsible for the alignment of the organisation's culture with the risk management policy, determination of performance indicators, ensuring legal and regulatory compliance, allocation of accountabilities and responsibilities with regard to risk management within the organisation and ensuring that the risk management framework continues to remain appropriate.

The design of the framework for managing risk consists of various subsequent steps. First, it is necessary to develop an understanding of the organisation and its context. Here it is important to take into account the internal and external context of the organisation, as these factors may significantly influence the design of the risk management framework. The evaluation of the external context should take the social, cultural, political, legal, regulatory, financial, technological and economic aspects into account. The internal context would include focusing on, e.g., organisational structures, roles and responsibilities, policies and objectives, and the organisational culture. In a next step, the risk management policy has to

[95] Purdy (2010), p. 881.
[96] ISO 31000 (2009), p. 9.

be established. The risk management policy should primarily contain the organisation's rationale and goals for risk management, the responsibilities within the organisation, as well as the commitment of senior management, e.g. with regard to allocation of resources. Moreover, the organisation has to assign accountability and authority in combination with the appropriate competence for managing risks. The design of the risk management framework furthermore requires an appropriate integration into existing organisational processes, so that risk management becomes an integrated part of these processes. As another aspect, the organisation would have to establish internal and external communication and reporting mechanisms to be able to communicate with its internal and external stakeholders.

The next step in the framework for risk management is its implementation. This implementation step takes into account the realisation of the framework itself and of the actual risk management process. During the monitoring step the organisation has to ensure that the risk management is effective and stays well within the defined policy. Finally, the risk management framework should be continually improved, taking into account results of monitoring and reviews.

The risk management process itself simply may be divided into activities that identify risks, activities that analyse their probabilities and impact and finally activities where the handling plan is evaluated and established[97]. Many publications illustrate the general risk management process as loop model emphasising the process as an on-going and learning process[98,99]. This goes along with the process model according to ISO 31000. Only few publications depict the risk management process as linear[100]. The risk management process according to ISO 31000 is shown in Figure 8.

[97] Agerberg (2012), p. 24.
[98] Winch (2010), p. 346.
[99] Baker et al. (1998), p. 567.
[100] Simu (2006), p. 23.

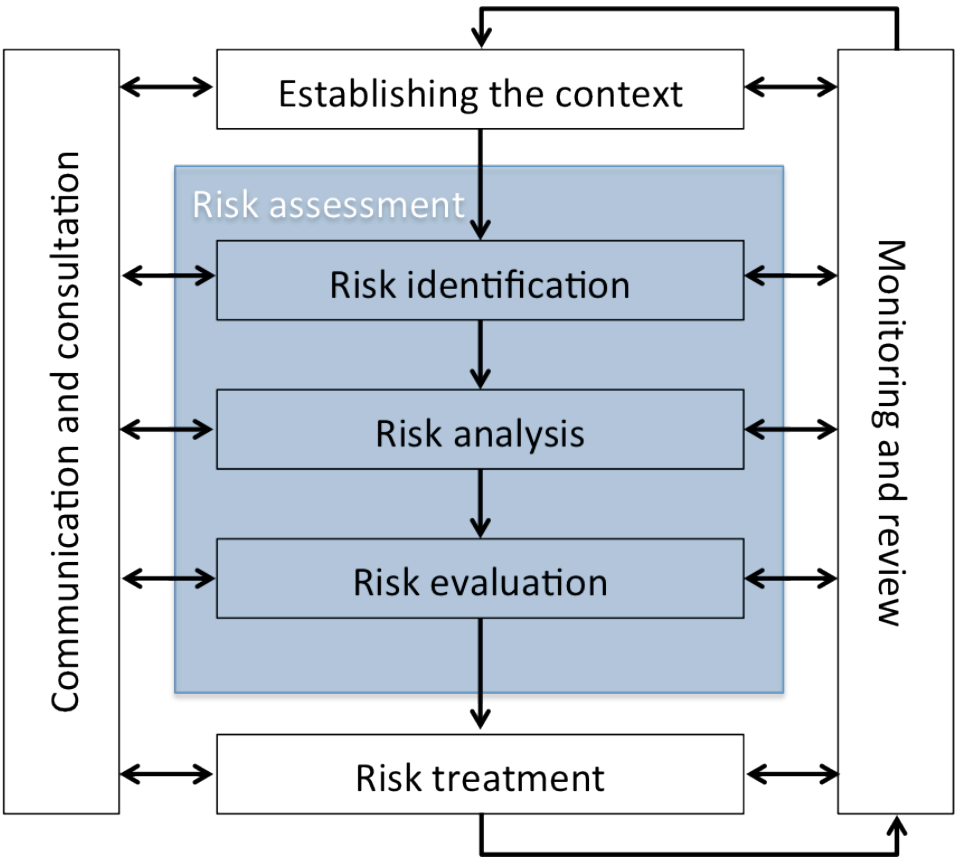

Figure 8: Risk management process according to ISO 31000[101]

As can be seen in Figure 8 the risk management process consists of four major phases, namely risk identification, risk analysis, risk evaluation and risk treatment. These process steps are augmented by risk communication and risk monitoring and review. It is clear that the risk management process has to be tailored with regard to the specific context of an organisation, as it is impossible to design a risk management strategy that is suited for all organisations[102]. For effective information exchange, it is important that all relevant stakeholders are addressed, consulted and informed during all relevant steps of the formal risk management process. Hence, communication and consultation is one important aspect of risk management and ISO 31000 requires that plans for communication and consultation be in place.

Before starting the actual risk assessment workflow, the establishment of the external and internal context within the risk management process has to be performed. According to ISO 31000 the external context takes into account the objectives and concerns of the external stakeholders. Hence, the risk management process and the risk criteria would depend on the social, cultural, political, legal, regulatory and economic aspects of the external stakeholders that have to be addressed. Alignment of the risk management process with the internal context means that the organisational culture, processes, structures and strategies would influence the risk management process and therefore the way in which the organisation seeks to achieve its risk management objectives. ISO 31000 states that the context of the risk management process will vary according to the needs of an organisation. Following

[101] ISO 31000 (2009), p. 14.
[102] Agerberg et al. (2012), p. 16.

aspects are, amongst others, important to consider: definition of goals and objectives of the risk management activities, definition of responsibilities within the risk management process, and definition of the risk assessment methodologies.

For the evaluation of risks that have been identified during the risk management process, risk criteria have to be defined. Risk criteria are used to evaluate the significance of risk. For instance, some criteria can be derived from regulatory requirements or may be imposed by customers (both external context factors). Additionally factors are to be considered when defining risk criteria: definition of likelihood (i.e. probability of occurrence of a certain hazard), definition of the level of risk (e.g., risk as product of severity, likelihood and detectability), and the level at which risk becomes acceptable.

When the organisational set-up is understood, the risk assessment, which consists of risk identification, analysis and evaluation, can be performed. The primary aim of the first step of risk assessment, i.e. risk identification, is to generate a list of risks based on hazards that may be capable of causing deviations with regard to the organisation's objectives. This list is called risk register[103]. A comprehensive risk register is required as a certain risk that is not identified, cannot be included in the further analysis and thus cannot be controlled nor managed adequately[104]. Moreover, the overall success of a risk management system heavily depends on the sound identification of risks, but as this is not possible by senior or risk managers' experience alone, all relevant employees of all levels of an organisation have to be involved[105]. In fact, the employees can be regarded as the real source of risk identification, and are of themselves sources of risk and potential losses[106]. According to the literature, risk identification is one of the less formalised elements in the risk management process[104,107,108]. Rigorous risk identification requires a sound knowledge of the organisation, its processes, the market in which it operates, the regulatory and cultural environment in which the organisation operations are performed, as well as a clear understanding of the organisation's objectives. These aspects are part of the established external and internal context of risk management. ISO 31000 states that the risk identification should include all relevant risks, whether or not their associated hazards are under the control of the organisation. Beside the risk itself, all significant causes and consequences have to be considered. There are a number of techniques available assisting the risk identification process, e.g., brainstorming, questionnaires, business studies, industry benchmarking, scenario analysis, interviews, workshops, incident investigation and audits. Agerberg suggests the basic content of a risk register according to Table 8.

[103] Project Management Institute (2004), p. 289.
[104] Bajaj et al. (1997), p. 363.
[105] Islam (2012), p. 259.
[106] Close (1974), p. 435.
[107] Winch (2010), p. 346.
[108] Agerberg et al. (2012), p. 17.

Table 8: Risk register template[109]

			Impact		Probability				
No.	Risk	Date	Money	Time	Low	High	Mitigation plan	Result	Risk owner
1 2 3									

A risk register may include information about the identified risk, its impact, probability, mitigation plan, results and risk owner.

The next step within risk assessment as part of the overall risk management process is risk analysis. According to ISO 31000 risk analysis provides an input to the subsequent step of risk evaluation. By analysing risks based on the established risk register, causes, impacts, severity and probability for each risk are established. This process is further used to establish the relationship between the risk effect and the risk causes triggering it[110]. ISO 31000 states that risk analysis can be performed qualitatively, semi-qualitatively and quantitatively and with varying degrees of detail. Furthermore, the choice of the risk analysis technique will be based on the nature of the identified risk and the available resources. Singh provides an overview of qualitative and quantitative techniques used for risk assessments (Table 9).

Table 9: Qualitative and quantitative risk assessment techniques[111]

Qualitative techniques	Quantitative techniques
FMEA	Monte Carlo analysis
Fault tree analysis	Scenario planning
Cause-and-effect analysis	Sensitivity analysis
Risk categorisation	Expected value analysis
Risk matrix analysis	Decision tree analysis
Delphi technique	Modelling and simulation
Brainstorming	Probability distribution
Checklist analysis	
Expert judgement	

It has to be pointed out that some of these approaches are less applicable as they require more detailed information[112]. Detailed information may not be available, e.g., at an early

[109] Agerberg et al. (2012), p. 17.
[110] Zhang (2007), p. 694.
[111] Singh (2012), p. 28.

stage of a project, product development or pilot scale process establishment. Some of these techniques will be described in greater detail in the following sections.

Qualitative methods can be used to evaluate identified risks in a simple and rapid way[113]. Hence, qualitative methods are important tools in organisations with scarce resources available for risk assessments[114]. The most frequently used qualitative method is the risk matrix analysis[115]. A risk matrix consists of two dimensions, i.e., severity and likelihood, and is used to rank risks according to the combination of both dimensions with regard to each risk. Figure 9 shows a typical example of a risk matrix. The combination of severity and probability can result in different risk categories (i.e., green, yellow and red). For instance, a risk with a high severity (major effect) and a higher probability of occurrence would result in the red category and therefore judged as not acceptable.

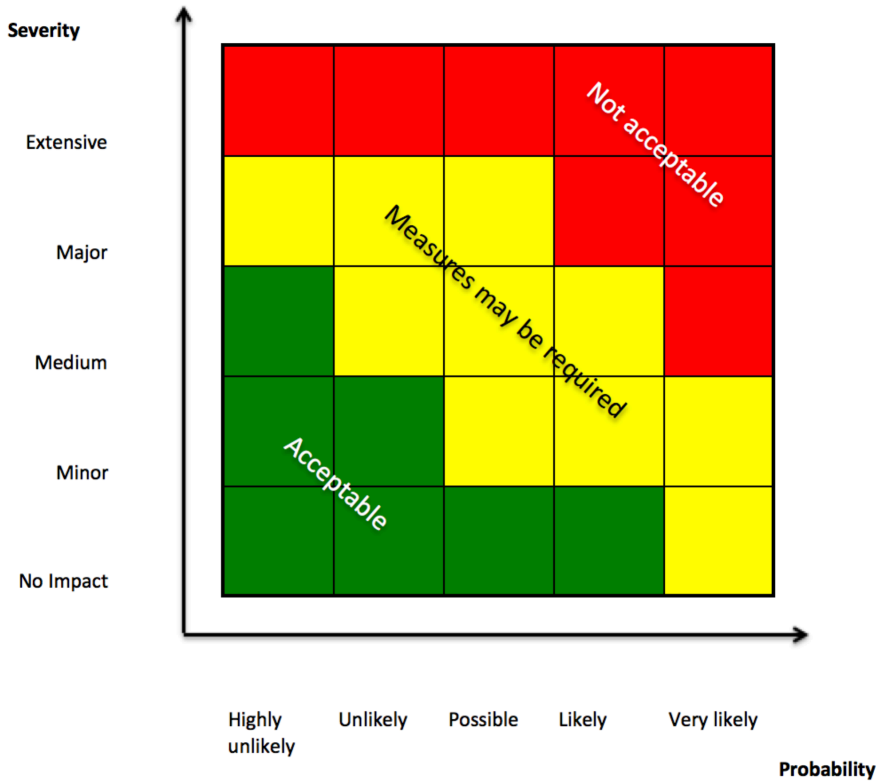

Figure 9: Risk matrix

The quantitative risk analysis tools provide numerical values with regard to risks and their consequences. The results can then be compared with established risk acceptance criteria[114] in the phase of risk evaluation. As quantitative tools require a higher level of knowledge by risk managers and are more time consuming than qualitative methods, they are more suited for large and medium-sized projects[116].

[112] Dey (2010), p. 99.
[113] Agerberg (2012), p. 20.
[114] Baker et al. (1998), p. 567.
[115] Project Management Institute (2004), p. 286.
[116] Smith et al. (2006), p. 87.

Risk evaluation is the final step in the risk assessment process according to ISO 31000. During this step it is decided whether an analysed risk requires treatment or not. The evaluation phase aims to compare the results from risk analysis with the given risk criteria in the present context[117].

The next step of the risk management process according to ISO 31000 as depicted in Figure 8 is risk treatment. Risk treatment is about modifying risks by establishing controlling activities, mitigation actions and avoidance initiatives aiming to reduce the severity and/or the impact of risk[118]. ISO 31000 describes different options for risk treatment:

- Risk avoidance: terminate the activity which gives rise to the risk
- Taking or increasing a risk; this may be legitimate in order to exploit opportunities
- Elimination of risk source
- Change the likelihood and/or the consequences
- Risk sharing (share the risk with another party)
- Accept the risk by informed decision

Hopkin suggested an approach how to treat risks based on their severity and likelihood (Figure 10).

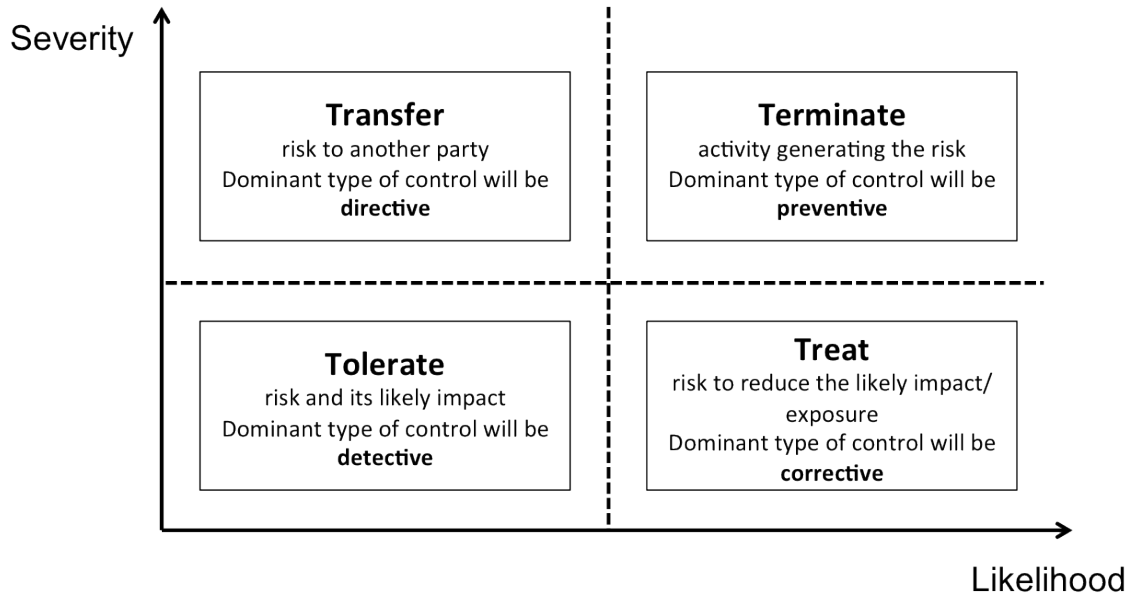

Figure 10: Risk treatment matrix[119]

In the case the impact is not too severe, risk tolerance or treatment, based on the likelihood, is suggested. High severity would lead to risk transfer or termination of risk.

Monitoring and review is the final step in the risk management process. According to ISO 31000 all aspects of the risk management process should by encompassed by the monitoring and review process (e.g., ensuring appropriate controls, analysing and lessons learned, detecting and evaluating changes in the external and internal context). It has to be empha-

[117] Smith et al. (2006), p. 40.
[118] Bustad (2013), p. 19.
[119] Hopkin (2012), p. 224.

sised that this step is not the end of the process as the whole risk management approach can be regarded as cyclic. This phase can be seen as one of the most important phases in the risk management process[120].

Besides the ISO 31000 risk management standard, other standards have been published all over the world with the aim to describe requirements of a risk management process (e.g., AS/NZS 4360 of Australia and New Zealand, JIS Q 2001 in Japan, CAN/CSA Q850 in Canada or COSO ERM in the United States). The ONR 49000 series of the Austrian Standards Institute adopts the ISO standard and additionally contains aspects for a practical implementation of risk management[121]. Figure 11 depicts the elements of the ONR 49000 series.

Figure 11: Elements of the ONR 49000 series[121]

ONR 49001 defines the systematic risk management process, taking into account the PDCA-cycle. ONR 49002 provides information on the integration of risk management into existing management systems, describes methods of risk assessment and relates emergency-, crisis- and continuity management to risk management. Finally, ONR 49003 sets forth requirements for the qualification of risk managers.

3.4 Aspects of risk management in selected industries

The following sections provide an overview on how risk management is employed in different industries. Obviously, different hazards and harms have led to distinctive approaches with regard to risk evaluation and risk treatment. Hence, it has to be emphasised again, that taking into account the context of risk management is an important prerequisite for setting up a risk management system.

[120] Tah et al. (2000), p. 107.
[121] Austrian Standards Institute (2010)

3.4.1 Risk management in the offshore oil and gas sector

The oil and gas industry is a sector with relatively high risk exposure[122]. Compared to other industries this sector is known for advanced quality risk management[123]. Risk management in the offshore industry is mainly focused on safety of humans and installations, prevention of environmental damages and production regularity[124].

The use of risk-based approaches in the offshore industry began in Norway in the late 1970s[125], where several accidents demonstrated that even arrangements that were regarded as safe (i.e. wellhead and production platforms separated from accommodation platforms) are associated with remarkable hazards[126]. According to the *Regulations Concerning Safety Related to Production and Installation*, that have been issued in 1976 by the Norwegian Petroleum Directorate, risk evaluation should be performed in the case living platforms are located on a drilling platform[126]. The UK introduced the Offshore Installations Regulations in 2005 that aim to reduce risks from hazards with regard to the health and safety of the personnel[127]. In the UK as well in Norway it is the requirement that all offshore installations have a so-called safety case (i.e. a document, which provides evidence that risks of major accidents are effectively controlled) in order to get permission to operate[128]. Risk analysis in the line of establishing a safety case is a so-called quantitative risk analysis/risk assessment (QRA) that involves risk analysis as well as an evaluation of the results and is often preferred to as probabilistic risk assessment (PRA), probabilistic safety assessment (PSA), concept safety evaluation (CSE) or total risk analysis (TRA)[128]. In the oil and gas industry risk treatment is mainly based on introducing safety barriers which are used to prevent, control, or mitigate potential hazards and may be of active or passive, physical, technical or organisational nature[129]. Table 10 lists examples of risk influencing factors grouped into different risk categories.

Table 10: Risk categories and risk influencing factors in offshore risk management[128]

Risk categories	Risk influencing factors
Evironmental surroundings (e.g., weather, water depth, seabed conditions)	Air temperature, water temperature, wind, rain, waves, earthquake, and seawater salt.
Environmental-geological risks (e.g., complexity and uncertainty of geological conditions, seismic activities)	Drilling margins, pressure, temperature, leak off, blowout rate, sandstone, and crack and cave.
Facility-technological risks (quality of drilling vessel, well equipment)	Reliability and validity of the instrumentation, well control equipment, power generation and emergency power supply, cement,

[122] Baker et al. (1998), p. 567.
[123] Baker et al. (1999), p. 205.
[124] Brandsaeter (2002), p. 231.
[125] Gjerstad (1989)
[126] Smith (1995), p. 513.
[127] HSE (2006)
[128] Skogdalen et al. (2012), p. 61.
[129] Sklet (2005), p. 13.

Risk categories	Risk influencing factors
	blowout preventer.
Operational risks (e.g., internal processes, people and systems)	Management, communication, documentation, work practice.

The International Organization for Standardization (ISO) has issued a group of standards reflecting a risk-based approach in the offshore industry[130]:

- ISO 10418:2003 - Petroleum and natural gas industries – Offshore production installations – Analysis, design, installation and testing of basic surface process safety systems[131]
- ISO 13702:1999 - Petroleum and natural gas industries – Control and mitigation of fires and explosions on offshore production installations – Requirements and guidelines[132]
- ISO 15544:2000 - Petroleum and natural gas industries – Offshore production installations – Requirements and guidelines for emergency response[133]
- ISO 17776:2000 - Petroleum and natural gas industries – Offshore production installations – Guidelines on tools and techniques for hazard identification and risk assessment[134]

In contrast to the pharmaceutical industry, risk management in the oil and gas sector has a longer tradition, mainly caused by regulatory requirements that have been introduced earlier than the relevant requirements for the pharmaceutical industry. Moreover, the focus of the risk-based approach of the oil and gas industry is mainly set on occupational health and safety, whereas the pharmaceutical risk management refers to patients' safety and health. However, the main steps of the risk management process are similar.

3.4.2 Risk management in the food industry

As all consumers have the right to expect and demand safe food of good quality, food businesses have to meet specific safety and quality responsibilities by implementing quality assurance systems along the food production chain. Good hygiene practice in combination with a sound implementation of hazard analysis and critical control points (HACCP) is an appropriate approach to assure food quality.

Hazard analysis and critical control points in the food industry is used to identify potential food safety hazards (i.e. physical, chemical and biological hazards) and to introduce key actions, known as critical control points, that can be taken to reduce or eliminate the risk of

[130] Vinnem (2007), p. 12.
[131] ISO 10418 (2003)
[132] ISO 13702 (1999)
[133] ISO 15544 (2000)
[134] ISO 17776 (2000b)

the hazards being realised[135,136]. HACCP ensures quality of food without solely relying on end product testing and can be used for planning ahead for correction of problems when prevention fails. In fact, HACCP originates from the need to assure food safety and was first developed and used by the Pillsbury Company in the late 1960s to provide safe food for the US space program[137].

HACCP consists of seven steps:

1. Conduct a hazard analysis and identify preventive measures for each step of the process; for instance, with regard to a cooking step in the preparation of a meal, a potential hazard would be the survival of pathogens due to inadequate cooking time or temperature.
2. Determine the critical control points; e.g., the cooking step would be a critical control point, as measures are necessary to deal with the identified hazard of pathogens.
3. Establish critical limits; e.g., specific temperature over a certain time for cooking the meal.
4. Establish a system to monitor the critical control points; e.g.; taking the temperature of the meal during cooking.
5. Establish the corrective action to be taken when monitoring indicates that the critical control points are not in a state of control; e.g., if the required internal temperature is not reached, a corrective action would be to continue cooking the meal.
6. Establish a system to verify that the HACCP system is working effectively.
7. Establish a record-keeping system.

ICH Q9 suggests HACCP as a systematic, proactive and preventive tool for assuring pharmaceutical product quality[138]. The hazard groups taken into account by HACCP, i.e. physical, chemical and biological hazards are similar to relevant hazards in the pharmaceutical industry. That's why it can be used as valuable tool within pharmaceutical quality management.

Additionally, an important advantage of HACCP is the ability to identify risks early in the development or during scale-up of a process or product so that they can be effectively managed and mitigated[139].

3.4.3 Supply chain risk management

Supply chain risk management has recently become increasingly important, as the unpredictability of the economic environment, variable customer demands, growing competition, along with market dynamics and improvement initiatives within organisations imply that the supply chain never actually reaches a stable steady state[140]. Hence, managing risk in the supply chain is a critical aspect for competing in the current, increasingly turbulent and unpredictable business environment[141]. Another reason for increasing supply chain risks is the trend towards outsourcing where additional dependencies are created and the network

[135] 21 CFR 120
[136] WHO (2003), p. 99.
[137] Raschiatore (2013), p. 295.
[138] ICH (2005), p. 12.
[139] Walker et al. (2013), p. 33.
[140] Haywood et al. (2004), p. 72.
[141] Colicchia et al. (2012), p. 403.

complexity rises[142]. Supply chains of the automotive industry have increased vulnerabilities in comparison to other industrial sectors through the widely use of just-in-time or just-in-sequence concepts[143,144].

Supply chain risk is defined as the variation in the distribution of possible supply chain outcomes, their likelihoods and their subjective values[142]. Kersten et al.[145] define supply chain risk as a potential harm associated with a certain probability that affects more than one organisation within the same supply chain, caused by a company within the supply chain or by the supply chain's environment. Supply chain risk management includes the identification of potential sources of risk and implementation of appropriate measures through a coordinated approach among supply chain members, to reduce supply chain vulnerability[146]. Hence, the main aim of supply chain risk management is to protect the organisation from negative events[147]. Especially the automotive industry is well known for their efforts to improve its supply chains according to the demands of their business environment[148].

In supply chain risk management five risk categories can be identified (see Figure 12): Demand risk relates to the processes, controls, asset and infrastructure dependencies of the organisations downstream and adjacent to the own organisation. The group of supply risks contains potential hazards with regard to the flow of product or information arising from within the network, upstream of the own company. Process risks refer to hazards, their causes, effects and likelihood with regard to internally owned assets and the reliability of supporting transport, communication and infrastructure. Control risks originate from assumptions, rules, systems and procedures that govern how an organisation controls its internal processes.

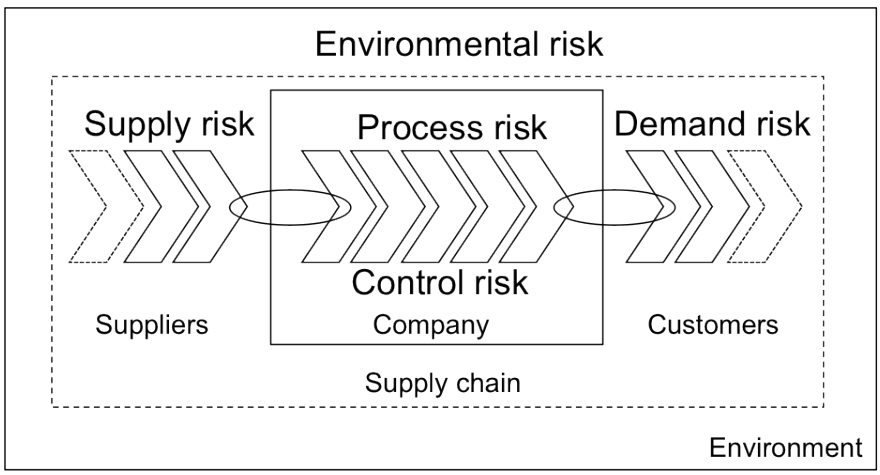

Figure 12: Supply chain risk categories[149,150]

[142] Jüttner et al. (2003), p. 16.
[143] Svensson (2004), p. 728.
[144] Thun et al. (2007), p. 1.
[145] Kersten et al. (2007)
[146] Christoper et al. (2003), p. 9.
[147] Colicchia et al. (2012), p. 404.
[148] Thun et al. (2011), p. 242.
[149] Christopher et al. (2004), p. 10.
[150] Kersten et al. (2008), p. 9.

There are no internationally accepted standards (e.g. ISO) that define requirements for supply chain risk management. The Supply Chain Risk Leadership Council (SCRLC), a cross-industry council including supply-chain organisations, outlines an approach to supply chain risk management[151]. The supposed risk management process is similar to the ISO 31000 approach. It focuses on (1) identifying internal and external environments, (2) risk identification and assessment, (3) risk treatment and (4) continual monitoring and review of risks and their treatment. For a comprehensive list of possible supply chain risks refer to the working document of the Supply Chain Risk Leadership Council[151].

Also the pharmaceutical industry is exposed to various supply chain risks, but a sound supply chain management as realised, e.g., in the automotive industry, is absent. However, several activities are performed to assess the direct suppliers, e.g. with regard to delivered product quality (i.e. supplier qualification).

3.4.4 Financial risk management

Financial risk is the probability that an investment's actual return will deviate from expectation, including the possibility of losing some or all of the original investment[152]. It has to be emphasised that financial risk does not only include negative effects but also upside risks (i.e. returns that exceed expectations)[153]. Van Deventer et al.[154] give the following definition of financial risk management:

Risk management is the discipline that clearly shows management the risks and returns of every major strategic decision at both the institutional and the transaction level. Moreover, the risk management discipline shows how to change strategy in order to bring the risk return trade-off into line with the best long- and short-term interests of the institution.

Decisions involved in the management of financial risks are the choice among alternative portfolios, whether to change a portfolio or take a new position, whether and how to hedge risks, the choice of position sizes, and decisions about leverage and capital allocation.[155]

Main risks associated with financial decision-making are the risk of economic loss arising from changes in the value of the underlying, exchange risks and credit risks.

The basic tools of financial risk management are forwards, futures, swaps and options[156]. Table 11 provides an overview of these instruments.

Table 11: Overview of basic instruments of financial risk management[157]

Instrument	Background
Forwards	Forwards are contracts entered into today in which the exchange will take place at some future date. Contract terms, price, date and the characteristics of the underlying asset are determined when signing the contract, but no money is ex-

[151] Supply Chain Risk Leadership Council (2011)
[152] Namazian et al. (2011), p. 3241.
[153] Damodaran (2012), p. 16.
[154] Van Deventer et al. (2013), p. 719.
[155] Dowd (1999), p. 65.
[156] Smithson (1998), p. 27.
[157] D'Arcy (2001), p. 9.

Instrument	Background
	changed at this point. At the agreed date in the future, both parties are obligated to realise the transaction. Forwards are not exchange-traded. Basically, the buyer (long position) expects the underlying asset price to increase, while the seller (short position) hopes that it will decrease in near future.
Futures	Similar to forwards, also futures are entered in today for an exchange that will take place at some future date. Futures are traded on an exchange and have interim partial payments (marking to market). Marking to market means that cash payments flow from one party to another, based on the changes in the value of the futures contract.
Swaps	Swaps are agreements between two parties to exchange a series of cash flows based on a predetermined arrangement. One of the most common swaps is an interest rate swap in which one party pays a fixed interest rate and the other pays a floating interest rate based on a set index such as the London Interbank Offer Rate (LIBOR).
Options	An option provides the right but not the obligation to engage in a financial transaction at a predetermined price in the future, where the owner of the option has the choice to consummate the transaction. The seller is obliged to fulfil the contract if the buyer chooses. As an option represents a one-sided risk, there is an initial cost when purchasing an option, i.e. option premium.

As financial risk instruments are complex and often only understood by those in the financial areas of a company, the use of these tools to manage financial risks is generally not coordinated with the approach used to manage other risks[158].

Basically, financial risk management independently developed from other risk-based approaches and uses specific methods and tools that cannot be found in other sectors.

3.5 Pharmaceutical risk management

3.5.1 Introduction

It is widely accepted that risk has always been an inherent part of pharmaceutical industries' operations, as new products launches and clinical trials fundamentally involve some degree of risk. Moreover, risk is present during the whole life cycle of a medicinal product, starting from the early attempts to find promising molecules till routine manufacturing and product discontinuation. Hence, the pharmaceutical sector faces an unprecedented number of risks as a result of a myriad of pressures and changes, including steadily increasing regulatory requirements, globalisation and operational efficiency[159]. There are several risk categories

[158] D'Arcy (2011), p. 14.
[159] Carey (2013)

the pharmaceutical industry has to face. Although there are a variety of different stakeholders, including patients as well as governments and the industry, the protection to the patient by managing the risk to quality should be considered of prime importance[160]. Hence, the quality of a medicinal product is of upmost importance as it is directly linked to the health of patients and potentially affects the safety and efficacy of a product. Risk to pharmaceutical product quality is defined as the combination of the severity or the impact of an unwanted event and the likelihood that the event will occur to a degree, which will adversely affect product quality[161]. Baseman et al. list some hazards and associated harms with regard to pharmaceutical product quality (Table 12). From a manufacturing perspective, anything that has a high impact or is close to the product will be high risk[162].

Table 12: Hazards and harms with regard to quality of a pharmaceutical product[161]

Hazards (causes)	**Harms (effects)**
Product contaminated	Injury to patient
Ineffective product	Disruption of product supply
Product not sterile or impure	
Product sub potent or super potent	
Product mislabelled	
Product unsealed or improperly sealed	
Product missing or unusable product	
Lack of product supply	
Noncompliance with regulations	
Product rejection	
Inefficient process	
Misuse of product	
Poor process yield	
Failure to receive product approval / loss of product approval	

A collective risk is a special case of a quality risk that has to be considered. This type of risk results from a series of risks or failures that have been identified but may not appear serious if they individually occur, however, collective appearance could have a remarkable product impact[162].

However, the risk to product quality is just one component of the overall risk. For instance, discovery risks have to be addressed in early stages of pharmaceutical research and development where noteworthy amounts of resources are spent to identify molecules with

[160] ICH (2005), p. 1.
[161] Baseman et al. (2013), p. 8.
[162] Nally et al. (2007), p. 222.

pharmacological activity. Market risks would take into account that the sales forecasts will not be met[163].

Expectations of regulators with regard to quality risk management (QRM) are defined through regulations or guidance documents by regulatory authorities, consortiums and health organisations all over the world. EU GMP-guidelines (Chapter 1: Pharmaceutical Quality System) require that the design of the pharmaceutical quality system should incorporate risk management principles and the use of appropriate tools[164]. The document further describes QRM as a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. The following main principles of QRM are outlined: (1) the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient; (2) the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk[165]. Recent authority observations show the importance of having a fully integrated and appropriately executed QRM system. Table 13 lists examples of observation deficiencies.

Table 13: Examples for authority-observed QRM deficiencies[166]

Policy/Procedure (System level) deficiency	**Risk assessment deficiency**
No consideration given to QRM	Inadequate or no assessment of impact on product quality
Inappropriate application of QRM	Lack of evidence supporting decisions
Improper implementation	Lack of process understanding and/or regulatory requirements
Variable tolerance of risk Systematic approach not applied to the review of assessments.	There is a desired outcome and risk management is just used to justify it (invalid assumptions – suit the desired outcome)

Hence, regulatory authorities attach great importance with regard to a correct and adequate implementation of risk management principles and therefore, the adoption of risk-based approaches can be seen as one important aspect in the planning and realisation of a pharmaceutical quality system.

3.5.2 The pharmaceutical risk management process

The guideline ICH Q9 provides a standard for quality risk management in the pharmaceutical industry[167]. It explains what quality risk management is, how it can be applied to pharmaceuticals and how it can provide a common language with an agreed process for the

[163] Spilker (1998), p. 325.
[164] European Commission (2013), p. 2.
[165] ICH (2005), p. 2.
[166] Long (2013), p. 51.
[167] ICH (2005), p. 1.

pharmaceutical industry and regulators[168]. The EU GMP guideline directly refers to ICH Q9[169]. According to ICH Q9, pharmaceutical *quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of a medicinal product across the product life cycle*. As the focus of ICH Q9 primarily lies on the risk management process itself, there are many similarities between ICH Q9 and the risk management standard ISO 31000 (Table 14).

Table 14: Comparison between requirements of ICH Q9 and ISO 31000 with regard to risk management[170]

ICH Q9	ISO 31000:2009
1. Introduction	
2. Scope	
3. Principles of Quality Risk Management	3 Principles for managing risk
4. General Quality Risk Management Process	
4.1 Responsibilities	4.2 Mandate and commitment
4.2 Initiating a Quality Risk Management Process	4.3 Design of framework for managing risk 4.4 Implementing risk management
4.3 Risk Assessment	5.4 Risk assessment
4.4 Risk Control	5.5 Risk treatment
4.5 Risk Communication	5.2 Communication and consultation
4.6 Risk Review	5.6 Monitoring and Review
5. Risk Management Methodology	Not part of the standard
6. Integration of Quality Risk Management into Industry and Regulatory Operations	1 Scope
7. Definitions	2 Definitions
8. References	
Annex I: Risk Management Methods and Tools	Not part of the standard
Annex II: Potential Applications for Quality Risk Management	

It has to be emphasised that ICH Q9 guideline solely focuses on the quality aspect of risk management, whereas ISO 31000 standard has a much wider applicability as it can be used for all types of organisational risks. However, there is a high level of consistency between the main bodies of both guidance documents, i.e. the risk management process. However, ISO 31000 is not only focused on risks related to quality but also on, e.g., occupational health and safety, legal and regulatory obligations and governance and reputation[170].

The model for the quality risk management process as propagated by ICH Q9 is outlined in Figure 13.

[168] Baseman et al. (2013), p. 9.
[169] European Commission (2013), p. 8.
[170] Leitgeb (2011), p. 31.

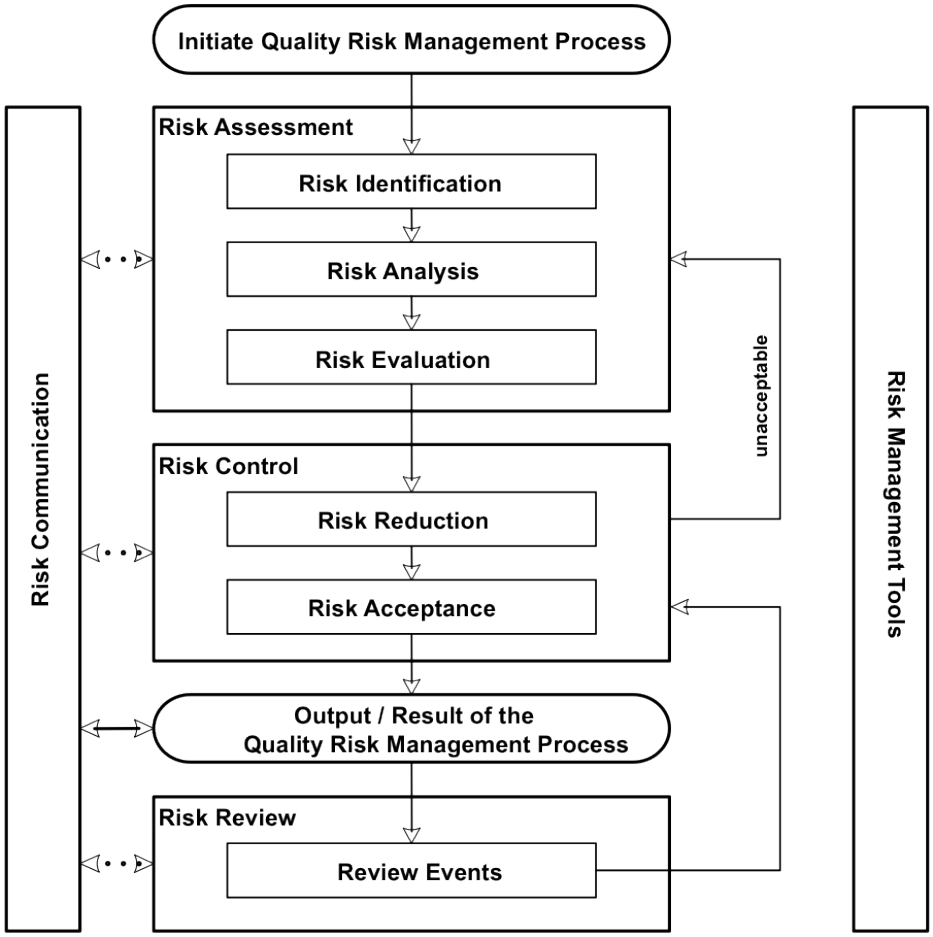

Figure 13: Overview of the quality risk management process according to ICH Q9[171]

The first step in the risk management process according to ICH Q9 is its initialisation. This step is further used to plan the QRM process and is supposed to cover the following aspects:

- The primary problem and/or the risk associated with this problem are to be defined.
- Subsequently, background information on the potential risk is collected and compiled.
- A risk owner should be identified and required resources allocated (if required).
- Timelines and deliverables for the QRM process should be specified.

Hence, the initiating phase involves understanding the risk event by defining the context, the scope and the acceptance criteria for QRM, where the scope clearly establishes the boundaries of the process, system or project being assessed[172].

Risk assessment is the next step in the QRM process workflow and consists of risk identification, risk analysis and risk evaluation. According to ICH Q9, the answer to the following three questions could be of help in the subsequent assessment process: (1) what might go wrong? (2) What is the likelihood (probability) that something will go wrong? (3) What

[171] ICH (2005), p. 2.
[172] Lotlikar (2013), p. 152.

are the consequences (i.e. severity)? Risk assessments are conducted on the basis of historical data, analytical methods, and knowledge and sometimes gut feeling[173].

Risk identification, that addresses the "what might go wrong" question, requires the identification of potential hazards with regard to the risk question of the problem description by systematically using available data and information. This information may include historical data, expert opinions and the concerns of stakeholders.

Subsequently, according to ICH Q9 risk analysis is the estimation of the risk associated with the identified hazards. In this step the likelihood of occurrence and the severity of harms (effects) are linked. Hence, the key activities to be performed during risk analysis include the understanding of the effect of risk to rank the significance of risk (e.g., by scoring 1 to 10, where 1 means low impact and 10 equals high impact)[174] and the estimation of the probability of occurrence (e.g., 1 in 1 year or 10 times a year). Risk is often expressed by the calculation of a risk priority number as the product of severity and probability. The identified risks have to be ranked or scored somehow in order to compare them with set risk acceptance criteria during the step of risk evaluation.

Risk evaluation compares the identified and analysed risks against given risk criteria. Risk below a certain limit would be acceptable for the organisation. In some cases, it may not be possible to completely eliminate risk and for those risks, that are determined to be unacceptable, the organisation may employ measures to achieve risk acceptance[173].

Finally, in the phase of risk control the organisation must decide whether to reduce and/or accept a risk. Risk reduction is realised by processes of risk mitigation or risk avoidance. To reduce a risk, the severity and/or the probability of harm can be lowered. Risk acceptance is a formal decision to accept the residual risk.

Risk communication accompanies the whole risk management process. This is an important part of the process as information about risk and the outcome of the risk management process are shared between the decision makers and other relevant stakeholders. It is important to emphasise that the risk management process must be monitored and reviewed to ensure that mitigating actions remain effective[173] and new risks are adequately addressed.

3.6 Risk management tools

ICH Q9 suggests some tools and methods to be used in the risk management process[175]. This section provides a brief overview of key principles on the theory of these tools and gives some examples with regard to the most important methods.

Following risk aspects as possible aid to ringfence the system of interest with regard to quality risk could be addressed in the line of risk management[176]:

- System risk with regard to facilities and people: e.g., interfaces, operator risks, environment, premises, equipment, …
- System risk with regard to the organisation: e.g., quality systems, controls, measurements, documentation, and regulatory compliance.
- Process risk, taking into account process and quality parameters

[173] Walker et al. (2013), p. 18.
[174] Lotlikar (2013), p. 152.
[175] ICH (2005), p. 5.
[176] Ronninger et al. (2006)

– Product risk with regard to quality, safety and efficacy of a product

As one of the basic principles of ICH Q9 states that the level of effort, formality and documentation of the risk management process should be commensurate with the level of risk, different tools are available, depending on the level of detail required (Table 15).

Table 15: Selection of different tools to be used at different levels of detail[177]

	general → detail			
	System Risk (facility & people)	System Risk (organisation)	Process Risk	Product Risk (safety & efficacy)
Risk ranking & filtering	X	X	X	
FMEA		X	X	
HACCP		X	X	
Process mapping			X	
Flow charts			X	X
Statistical tools				X
Check sheets	X			X

In the following generic tools that are most often used for risk management in different industrial fields are briefly discussed. As those methods are also propagated by ICH Q9 they are supposed to have particular importance within the pharmaceutical risk-based approaches.

3.6.1 Basic risk management facilitation methods

Basic risk management facilitation methods help the risk management team to get a common understanding of the process being analysed and assist in identifying hazards and their causes. Walker et al. provide an overview of some basic tools (Table 16).

Table 16: Basic risk management facilitation methods[178]

Risk management method	Description	Potential application
Diagram analysis – Flow charts – Check sheets – Process mapping – Cause/effect diagrams (e.g. fishbone)	Simple techniques to gather and organise data, structure risk management process, and facilitate decision-making.	Compilation / structuring of observations, e.g. with regard to deviations or complaints.

[177] Ronninger et al. (2006)
[178] Walker et al. (2013), p. 42.

Risk management method	Description	Potential application
Risk ranking and filtering	Comparing and ranking risks, e.g., by taking into account quantitative or qualitative factors for each risk.	Prioritisation of risks to plan further activities.
5 Why analysis	Technique of repeatedly asking "why" a problem occurred.	Identification of cause-and-effect relationships.
Pareto analysis	Prioritisation of information with regard to the Pareto principle.	Identification of hazards having the most impact to reduce risk.
Histograms	Used to display frequency distributions of the data set.	Identification of outliers from risk assessment data.
Control charts	Used to determine whether a process is in a state of statistical control.	Analysing process stability and capability as basis for improvement.

3.6.2 Failure Mode and Effects Analysis (FMEA)

Failure mode and effects analysis (FMEA) is commonly used in a variety of industries for risk management purposes, where the simple quantification of risk (e.g., by a risk matrix only) is insufficient, and where identification of risks and means of mitigation are paramount[179]. FMEA can be used to identify and prioritise failures of products, processes and systems at an early step of development before non-conformances would reach the customer.

FMEA was introduced in the 1940s for military use by the United States[180]. Industry in the United States adopted FMEA in the 1970s, in part because of industrial disasters such as the chemical plant explosion in Flixborough, UK, in 1974[181].

The FMEA methodology is a systematic approach to identify potential failures to fulfil an intended function, to identify possible failure causes so the causes can be eliminated, and to locate the impacts of failures so the effects can be reduced[182]. FMEA can be used to methodically break down the analysis of complex processes into manageable steps. According to ICH Q9, FMEA can be applied to equipment and facilities and might be used to analyse a manufacturing operation and its effect on the product or the process. For an example of a practical application of an FMEA, refer to Adam et al.[183] who performed an FMEA to assess the impact of variability of potentially critical input parameters on blend homogeneity of a pharmaceutical process. Table 17 lists the subsequent steps of an FMEA and links these steps to the risk management model according to ICH Q9.

[179] Product Quality Research Initiative (2008), p. 1.
[180] United States Armed Forces (1949)
[181] Harclerode et al. (2013), p. 372.
[182] Dyadem Press (2003), p. 15.
[183] Adam et al. (2011), p. 109.

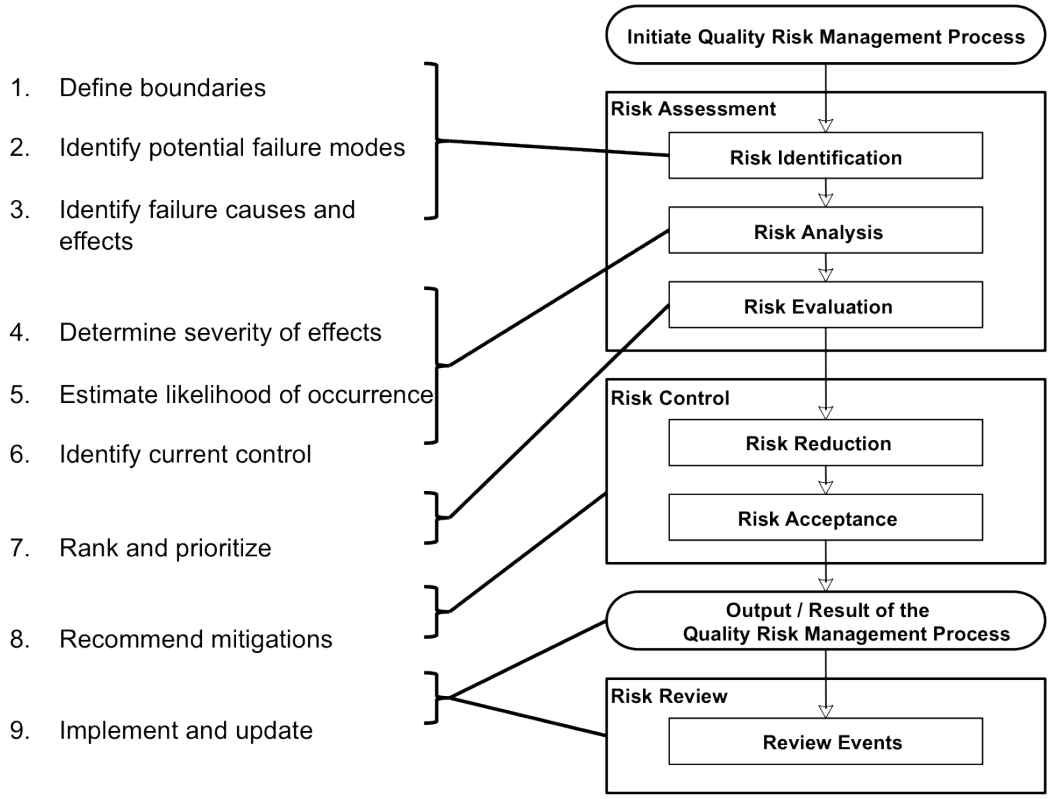

Table 17: Correlation between FMEA and the risk management approach[184]

The core aspect of an FMEA is the calculation of a risk priority number (RPN), the combination of the severity, probability and sometimes detectability of a failure mode[185]. Based on this RPN identified risks can be prioritised and mitigated.

Table 18 highlights advantages and disadvantages of the FMEA used as tool in risk management.

Table 18: Advantages and disadvantages of the FMEA[186]

Advantages	Disadvantages
- Accepts a high degree of complexity - Results can be correlated directly with actual risks - The effect of different strategies of risk mitigation / detection can be modelled easiliy - Provides a well-documented record of improvements from corrective actions implemented	- Significant resources are required to obtain valuable output - a moderator could be required

[184] Walker et al. (2013), p. 27.
[185] Benes et al. (2012), p. 204.
[186] Walker et al. (2013), p. 28.

Advantages	Disadvantages
- Provides useful information in developing test programs (e.g., qualification and validation of equipment and processes) - Provides historical information useful in analysing potential product failures during the manufacturing process - Provides ideas for improvements in similar designs and processes	

3.6.3 Fault Tree Analysis (FTA)

According to DIN 61025 FTA evaluates (system) failures one at a time and can combine multiple causes of failure by identifying causal chains[187]. For instance, FTA can be used to investigate complaints or deviations in order to fully understand their root causes. Figure 14 gives an example of an FTA performed with regard to the problem that a pharmaceutical primary packaging is hard to open.

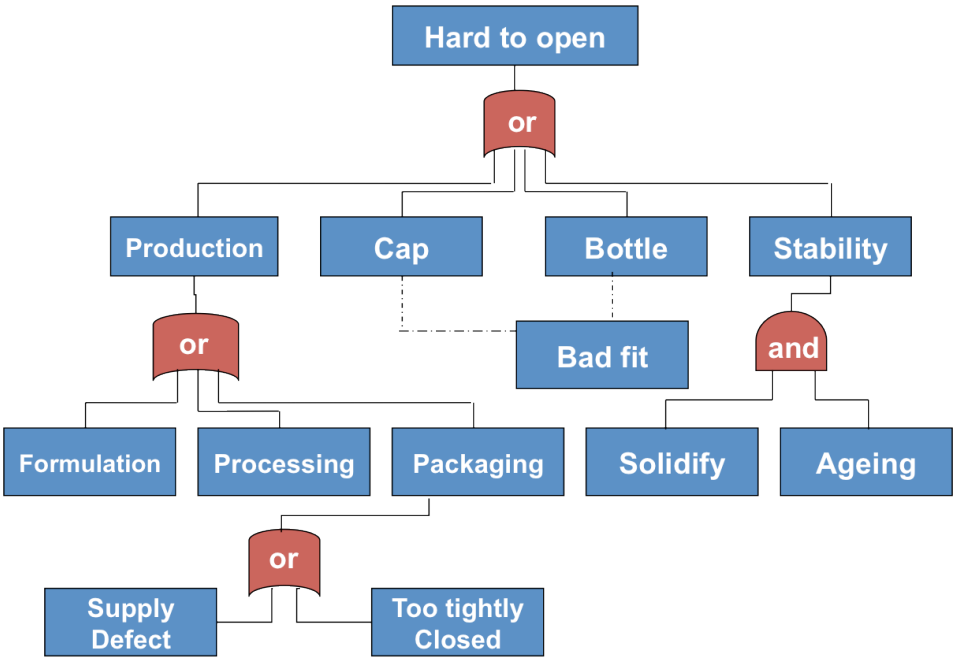

Figure 14: Fault tree analysis[188]

This technique is used for analysing hazards that have already been identified with other techniques and can be quantitative in the case data on component failure rates are available[189].

[187] DIN (2007)
[188] Ronninger et al. (2006)
[189] Walker et al. (2013), p. 32.

3.6.4 Design of experiments (DoE)

One of the main reasons for the performance of risk management is the identification and prioritisation of risks for further treatment (e.g., mitigation). Hence, it is evaluated, which factors or causes would have the most influence on a given risk question or on a certain harm. Often, various factors that may have specific effects on outputs have been identified. Now it would be of interest, if these factors really do have an effect on some harm and if so, could this effect be quantified. Figure 15 represents a special case, where it is of interest how potentially critical input parameters effect various responses. The process itself in this example can be regarded as black box.

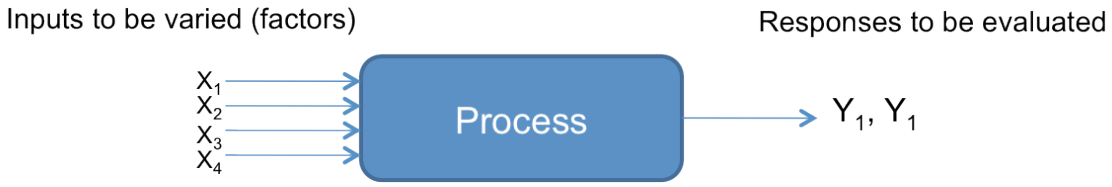

Figure 15: Process characterisation

Design of experiments is a valuable approach to assist in factor prioritisation and quantification of correlations between inputs and responses. DoE is a powerful toolset to design (plan) and evaluate experiments by statistical means. In its core, DoE provides a set of representative experiments, in which all factors under investigation are varied simultaneously and systematically. From this set, a model is derived which captures the relation between factor settings and experimental results. This model, for instance, can then be used to predict future outcomes of the experiment. The main aim of DoE is to maximise the information content from experimental series (i.e., relationship between inputs and output) while keeping the number of experiments low. According to Eriksson et al.[190] the setup of an experimental design consists of 7 steps:

(1) Define the problem and the goal of the experimental work (e.g., why is an experiment done? What are the desired results?).
(2) Specify the input factors. These are variables that are to be changed to give different results on the measured responses.
(3) Specify the responses; e.g., a specific harm, for instance, the content of toxicological by-products in a pharmaceutical product.
(4) Select the experimental objective.
(5) Select the appropriate regression model (is often be done automatically by a DoE-software).
(6) Select the supporting design (is also often be done automatically by a DoE-software, based on specified inputs, outputs and experimental objectives).
(7) Generate the worksheet, i.e. the final investigation/experimentation plan.

The selection of an appropriate experimental objective is an important step in design generation, as it is linked with the following aspects: required resources, information that has already to be available at the beginning and required outcome. DoE applies to three main

[190] Eriksson et al. (2008), p. 27.

experimental objectives: screening, optimisation and robustness testing. In screening, one is interested to determine which factors are most influential and what are the appropriate ranges for these factors. Hence, screening could be applied well in phases of risk management when there is little information available to get a first hint on factor-output relationships. Optimisation is about finding an optimum with regard to input factor combinations. In the case of different response variables (e.g., different harms) a compromise may be necessary to meet conflicting demands on the outputs. Finally, robustness testing would be performed in late phases of development, e.g., when an analytical method has already been established in order to find out how slight changes in input factors might affect the output.

A common design family is the full factorial design. They are most useful in early experimental stages and form the basis for other classical experimental designs[191]. Full factorial designs are important for a number of reasons: (1) they require relatively few runs per investigated factor, (2) they can be upgraded to composite designs, which are used in optimisation, (3) they form the basis of two-level fractional factorial designs, which are of great value at an early stage of a project, and (4) they can be easily interpreted by using common sense and elementary arithmetic[192]. Refer to Figure 16 for an overview of different commonly used experimental designs.

DoE addresses the risk identification and risk evaluation steps of the risk management process and can be a valuable primer for subsequent sound risk assessments. Often, potentially critical factors are identified, e.g., by the meanings of a fishbone diagram. Afterwards these factors are introduced in a DoE approach to see if they are really critical or not, i.e. if there is a correlation between the factors and the harms. If so, DoE can further be used to optimise the output, i.e. reduction of harm (this refers to optimisation strategies of experimental designs).

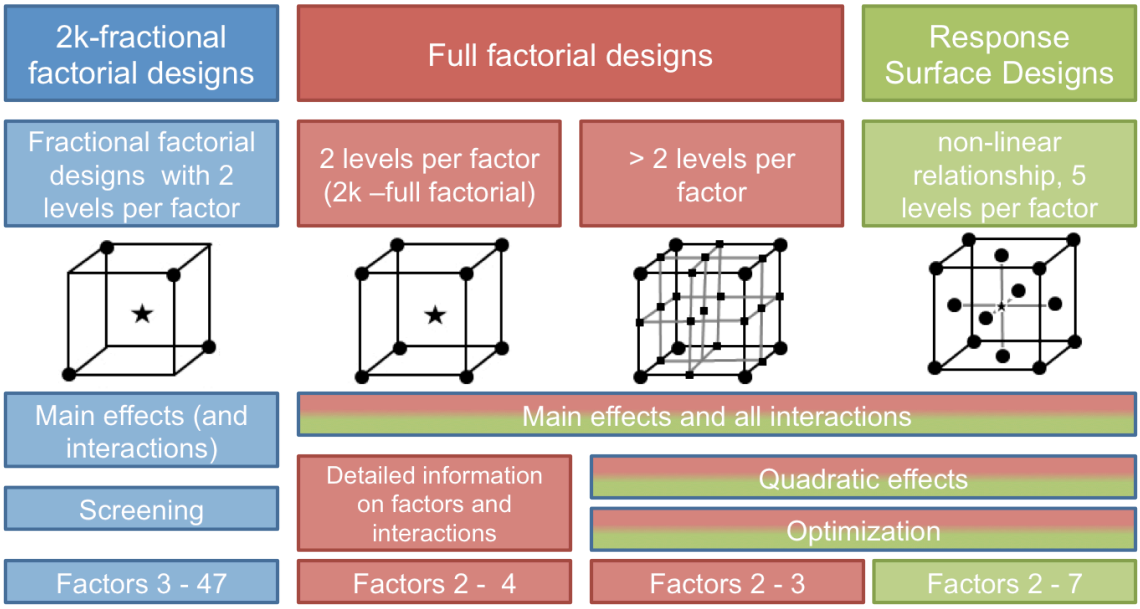

Figure 16: Overview of common experimental designs, their ability to resolve effects and the amount of factors to be introduced.

[191] Montoro et a. (2013)
[192] Eriksson et al. (2008), p. 53.

DoE is specifically propagated by ICH Q8 as a valuable tool to assist in pharmaceutical development by prioritising potentially critical input factors for further investigation[193].

[193] ICH (2009), p. 9.

4 Integration of risk management into existing quality systems

4.1 Preliminary aspects of management system integration

The integration of quality risk management into an existing pharmaceutical quality management system is obviously a challenging task.

As a major aspect, different stakeholder interests have to be considered. Even though the regulatory agencies have issued guideline documents for industry implementation of QRM[194,195], and even documents to brief its own officers on QRM[196] have been prepared, there is a considerably high degree of uncertainty by regulators with regard to realisation of these quite new regulatory requirements. However, also other stakeholders would have to be taken into account, e.g., the company owner who demands a straight and timely integration of these new requirements and doesn't want to see his business jeopardised by ineffective new systems or never-ending integration projects. Moreover, staff from all levels of the organisation demands intuitive approaches regarding QRM that would have to fit seamlessly into existing systems and operations. Suppliers may also be affected by QRM integration, as they are part of the supply chain that has to be evaluated with regard to risks potentially resulting in product defects and patient harm and hence, different information would be requested from suppliers during risk assessments. Finally, end-customers represent another essential stakeholder group, as they demand medicinal products of constantly high quality. Inappropriate QRM procedures could have the potential to oversee major risks and hence could compromise quality, safety and efficacy of pharmaceutical products.

The integration process is made even more difficult because there are many pharmaceutical quality systems and many different types of products that have to be considered[197]. In order to obtain an efficient final state of integration the new system would have to be embedded into existing management systems and make use of the elements of already existing systems. In an integrated management system, that may combine quality management (e.g., GMP or ISO 9001), environmental management (e.g., ISO 14001), and occupational safety and health management (e.g., according to OHSAS 18001) the compatibility and integration of risk management (according to ICH Q9) has to be ensured[198].

In general, an integration process aims to create a new entity or results in an incorporation of system elements to become part of an entity[199]. According to a systems theory approach integration is the combination of separated system elements to become an entity by creating something new that has not existed before[200]. On the other side, separation is the deliberate distinction of sub-systems, leading to the creation of specific system elements with regard to a certain level of the system under consideration[200]. Hence, total integration and separation are two possible extremes of integration. Based on the definitions above, several approaches towards system integration with regard to the degree of integration can be employed. Ax et al. supposed that the benefit of integration would increase with increasing

[194] ICH (2005)
[195] ICH (2008)
[196] PIC/S (2012)
[197] Harclerode (2013), p. 367.
[198] Austrian Standards (2010), p. 1.
[199] Büntig (1996)
[200] Baumgartner et al. (2006), p. 38.

degree of integration, till a point is reached where a further increase of integration degree would lead to a decrease of integration benefit[201]. Baumgartner et al.[202] describe different approaches of integration, i.e. adsorption, absorption and resorption. In the case of adsorption (i.e. the additive approach) new system elements are added to an already existing system and no further alignment of the sub-systems is performed. Absorption leads to a higher degree of integration compared to the additive approach. However, no complete integration of sub-systems is realised. Resorption results in the highest degree of integration as the individual management systems that were brought together completely merge to an integrated management system approach. For a comprehensive review of the different types of integration refer to Baumgartner et al.[202].

In this work, the integration of the elements of risk management into the existing quality management system is performed according to the partial-integrated absorption approach[202]. Point of departure is the structure of the already existing quality management system according to GMP (see above), and the requirements of risk management are considered in this structure. To achieve the partial integration, relevant elements of the quality system are assessed with regard to additional requirements of risk management. Where additional requirements exist, the existing system elements are complemented accordingly. There is no requirement to completely integrate risk management into the existing system. Certain elements may still remain separate after integration[203].

Partial absorption is often used to combine different systems that were (or have to be) established as a result of additional regulatory or normative requirements. For instance, an existing quality management system according to ISO 9001 may be augmented by elements of an environmental management system according to ISO 14001. Very often, the integration approach is primarily focused on the integration of the documentation system[202]. Hence, the first step of integration is performed by unifying standard operating procedures with regard to content and appearance. Felix et al.[204] suggest the following steps of a partial integration:

(1) Identification of standard operating instructions of the basis system governing higher-level procedures that are valid for all system elements (e.g.; training, documentation). In this step the integration task refers to the general appearance of the documents that takes account of the basis system and the system to be integrated.
(2) Amendment of procedures of the basis system with regard to specific requirements of the system elements to be integrated (e.g., the procedure for supplier qualification is supplemented by supplier risk assessments).
(3) Attachment of additional procedures required by the system to be integrated that do not fit to existing procedures of the basis system and therefore have no real potential for integration.

ONR 49002-1 describes how risk management can be embedded into an existing management system[205]. It clearly emphasises that according to the theory and practice of business management, tools for management can be used to direct and control an organisation more effectively and that risk management can be regarded as such a tool. ONR 49002-1 points out that the principles of risk management should be systematically applied in an organisa-

[201] Ax et al. (1979), p. 894.
[202] Baumgartner et al. (2006), p. 46.
[203] Felix (1999), p. 137.
[204] Felix et al. (1997), p. 49.
[205] Austrian Standards (2010), p. 4.

tion to reduce uncertainty and to assist in decision making and hence, decisions for organisation development, market positioning, or ensuring efficiency and quality in supplying customers with products and services are measures accompanying the risk management process. When embedding risk management into existing management systems, the main aim is to create and to use as many synergies as possible and therefore, the risk management process should be realised as a link between management responsibility and other aspects of the organisation that are required in the line of product realisation[206].

In this work the integration of risk management is realised by the means of ONR 49002-1 and additional aspects of a risk management system have been added as management responsibility to the existing quality management system. Figure 17 depicts the integration according to ONR 49002-1. This is also valid for application within a pharmaceutical quality management system. The risk management process is integrated in a horizontal way and its functions can directly refer to possible fields of application.

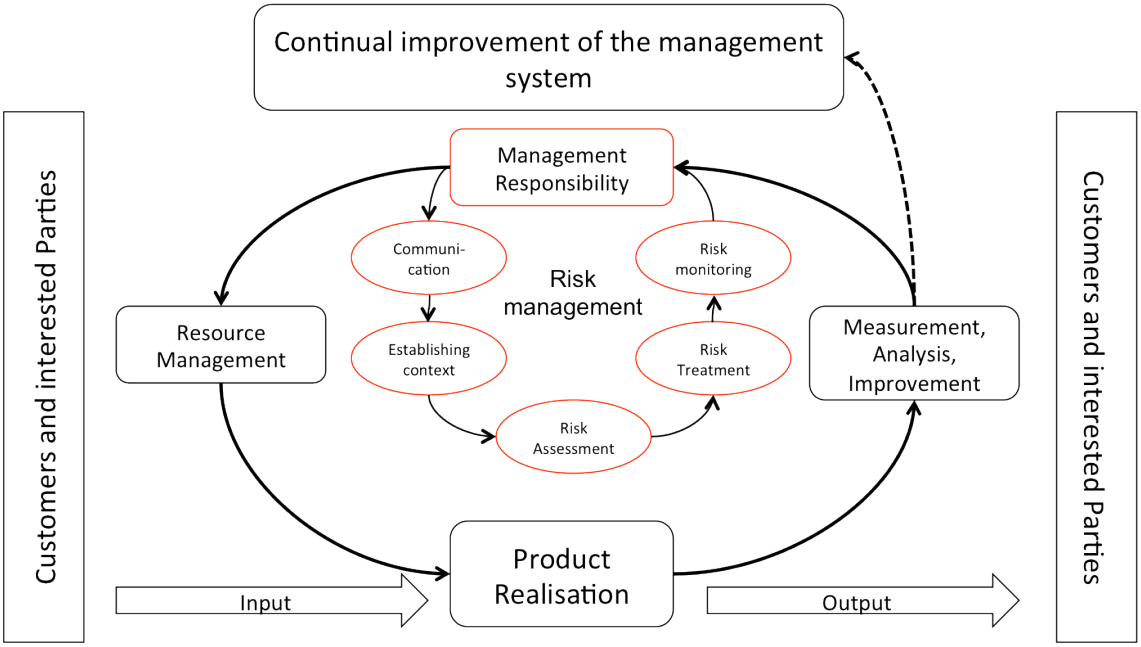

Figure 17: Possible integration of risk management into an existing quality management system[206]

In the model according to Figure 17 risk management arises from the management responsibilities but is not limited to management itself as it extends to resource management, product realisation, and to processes of measurement, analysis and improvement. This approach is applicable to an existing quality system according to ISO 9001. However, it is also valid for a GMP-based quality system as this is similarly structured.

The partial integration of management system elements like risk management into an existing basis system can be regarded as a change process and can go along with a more or less distinctive transformation of organisational strategy, structures and culture. In general, there is a constant need for organisations to adapt to a changing environment in order to

[206] Austrian Standards (2010), p. 5.

maintain their market position and to enable a future growth[207]. Especially the actual rate of technological advancement requires a need for change in the future[208].

Basically, changes of first and second order can be distinguished[209]. A change of first order describes a change that goes along with the continual improvement of structures, processes and systems whereas company's strategy remains unchanged. Second order changes strive to additionally change company's strategy and culture and hence, these kinds of changes are more profound. Figure 18 presents four types of changes that may be differentiated:

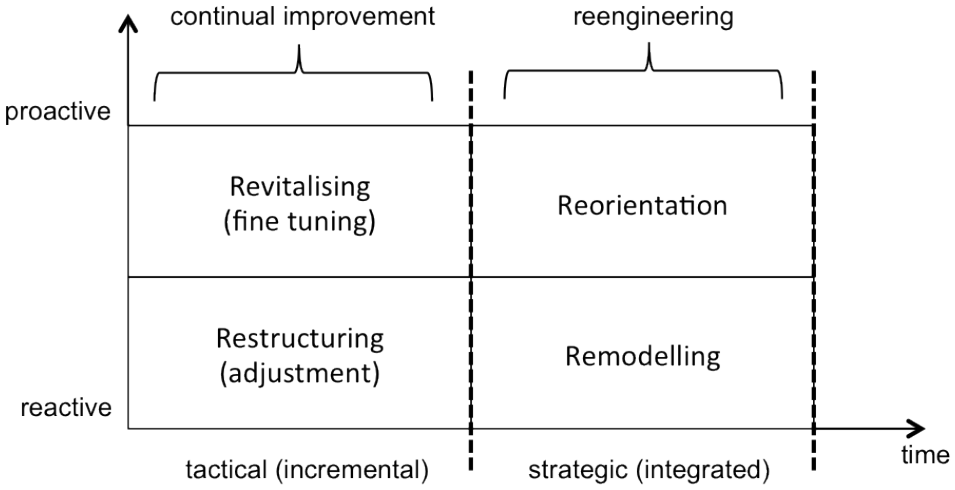

Figure 18: Four types of changes[209,210,211]

Restructuring is a reactive approach and existing structures are improved according to internal or external requirements (e.g., regulatory demands). Restructuring processes mainly affects procedures, systems and structures. Revitalising is performed to proactively implement changes that will be required in the near future. Reorientation means a proactive profound change of the organisation that also affects its strategy and culture. The main aim is to remain competitive in the future. Finally, remodelling is a fundamental organisational change that is reactive and caused by various internal and external triggers. With regard to the implementation of quality risk management, this change can be regarded as reactive and tactical and thus as a restructuring process, as it is only a result of external requirements. Of course, in other organisations the integration of risk management can be regarded as some kind of reorientation, as not only the fulfilment of regulatory requirements causes the change but also the wish to become a more efficient and flexible organisation and thus additional changes in strategy and culture are required.

Resistance to change is often a reason for difficulties in implementing and the failure of change initiatives[212]. For instance, one of 500 Australian organisations indicates resistance as the most common problem faced by management in change implementation[213]. There

[207] Biedenbacha et al. (2008), p. 123.
[208] Armenakis et al. (2009), p. 127.
[209] Baumgartner et al. (2006), p. 100.
[210] Schneeberger (2006), p. 66.
[211] Nadler (1989), p. 72.
[212] Erwin et al. (2009), p. 39.
[213] Bovey et a. (2001), p. 372.

are numerous models for change processes within organisations to effectively implement change and to deal with resistance. For instance, Lewin and Gold[214] suggest a three-phase model, consisting of unfreezing, moving and freezing with regard to organisational change. Other stage models of organisational change are supposed, e.g., Judson's five phase model[215] or Kotter's eight steps for effective change[216]. Isabella[217] proposed a four-stage model including: anticipation, where information about the change is collected; conformation, as the implications of the change are begun to understand; culmination, where results of the pre- and post-change phase are compared and assimilated; and aftermath, where consequences of the change are evaluated. According to Jaffe et al.[218], organisational members experience four reactions when moving through the change process: (1) denial (i.e. refusal to believe that the change will be implemented), (2) resistance (organisational members do not participate or try to avoid implementation), (3) exploration (i.e. experimentation with new behaviours), (4) commitment as the final phase, where the change is accepted.

The eight steps of transformation according to Kotter[216] set the basis for other models and have been comprehensively reviewed by other authors (e.g., Smith[219], Appelbaum et al.[220]). These steps will be discussed with regard to the integration of risk management into an existing quality management system:

(1) A sense of urgency about the need of change is to be established, as people are not willing to change if they are unable to see the need to do so. In the case of the integration of quality risk management into an existing quality management system the need for change primarily arises from regulatory requirements. However, sound risk management could also lead to more efficient and effective processes and results within the organisation and hence, also business drivers exist. As people involved in the pharmaceutical industry are common with changes as a result of new requirements, the urgency about the need of change can be well established.
(2) The second step requires the assembly of a group with enough influence in the organisation to lead the change. With regard to risk management integration all relevant owners of existing processes that would be amended with risk management requirements should be included, i.e. department heads of quality, manufacturing, maintenance, process technology, materials management, and of course a member of the executive board.
(3) A vision and a strategy of what the change is about are to be created. Whelan-Berry et al.[221] define the change vision as a key part of a change process. It is supposed that this requirement is most important for complex changes with marked impacts. In the case of risk management, the development of a sound vision or strategy for change implementation was not deemed necessary for successful implementation, as in the first step of integration, the fulfilment of regulatory requirements was in the focus and hence, no other main targets were pursued. The vision for risk management is part of the risk management policy.
(4) The reason for the change has to be communicated. People have to be informed why the change is needed and how it will be achieved. Communication can be regarded as a critical element in the change process as it can reduce uncertainty, de-

[214] Lewin (1999), p. 36.
[215] Judson (1991)
[216] Kotter (1995), p. 58.
[217] Isabella (1990), p. 7.
[218] Jaffe et al. (1994), p. 158.
[219] Smith (2005), p. 152.
[220] Appelbaum et al. (2012), p. 764.
[221] Whelan-Berry et al. (2010), p. 175.

crease ambiguity and can affect the kind of positive or negative responses to organisational change[222,223]. This communication is firstly realised at the level of department heads that have to be convinced about the need for change. Subsequently, supervisors would communicate relevant change aspects to their employees.

(5) Step five is about empowerment and involvement of people in the change effort. During the integration of risk management this is realised by consulting matter experts about their opinions and suggestions for integration. This is particularly important as people think about the changes and how to achieve them rather than thinking why they don't like the changes and how to stop them.

(6) By generating short-term wins a justification for the change can be established. Managers who implement changes should find evidence that the change has achieved the desired results[224]. Moreover, short-term wins also help to remove resistance to change by reinforcing the change vision in the minds of employees[225]. In the case of the risk management change, the realisation of this step is rather difficult as in the first phase of risk management integration, the main focus is to achieve regulatory requirements that is required for long-term success on the market. Short-term wins can be generated by successful audits of the integrated management system by external stakeholders (i.e. customers and regulators).

(7) The implementation of the actual change can be used as starting point to introduce more changes. This requires the actual change to be successful. Management will require first successes to plan for the further change process, and be able to justify the costs of the change process[226].

(8) Step eight is important for long-term success and institutionalising the change, as new approaches are to be incorporated in the corporate culture. Further development of change management within an organisation would require further steps after actual implementation, for instance, a common view on risk awareness, risk perception etc. This has to be realised by a cultural change and is not in the focus of the present implementation of risk management.

It has to be emphasised that communication is one of the most important tools to deal with resistance during the change process. Hence, the new risk management approach should also be adequately included in the employee-training program. As the training program is continuously reviewed and updated, changes to the existing system and procedures can be easily communicated to the relevant persons who have to work with the new requirements.

4.2 Integration of risk management

This section deals with the practical integration of risk management into existing quality systems. In the following chapters the structure of existing quality (sub-)systems within an established quality management system is analysed with regard to the applicability of additional risk management requirements. Subsequently, integration is performed by augmenting the existing processes with the new risk requirements, where feasible. If the integration

[222] Bordia et al. (2004), p. 345.
[223] Nelissen et al. (2008), p. 306.
[224] Ford et al. (2008), p. 191.
[225] Drtina et al. (1996), p. 20.
[226] Peifer et al. (2005), p. 297.

of some requirements is not possible or expedient, then these elements will remain separate. For every quality system under consideration possible risks are defined and risk management tools are presented to address these risks.

Table 7 lists a number of quality systems used in the pharmaceutical manufacturing. The following elaboration specifically focuses on systems employed in quality assurance, i.e. change control, deviation management, raw material supplier qualification, complaint management and planning of self-inspections. The chosen quality systems represent major aspects of the pharmaceutical quality assurance system and their enhancement with regard to risk management can be well used as primer for further integration activities. Moreover, the selected quality systems involve different departments and organisational units within a pharmaceutical company, and therefore they are suitable to give the whole organisation a first understanding of risk management.

4.2.1 Risk management policy

The risk management system typically contains a risk management policy that describes the overall intentions and directions of the company related to risk. Generally, the risk policy includes the commitment of the company to comply with applicable regulatory requirements and should facilitate continual improvement of the risk management system.

As part of the integration approach the risk policy becomes a part of the overall quality manual. According to ICH Q10[227] a quality manual should be established and should contain the description of the pharmaceutical quality system. Therefore, the quality manual includes the quality policy that can be seen as equivalent to the risk management policy and hence, describes the overall intentions of the company related to quality. This policy can be easily augmented by risk management requirements. Moreover, the quality manual explains the scope of the quality system. A major aspect is the identification and description of pharmaceutical quality system processes, as well as their sequences, linkages and interdependencies. These descriptions have to be updated with regard to risk management. The quality manual further defines management responsibilities within the pharmaceutical quality system including responsibilities for risk management, as leadership is essential to establish and maintain a company-wide commitment to quality and risk management.

4.2.2 Risk-based change control

Change is inevitable in the pharmaceutical industry as suppliers change their processes, sources and specifications for raw materials, equipment needs to be repaired, serviced or replaced, manufacturing locations are changed, batch sizes are increased or decreased and technology advances require changes to the existing operations[228]. A formal change control process is a major requirement of modern pharmaceutical quality management to assure that any changes to established products, processes, equipment, facilities, etc. are properly evaluated and implemented to protect product quality and to ultimately assure safety and efficacy of a pharmaceutical product[229].

[227] ICH (2008), p. 4.
[228] Waterland et al. (2003), p. 731.
[229] Harclerode (2013), p. 368.

An important aspect of change control is the impact a change might have on regulatory filing, manufacturing parameters, specifications and technical services[230]. For instance, FDA discriminates between three main types of changes, i.e. major, moderate and minor changes. Major changes require agency's approval before implementation. This type of change is likely to have a detectable impact on the critical quality attributes of a product. E.g., the change in the type of solvent used for final crystallisation of an active pharmaceutical ingredient would be regarded as a major change[231].

Change control is a critical element in a pharmaceutical quality management system as inadequate change control procedures end up creating a huge risk of non-compliance[231].

Table 19 lists examples for different groups of changes according to Buecker et al.

Table 19: Examples for different types of changes[232]

Type of change	Change
Manufacturing process changes	- form, fit, or function of the product (i.e., any change that could be perceived by a customer as a form, fit, or function change) - incorporation of a different process technology during manufacturing - new materials of construction - other product specifications
Product changes	- shift of specification ranges or widen of specification ranges to allow the acceptance of product that was previously out of specification - narrower specification range - new analytical method
Packaging changes	- new or modified packaging material with direct product contact
Labelling changes	- new format or wording regarding certificate of quality

ICH Q9 suggests the following areas of application for risk management[233]:

- Evaluation of the impact of changes on the availability of the final product.
- Evaluation of the impact on product quality of changes to facilities, equipment, material, or manufacturing processes.
- Determination of appropriate actions preceding the implementation of a change, e.g., additional testing, (re)qualification, (re)validation or communication with regulators.

[230] Sharma et al. (2008), p. 67.
[231] Sharma et al. (2011), p. 27.
[232] Buecker, J. et al. (2002), p. 68.
[233] ICH (2005), p. 16.

Different change control process flows are implemented in the practice. However, as pharmaceutical companies and especially their quality systems are similarly structured, change control procedures in different companies have certain similarities. Figure 19 shows a common change control procedure and considers requirements of quality risk management.

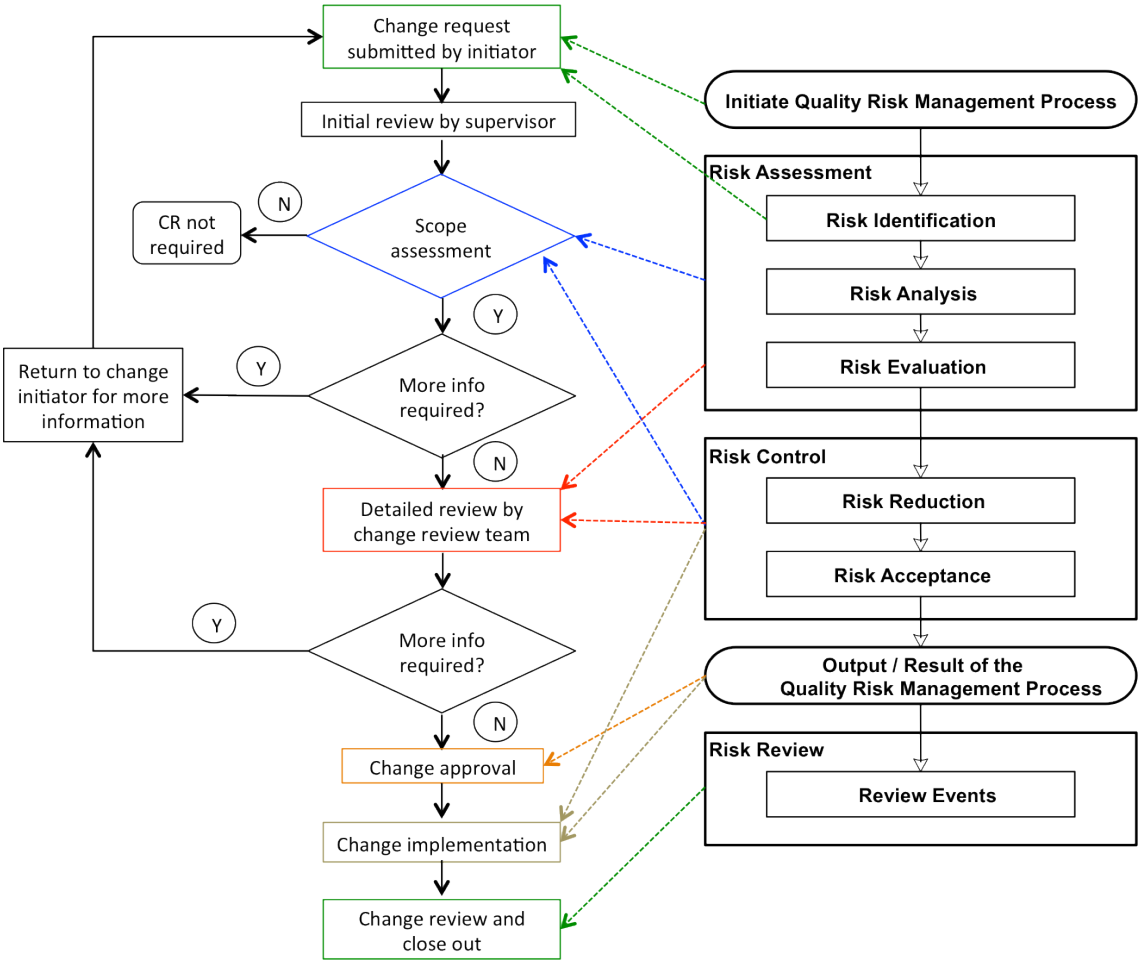

Figure 19: A typical pharmaceutical change control process. Risk management aspects are considered[234].

The first step in the risk-based change control process is the initiation of the change and the risk management process. The initiator can be any employee who recognises the need for change with regard to a certain procedure, equipment, product specification, etc. The change request contains relevant information, e.g., description of the change, reason and justification for change and, if available, supporting information. Additionally, the initiator identifies obvious risks that are associated with the change. E.g., 350-liter mixing vessel is used during the synthesis of a corrosive, temperature-sensitive pharmaceutical suspended solid[235]. There is a request to change the equipment to a 700-liter vessel in order to increase the batch size. Preliminary risks identified by the manufacturing supervisor, who initiates the change, may be the effect of new materials of construction with regard to corrosion,

[234] Harclerode et al. (2013), p. 369.
[235] Haclerode et al. (2013), p. 381.

changed mixing fluid regime, and temperature uniformity. This first risk identification as part of the change request makes the knowledge of the matter expert available for later assessment during the change control workflow.

The next step is the initial review by the supervisor as a control gate. Inappropriate changes can be refused (or redirected) at this time, before they would cause other people getting involved. This scope assessment relates to risk assessment. Change requests are screened against given risk criteria. For example, changes that do not impact product quality or regulatory compliance are out of scope of the formal change control system. The European Medicines Agency[236] issued a list of changes that require regulatory approval. Changes that do not fall within the listed changes therefore would be out of scope (in the case the focus is put on regulatory changes only). Other changes could be specifically allowed by established standard operating procedures[237]. These changes would also not require formal change control if they fulfil requirements set out in the relevant procedure. If more information is necessary at this point the change may be returned to the initiator.

The subsequent detailed review by a cross-functional change control review team is a major aspect of the risk-based approach. In this step a sound risk assessment including risk identification, analysis and evaluation is performed. Based on the outcome of the assessment, risk mitigation activities are planned and realised. In the case of the above-mentioned equipment change potentially impacted critical quality attributes are considered, based on the first risk identification during initiation step. Different methods, e.g., FMEA or fault tree analysis, can be used to analyse the risks associated with the change. FMEA is one risk management tool that can be used for analysis of potential failure modes within a system as a result of a change to determine the effects on the system and to deduce relevant measures to address these effects. In the case of change control the failures can easily by defined as any event that could affect the quality and/or regulatory compliance of a product[238]. Items with a calculated risk above a certain threshold limit would have to be addressed in the line of change implementation. Hence, actions for implementation would be recommended during this step of the change control process. For instance, the equipment change would require a detailed analysis of the changed mixing regime to assess the effects on temperature distribution inside the vessel.

The output of the risk-based change control approach is the change approval and the appropriate implementation of the change, considering the measures defined in the risk-control step. Risk review is performed after realisation of the change before formal close out. In this step the change control team reviews the change with regard to any deviations that might require further actions. Another element of risk review with regard to the change control process is realised by the annual product quality review. This review is a regulatory requirement and reviews all changes to a product, its processes, raw materials or analytical methods.

4.2.3 Deviation management

Deviations during pharmaceutical manufacturing impose a major risk with regard to the quality of a pharmaceutical product and its regulatory compliance. Potential risks result when a procedure is not followed, process parameters fluctuate or are not reached, and an analytical method cannot be performed because of equipment failure and so. As potential

[236] European Medicines Agency (2013)
[237] Haclerode et al. (2013), p. 370.
[238] Haclerode et al. (2013), p. 372.

effects of these deviations are risks they have to be addressed during the risk management exercise. During risk management of deviations the focus of interest lies on identification of root causes and definition of appropriate measures to mitigate deviation effects and to prevent the occurrence of future deviations.
The term *deviation* encompasses events often referred to as non-conformances, errors, discrepancies, failures, or problems and is defined as unexpected or unplanned departures from GMP, regulations, standards, procedures, or specifications that may affect product safety, quality, identity, potency, or purity[239].
The EU GMP Guideline states that any deviations have to be fully recorded, *investigated with the objective of determining the root cause and appropriate corrective and preventive actions implemented.* And further: *an appropriate level of root cause analysis should be applied during the investigation of deviations… This can be determined using Quality Risk Management principles*[240].

Risk management in combination with deviation management can be used to increase efficacy and efficiency of the deviation management process, as this process actually presents some problems[241]:

- In order not to "oversee" certain discrepancies that could cause problems when discussed during audits, there is a tendency towards reporting every non-conformance as deviation. This may lead to poor root cause investigation and superficially performed corrective and preventative actions.
- A sound handling of all deviations occurred can tie up resources that would be required elsewhere. Hence, from a business point of view, it is preferred to assign resources according to the importance of each deviation. Therefore, the level of investigation should be commensurate with the level of risk[242] and it is expected that the highest-risk deviations, which are fewer in number, will consume the major part of resources dedicated to deviation management[239].
- When each individual deviation is assessed for their criticality, this uses additional resources. The definition of critical points in the process and critical quality attributes of the product can be used to perform a first screening of deviations occurred.

Figure 20 presents a typical process flow of a deviation management system. Once a deviation occurred, e.g. a defined yield cannot be reached during a manufacturing unit operation, a deviation notification is issued, e.g., by staff members who detected the deviation. Next, the deviation is classified according to given criteria, e.g., major, minor and not-quality relevant deviations can be distinguished. The classification is commonly performed in a multidisciplinary team consisting of matter experts from production, quality control, quality assurance and distribution or sales department. Based on the classification, the level of investigation is determined. Different investigation activities would then be carried out as described in relevant standard operating procedures. After identification of the root cause(s), appropriate measures to mitigate the effects of the deviation and/or to prevent future occurrence of a similar deviation are defined and carried out. A review of the measurements is performed. In case they have turned out to be insufficient, additional actions may be defined. Following successful implementation, a formal closeout is performed.

[239] Bredehoeft et al. (2009), p. 1.
[240] European Commission (2013), p. 5.
[241] Heredia et al. (2008), p. 31.
[242] ICH (2005), p. 2.

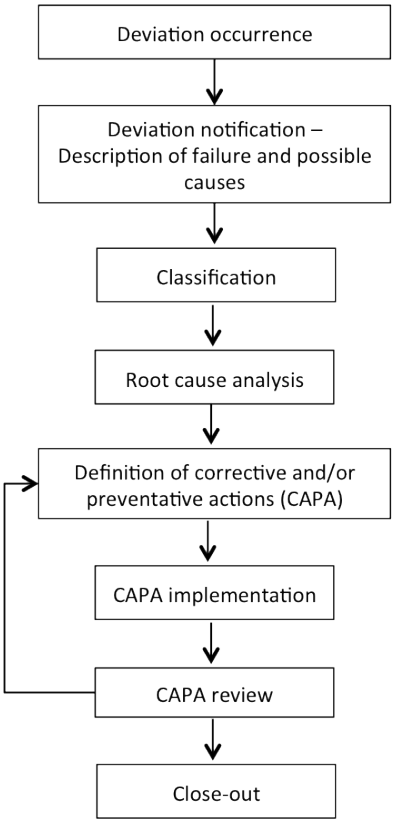

Figure 20: Typical deviation management process flow

According to Heredia et al.[243] using a risk-based approach with regard to prioritisation and decision-making can optimise deviation management. In a first step, deviation events are classified according to pre-established criteria with the aim to tailor the subsequent handling of the deviation based on the risk it presents to product quality and/or compliance. This step can be regarded as a preliminary screening phase that allows the subsequent handling of non-risky events to be simplified. With regard to decision-making, risk management is used to examine the impact of the deviation and to define appropriate corrective and preventative actions (CAPA). This requires a risk analysis of the process in which the deviation arose in order to find the root cause(s).

The integration of risk management into the existing deviation management system according to Figure 20 is performed based on an approach defined by Heredia et al.[243]. Figure 21 depicts this approach in a modified form. This process model integrates risk management into the deviation management system by defining an analysis, a classification and a treatment phase. The analysis phase states different questions with regard to the risk occurred. Depending on the answer, the deviation is classified into one of the following categories: Incident, non-critical deviation or critical deviation. In the case of an incident, the deviation is closed immediately, as the corrective actions required to solve it are described in relevant standard operating procedures. Non-critical deviations would lead to a case-by-case decision, performed by a cross-disciplinary team. During this assessment, it is checked whether the deviation has occurred before and if so, how many times. In the case the rate of occurrence exceeds a predefined limit, then the deviation will be regarded as a critical deviation. Critical deviations require a full assessment of its impact on product quality, including

[243] Heredia et al. (2008), p. 31.

sound root cause analysis. The recommended tool for this approach is a process FMEA. After the root cause has been identified corrective and preventative actions can be put in place and the FMEA is revisited to document the success of these measures. As last step, the final deviation report is issued and the deviation is closed.

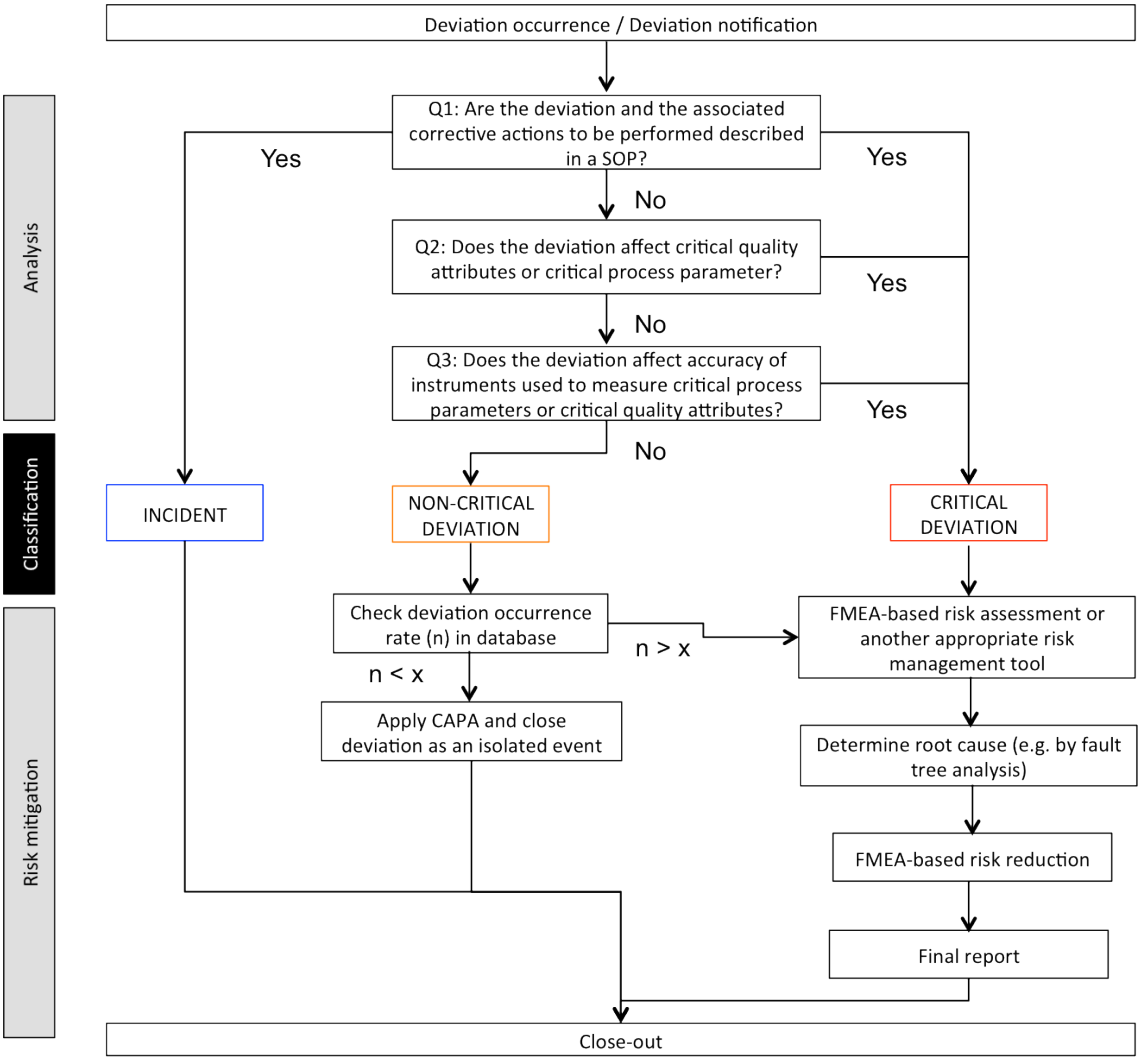

Figure 21: Risk-based deviation management process flow[244]

For this approach it is important that knowledge about potentially critical quality attributes and potentially critical process parameters is available. This could be regarded as a drawback for this approach as potentially critical factors play an important role in the analysis phase of the deviation management process. It is often difficult to establish the whole spectrum of potentially critical factors solely based on the already established routine manufacturing process. Hence, it would be of upmost importance to define critical parameters during the development phase of the pharmaceutical product and its associated manufacturing process. This information can then be used during the whole life cycle of the product including risk-based approaches. One possibility to do so is the use of a science and risk-

[244] Heredia et al. (2008), p. 31.

based approach in den development of pharmaceutical products, e.g., the quality-by-design approach[245,246].

To overcome this obstacle, Heredia et al. suggest another process model for deviation management that realises risk assessment without risk questions but makes use of FMEA in this first step of risk analysis (see Figure 22).

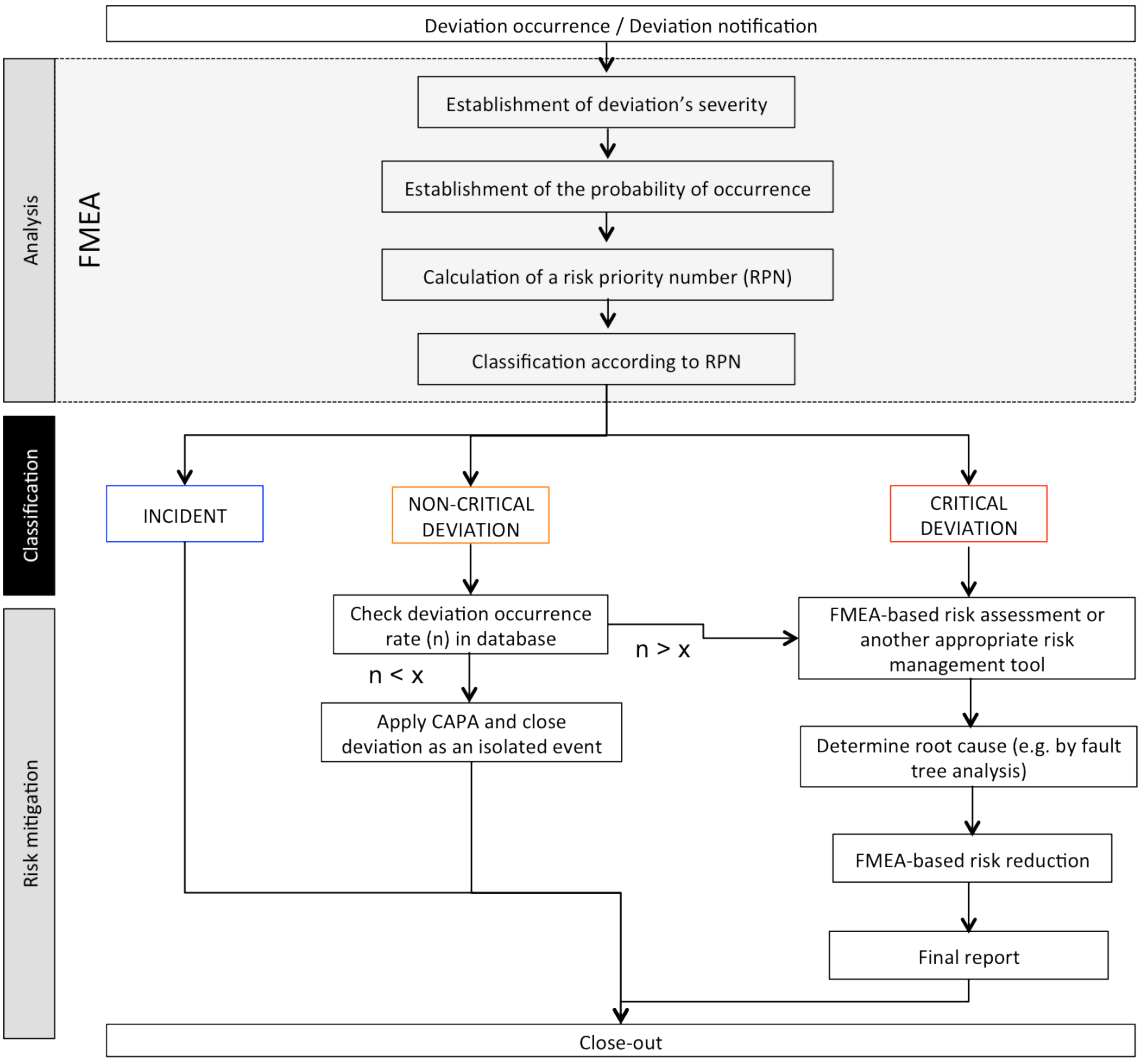

Figure 22: Risk-based deviation management process flow using FMEA in the analysis phase[247]

This approach classifies deviations according to a risk priority number calculated by the means of an FMEA. This is the main difference in comparison to the approach presented in Figure 21. The risk priority number is calculated by taking the severity of the effect of the deviation occurred and its frequency of occurrence into account. Different classification scales can be used, e.g., severity can range from 5 (deviation has a major effect on the quality of the product) till 1 (customer would not become aware of any quality defects). In

[245] Adam et al. (2011), p. 106.
[246] Toschkoff et al. (2012), p. 52.
[247] Heredia et al. (2008), p. 35.

comparison to the other process described above, the FMEA-based approach would require more resources in the analysis phase. However, no preliminary knowledge about potentially critical process parameters or potentially critical product quality attributes is required.

In summary, a deviation management system with an integrated risk-based approach could help the organisation to better discriminate between critical and non-critical deviations and to better manage the often conflicting interests of business, regulatory, and customer requirements including resource allocation[248].

4.2.4 Risk-based raw material supplier qualification

For pharmaceutical operations, qualification of suppliers is an important aspect of GMP. EU GMP[249] states that *the purchase of starting materials is an important operation* and *starting materials should only be purchased from approved suppliers*. Directive 2011/83/EC[250] requires that *the holder of the manufacturing authorisation shall ensure that the excipients are suitable for use in medicinal products by ascertaining what the appropriate good manufacturing practice is. This shall be ascertained on the basis of a formalised risk assessment*… .

Hence, in order to assure constant quality, efficacy and safety of a finished dosage form, it is required that pharmaceutical starting materials have the quality and purity appropriate for use in finished pharmaceutical products. Thus, the manufacturer of pharmaceutical products is highly dependent on the raw material suppliers to provide materials that are uniform in chemical and physical characteristics and thus are supplied with a constant high quality. An effective risk management process can assure the continuity of product supply and ensures that customers and patients receive products that are fit for purpose. It is obvious that numerous quality defects of the finished product may result from inappropriate raw material quality. Table 20 gives some examples of general hazards potentially caused by suppliers. Table 21 lists some specific hazards and effects associated with inappropriate raw material quality.

[248] Bredehoeft et al. (2009), p. 4.
[249] European Commission (2013), p. 3.
[250] European Union (2011)

Table 20: Examples of hazards potentially caused by suppliers[251]

Upstream supply chain hazards	
- Increase / decrease in demand - Capacity / resources change - Takeover / mergers - Legal status (regulatory restrictions in individual markets and of supplier) - Counterfeiting / fraud - Facility disaster - Materials, products, service supply interruption - Complex processes	- Termination of materials and services - Uncontrolled variation in materials - Unexpected contaminants in supplied product - Deliberate or accidental adulteration - Distribution / transportation / storage events - Lack of adequate documentation control

Table 21: Examples of hazards and effects associated with inappropriate raw material quality

Hazard	**Harm (potential effect)**
Particle size distribution out of specification	Deviating release rates leading to altered drug affects; problems during manufacturing (e.g., granulation, tablet pressing)
Impurities	Impurities may harm patients.
Raw material contains allergens that are not listed by supplier	Drug product may cause allergic reactions.
Contamination with iron particles (caused by abrasion)	Possible injury of gastrointestinal tract
Odour	May cause patients to be disgusted.
Cross contamination or mix up	Alteration of drug effects

Non-risk-based supplier qualification approaches are often based on a rigid quality system, that may only differentiate between APIs and other excipients, where considerable activities including supplier audits are only performed for API manufacturers whereas excipient suppliers have barley been acknowledged with regard to risks their activities may pose to starting material quality. Refined approaches may discriminate between different types of excipients, their manufacturing process and in how many finished products they are contained.

[251] The Chartered Quality Institute (2010), p. 15.

A sound risk-based approach with regard to raw material supplier qualification should take into account the following aspects:

- risk-based approval of suppliers
- risk-based supplier evaluation (i.e. supplier review)
- risk-based audit planning

Requirements for the approval of API-suppliers are set forth in EU GMP Part II (Basic Requirements for Active Substances used as Starting Materials)[252]. The manufacturer of a pharmaceutical medicinal product has to assure that these requirements are fulfilled by the API-supplier and hence, an audit of the supplier's manufacturing site is mandatory. Thus, a risk-based approach at this point is not deemed absolutely necessary. For instance, risk management might be used to determine critical aspects of API manufacturing and to focus audit efforts on these aspects. Moreover, a supplier might be risk-rated according to the business risk, e.g., in the case it is likely that a material supply interruption occurs, then alternative suppliers should be qualified.

Regarding the approval of suppliers of excipients, a sound risk-based approach is regarded as an efficient approach to assess specific quality risks as inherent part of a certain excipient. Based on this quality risk assessment, appropriate measures can by realised by the manufacturer of the pharmaceutical product to mitigate those risks.

The European Commission issued a draft guideline that describes a possible approach towards risk-based excipient supplier qualification[253]. This document provides a formalised risk assessment with the aim to ascertain appropriate GMP for excipients. It requires that an excipient risk management procedure should be incorporated into the existing quality management system of the manufacturing authorisation holder. Parts of the risk-based approach described in this section are based on this draft guideline.

Excipients may pose certain risks to the quality, safety and efficacy of medicinal products and hence, each excipient, taking into account the excipient supplier, is to be classified into "low risk", "medium risk" or "high risk". Based on the classification, appropriate measures have to be realised to tread this excipient and to mitigate identified risks.

The risk-based assessment is performed in subsequent steps (see Figure 23). First, an excipient risk profile is evaluated, including the risk associated with the use of the excipient in the final product. Based on the resulting risk, elements of GMP have to be identified that are needed to be in place at the excipient manufacturer's site in order to control and maintain the quality of the excipient. Subsequently, a risk profile of the excipient manufacturer is evaluated. Based on a potential gap between required GMP and actual GMP according to manufacturer's risk profile, the manufacturer of the finished product could define specific mitigation strategies. An on-going risk-review is to be performed.

[252] European Commission (2010)
[253] European Commission (2013)

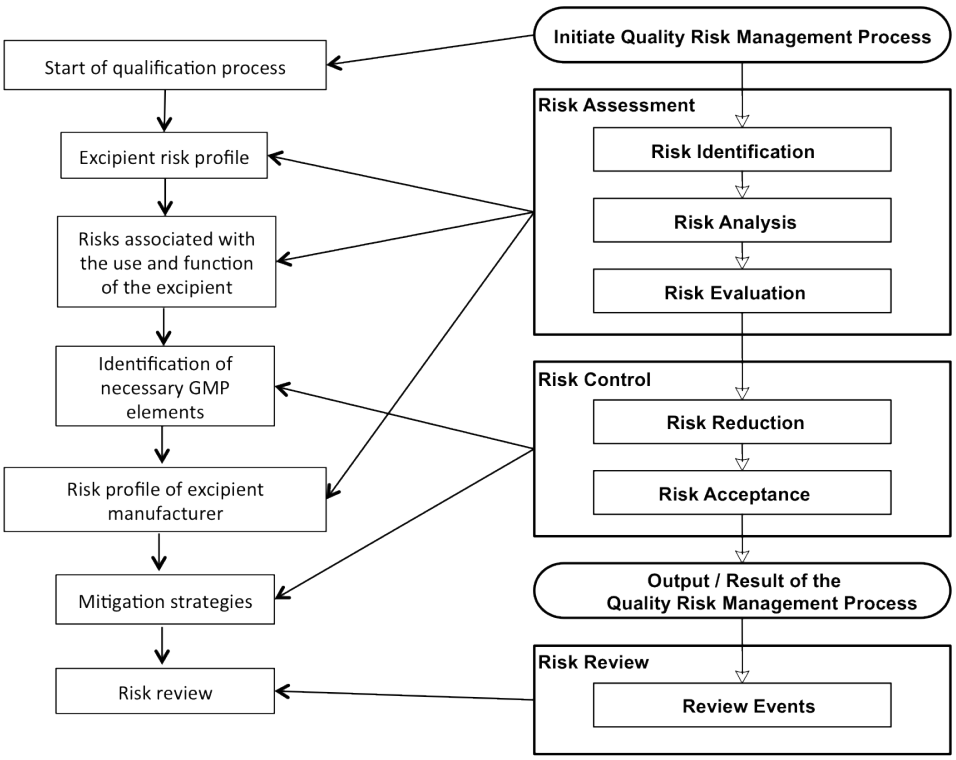

Figure 23: Risk-based approach towards the qualification of excipients[254]

Table 22 provides an example for the calculation of the excipient risk profile.

Table 22: Calculation of the excipient risk profile

Risk	**Assessment**	
Transmissible spongiform encephalopathy (Excipient may be from TSE-relevant sources)	0	0=not sourced from TSE-relevant sources 5=sourced from TSE-relevant sources
Chemical / biological manufacturing process or sourced from natural sources	2	1=natural sources 2=chemical sources 4=biological sources
Potential for microbiological or endotoxin contamination	2	0=no potential 2=low potential 3=medium potential 5=high potential
Potential for any impurity	1	0=no potential 1=low potential 2=medium potential 3=high potential
Use of dedicated equipment / facilities	3	0=dedicated equipment 3=non-dedicated equipment
Manufacturing process complexity	2	0=process is deemed simple 2=process is deemed complex 4=process is deemed highly complex

[254] European Commission (2013)

Risk profile	10	(Sum)

The excipient risk profile is the calculated sum total of the various risks. The risk profile will be used as input in the establishment of necessary GMP-elements.

Table 23 calculates the risk associated with the use and function of the excipient.

Table 23: Calculation of the risk associated with the use and function of the excipient

Risk	**Assessment**	
Dosage form and use of the medicinal product containing the excipient	1	1=solid oral dosage form 3=liquid oral dosage form 5=parenteral
Function of the excipient in the formulation	1	1=lubricant 3=disintegrant 4=filler
Total quantity used	2	1=25 kg/d 2=100 kg/d 5= >1t/d
Potential impact on the critical quality attributes of the medicinal products	1	1=low impact 3=medium impact 5=high impact
Risk profile	5	(Sum)

Based on the both risk profiles calculated, the manufacturing authorisation holder would have to determine the appropriate GMP requirements with regard to the excipient manufacturer. The requirements will vary based on the assessed risks. As different manufacturers place different requirements on their suppliers based on their own established quality system and their corporate culture, it is difficult at this point to define a limit, based on the calculated risk profile, determining the different levels of GMP that would be required. Hence, as a minimum the following requirements, amongst others, should be considered:

- An effective quality assurance system has to be established.
- Qualified personnel should be available.
- Job descriptions for relevant personnel should be defined.
- Employee training programs should be established.
- Premises and equipment should be appropriate to the intended operations.
- Documentation system in place.
- Quality control department independent from production.
- Complaint system in place.
- Performance of regular self-inspections.

Based on available information, a gap analysis of the required GMPs (as defined above) against the actual activities and capabilities of the excipient supplier is then performed. This gap analysis could contain an audit of the excipient supplier manufacturing site. Based on the evaluated gap, the manufacturing authorisation holder would have to implement certain

measures to mitigate the evaluated risks. For instance, if the potential for the presence of impurities is high, then additional analytical testing for these impurities could be implemented to mitigate the risk. Another possibility could be risk avoidance, i.e. selecting another supplier.

For risk review a regular supplier re-evaluation has to be performed. For this risk-based evaluation, the following aspects can be taken into account:

- Number of complaints of received batches of excipients
- Type and severity of defects on excipients resulting in complaints
- Loss of relevant quality system accreditation by excipient manufacturer
- Observation and trends in drug product quality attributes
- Results from audits of the excipient manufacturer

Based on the results of risk review, specific measures can be employed.

The third important aspect within a risk-based supplier qualification is the risk-based planning of audits of the supplier's manufacturing sites. Here, it has to be discriminated between first and follow-up audits. As pointed out above, first audits of API manufacturers are mandatory under the rules of GMP. Hence, the use of risk assessment is limited. First audits of excipient suppliers can be performed risk-based. Here, the above mentioned risk-profiles would provide evidence for the necessity of audit performance, by assessing the complexity of the manufacturing site, manufacturing process and the excipient, and the risk associated with the intended use of the excipient.

The need for follow-up audits can also be evaluated risk-based. For APIs follow-up audits are mandatory. With a risk-based approach, the frequency of these audits can be determined. Follow-up audits of excipients are not mandatory. However, based on their risk initially calculated and taking into account the performance of the supplier, audits could be required. Here, a risk matrix to calculate the overall risk from a combination of excipient and supplier risk and the results from the frequently performed supplier re-evaluation is suggested (Table 24).

Table 24: Risk matrix for audit planning

	Excipient's risk profile		
Supplier re-evaluation	LOW	MEDIUM	HIGH
LOW	**LOW**	**LOW**	**MEDIUM**
MEDIUM	**LOW**	**MEDIUM**	**HIGH**
HIGH	**MEDIUM**	**HIGH**	**HIGH**

For instance, a satisfying supplier re-evaluation would result in a low compliance and quality risk. In combination with a medium risk profile, the total risk would be low. A rather poor supplier re-evaluation in combination with a medium risk profile would result in high

risk. In the case of API manufacturers a low risk would lead to a re-audit frequency of, e.g., 3 years. A high total risk of excipient suppliers would also result in a 3-year audit frequency.

4.2.5 Pharmaceutical complaint management

In the pharmaceutical industry complaints refer to quality defects of products that have first turned out at the customer or end-user. Complaints may result from packaging material defects, e.g., a leaking bottle, a difficult to open cap or a missing tablet in the blister, or concern the pharmaceutical dosage form, e.g., the medicinal product has no effect, the solution colour is different, or a broken tablet was found[255]. According to EU GMP[256] all complaints concerning potentially defective products must be reviewed carefully according to written procedures. The aim of complaint management is to register an incoming complaint, perform appropriate investigations, implement CAPAs, if necessary, and respond to the customer.

See Figure 24 for a typical complaint management process workflow. The quality assurance department records the incoming complaint. The complaint officer is responsible to collect and document relevant information and to initiate the technical investigation process. During technical investigation, relevant documentations are checked (e.g., existing complaint files, batch documentation) and investigations are performed (e.g., analysis of complaint samples and retained sample; root-cause analysis with regard to the manufacturing process). In the case a root-cause for the complaint could be identified, the complaint is confirmed and a CAPA is initiated, along with the response to the customer. Non-confirmed complaints would result too in a response to the customer. All recorded complaints and associated CAPAs are reviewed frequently, e.g., in the annual management report.

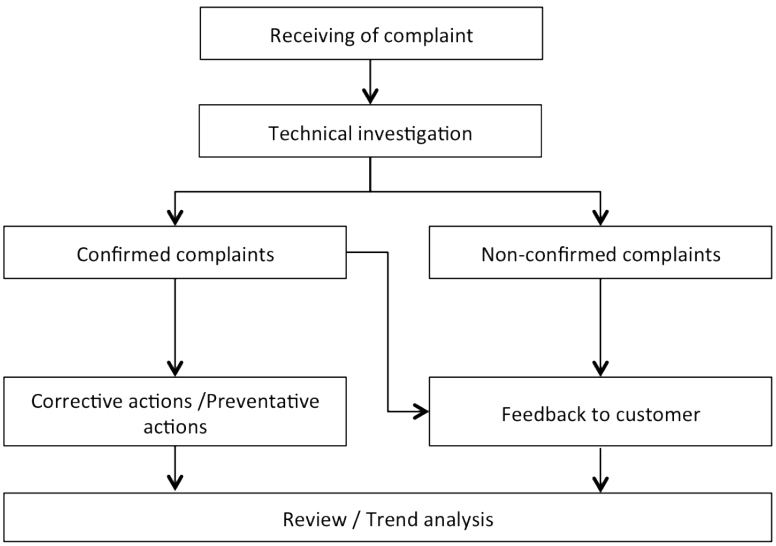

Figure 24: Complaint management process workflow

The technical investigation is the focal point for the integration of a risk-based approach. This step would include risk identification, analysis and evaluation and is the link to risk

[255] Braga (2007), p. 16.
[256] European Commission (2006), p. 2.

control. Based on the documented complaint, risk identification defines potential harms that may result from the complaint reason. By comparison with the complaint database, historical data is used to define the rate of occurrence of the complaint. The level of effort, formality and documentation of the complaint investigation is then commensurate with the level of the identified risks. In a next step, different tools for risk assessment, e.g., Ishikawa diagram or FTA, can be used to identify root causes for the complaint. The result of risk assessment is the decision to accept the complaint as justified or not. In the case of acceptance, potential effects on the patients are evaluated and CAPAs are initiated. Finally, risk control is realised by appropriate CAPAs and communication with the customer.

A good complaint management system is a possibility to improve product quality and the efficacy of the quality management system itself. Additionally, the risk-based approach will render the management process more efficient, leading to a shorter handling time and better use of resources. Moreover, complaints management is one of the main pillars of costumer management. An effective complaint management program can help to decrease customer maintenance costs, increase revenue and enables the company to track historical customer and product trends, useful to predict future market, product and customer needs[257].

4.2.6 Risk-based planning of self-inspections

A self-inspection consists of a periodic detailed examination of all or part of a quality assurance system by an internal team with the aim to verify that GMP is being applied and to propose any necessary corrective measures to responsible management[258]. The EU GMP Guideline states that self-inspections are required to monitor the implementation and compliance with GMP principles and to propose necessary corrective measures[259].

There are different possibilities to plan and conduct a self-inspection. For instance, self-inspections can be carried out department-wise, and every year all GMP-relevant departments are audited. Of course, because of limited resources, this target is hardly realised. Another option of self-auditing is a product-centred approach, where all relevant systems and processes that come in contact with a certain product may be inspected. One can also select a certain process, e.g., deviation management, and focus the self-inspection activities on the correct process workflow and its required inputs and outputs.

Regardless of the chosen type of self-inspection, the responsible quality assurance department is faced with scarce resources and some kind of prioritisation has to be performed with regard to self-inspection planning. The Pharmaceutical Inspection Convention (PIC/S), an international instrument between countries and pharmaceutical inspection authorities, has issued a recommendation for regulatory authorities for risk-based inspection planning[260]. Although this approach is intended for inspectorates to plan the frequency and scope of site visits, it is adapted here to result in a valuable risk-based approach towards prioritisation of self-inspection activities by assigning frequencies to the routine self-inspections. Figure 25 presents the risk-based self-inspection planning approach.

[257] Biswas et al. (2009), p. 2.
[258] Sharp (2005), p. 470.
[259] European Commission (2013), p. 4.
[260] PIC/S (2012)

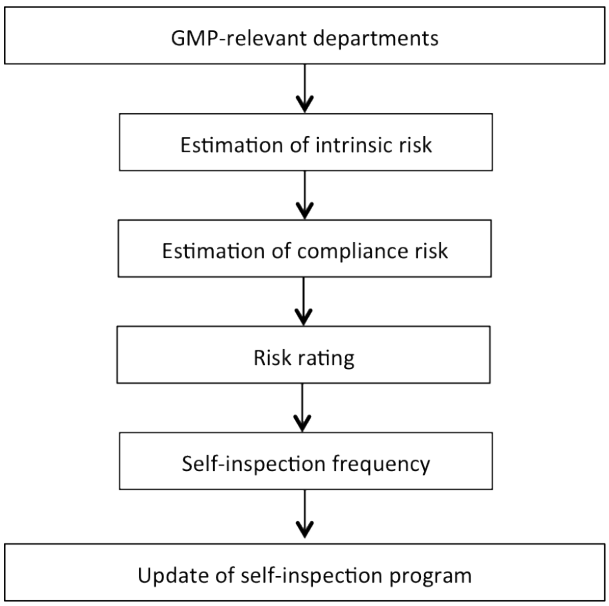

Figure 25: Risk-based self-inspection planning workflow

For every department of a company associated with GMP activities, two different kinds of risks are estimated, i.e. the intrinsic risk and the compliance risk.

The intrinsic risk is defined as the risk for product quality based on complexity, processes, tasks, procedures, personnel etc. of the individual department. Hence, this type of risk is inherent in the department, its processes and products and is not influenced by compliance aspects of the department. The intrinsic risk matrix is presented in Table 25.

Table 25: Intrinsic risk matrix

	Criticality		
Complexity	**1**	**2**	**3**
1	**1**	**2**	**3**
2	**2**	**4**	**6**
3	**3**	**6**	**9**

For calculating the intrinsic risk, the complexity of the department and its processes and the criticality of the (intermediate) products, processes and services provided by the department with regard to the quality and availability of the final product, are assessed. A score of 1-2 represents a low intrinsic risk, a score of 3 and four a medium risk and a score of 6 or 9 means a high intrinsic risk.

The compliance risk is based on the overall compliance status of the department. Key indicators for compliance issues are findings from previous audits, complaints with root-causes that were traced back to the relevant department, deviations, and recent changes of products, processes, services, equipment, premises etc. Table 26 presents the estimation of the compliance risk.

Table 26: Compliance risk estimation

Compliance issue	Compliance risk
> 5 major findings during the last self-inspection OR > 8 deviations and/or complaints with root-causes traced back to the department OR Major changes with regard to products, processes, services, equipment, and premises have been implemented.	HIGH
1 – 5 major findings during the last self-inspection OR 4 – 8 deviations and/or complaints with root-causes traced back to the department OR Minor changes with regard to products, processes, services, equipment, and premises have been implemented.	MEDIUM
No major findings during the last self-inspection OR < 4 deviations and/or complaints with root-causes traced back to the department OR No change-control relevant changes	LOW

After the intrinsic and the compliance risks have been estimated they are combined in the overall risk-rating matrix according to Table 27.

Table 27: Overall risk-rating of the department

	Intrinsic risk		
Compliance risk	**Low**	**Medium**	**High**
Low	**Risk Rating = A**	**Risk Rating = A**	**Risk Rating = B**
Medium	**Risk Rating = A**	**Risk Rating = B**	**Risk Rating = C**
High	**Risk Rating = B**	**Risk Rating = C**	**Risk Rating = C**

According to Table 27 there are three possible risk ratings: "A" represents a relatively low overall department risk and "C" represents a relatively high overall department risk. Based on the overall risk-rating, inspection frequencies are defined for each assessed department. Table 28 gives an example for suggested self-inspection frequencies.

Table 28: Self-inspection frequency for individual departments based on assessed risk

Risk Rating	**Inspection frequency**
A	Reduced frequency, 3-4 years
B	Moderate frequency, 2-3 years
C	Increased frequency, every year

Of course, the method described above can also be used for the prioritisation of processes to be self-inspected within a process-oriented quality assurance system.

5 Analysis of the potential of the integrated quality risk management system, further strategic development and outlook

Although the use of risk management and risk assessment in the pharmaceutical industry is not new, up to now these concepts have only found limited application. The prioritisation of resources based on risk to quality and to public health and safety makes sense and will lead to better productivity and effectiveness[261]. Hence, the ultimate goal of the risk management process is to bring focus and effort to that issues in an organisation that potentially result in the highest risk to product quality, compliance and/or patient safety[262]. As the risk and quality management processes are interlinked and corresponds with each other by various inputs and outputs, it is most likely to realise an integrated management approach in order to achieve optimised system output with regard to efficient and efficacious processes. In this work this integrated approach is described and examples for realisation are given with regard to different quality systems. The quality systems have been selected for integration, i.e. change management, deviation management, raw material supplier qualification, complaint management and self-inspection system, because of the following reasons: (1) Some of them have already existed before with some sort of risk-based approach, but not in that level of development. Hence, a further integration can be regarded as a system refinement and thus integration is not likely to fail due to the resistance of the organisation. Therefore, these systems are most suitable for a starting point for an extensive integration approach. (2) It is further recommended to start integration with above-mentioned systems because they show a high horizontal organisational integration with regard to different departments of a company. For instance, the risk-based change control system (see Figure 26) involves the interaction of various departments.

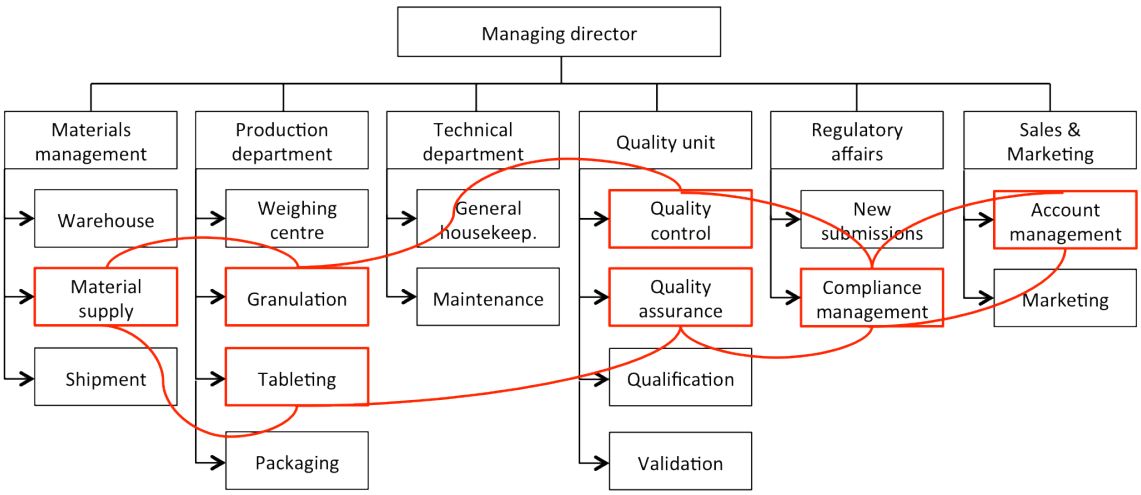

Figure 26: Horizontal organisational integration of risk-based change control (only GMP- and quality-relevant organisational structures are shown)

[261] Baseman et al. (2013), p. 3.
[262] Mollah et al. (2013), p. viii.

In the case of the change of a raw material, e.g., an existing disintegrant is replaced by another one, the change would require both inputs and activities from different organisational units, like material supply and quality assurance to assess the new supplier, manufacturing to test for manufacturability, quality control to have adequate test methods, compliance management to perform regulatory filing of the change, and account management to communicate the change to the customer. As this well-known and practiced system affects different departments it is suitable to act as primer for further organisational integration of other risk-integrated quality systems. This is also valid for the other quality systems for which integration is described.

Beside regulatory compliance, an increase of efficiency and efficacy is often referred to as an important (business) reason for risk management integration[263]. However, does an integrated risk-based approach always result in an increase of relevant performance indicators? First, very often, adequate key performance indicators that would enable the detection of risk management benefits are rarely established in existing quality systems. Relevant parameters could be, for instance, the required time to perform a change or to solve a deviation. These parameters are often considered in a quality management review. Hence, decreased process time would be a suitable indicator for assessing risk management's efficiency. When individual quality systems are associated with an activity based costing system, financial benefits may also be derived. However, the cost of risk management activities including setup and maintenance of the risk management system itself has to be taken into account. Therefore, the relation of risk management with financial benefits may be a difficult and blurred task. Nevertheless, the correlation between risk management activities and increased efficacy may be demonstrated more easily. For instance, faster handling of complaints would result in increased customer satisfaction, assessed by customer questionnaires (at this point not the patients are regarded as customers but other clients or intermediaries). Moreover, an increased robust regulatory compliance status of the whole organisation, leading to less audit findings with regard to customer and regulatory authority audits, might be indicative for an increased efficacy of the quality management system. This would strengthen the relationship between the company and its customers and the regulatory relevant bodies. For instance, a company having a relatively clean compliance record would likely be inspected less often or receive less attention than a company having repeatedly several major findings during regulatory audits. It is generally agreed, that risk-based approaches would benefit the compliance status of a company.

Hence, in order to steadily increase efficiency and efficacy of risk-based quality systems, integration activities have to be continued with the aim to encompass even more systems. Additional quality systems as listed in Table 7 would have to be assessed with regard to risk management requirements and integration has to be conducted. As a consequence, risk-based approaches should not be solely limited to quality assurance aspects and systems. For instance, as a pharmaceutical product manufacturing process has inherent risks that may impact product quality and patient safety, risk management has to be expanded with regard to production. Though potentially critical process parameters and their associated control strategy should be determined in the line of the drug development process, risk management can be applied at any point in the product life cycle[264]. A specific aim of using risk assessments with regard to manufacturing is to appropriately use resources to control, monitor and validate those manufacturing parameters that really do have an effect on final product quality. In the manufacturing environment, there are various sources of potential

[263] Baseman et al. (2013), p. 5.
[264] Raschiatore (2013), p. 276.

hazards, e.g., people, equipment, facilities, raw materials, formulation parameters, environment, or storage. One possible approach to assess and control those risks is the HACCP-method that has already been discussed briefly in section 3.4.2. Risks assessments performed by the production department can further be used as input to various quality systems, e.g. change management or complaint management, as described above. Thus, expanding risk management to the manufacturing floor would be an important step to a companywide integrated risk-based approach.

As already pointed out above, risks associated with the product and its associated manufacturing process can be well addressed in early stages of the product life cycle, which means during the development phase. Hence, it is suggested to further expand risk management approaches with regard to pharmaceutical research and development. Moreover, such integration would further enable the inclusion of various other organisational units in the risk management process. This horizontal integration that affects the whole life cycle of a product would further speed up full risk management integration in the whole organisation. These aspects would be well covered by the risk-based *Quality-by-Design* (QbD) approach. Moreover, QbD would enable the achievement of another goal: the departure of the integrated risk-based approach away from sole compliance thinking towards real improvement of processes and products and associated organisational structures. QbD enables the horizontal integration of risk management over the whole life cycle of a product, starting from early development till discontinuation. According to ICH Q8, QbD is defined as a systematic approach to development that begins with predefined objectives and emphasises product and process understanding and process control, based on science and quality risk management[265]. The fundamental assumption underlying QbD is that if critical sources of variability are understood, then product quality and performance can be controlled using the manufacturing process to mitigate variability in the material properties[266]. QbD focuses on science-based design and development of formulations and associated manufacturing processes in order to assure predefined product quality objectives[267]. Hence, QbD seeks to identify risks for quality, establishes appropriate measures as mitigation strategies and realises these measures as control strategies during routine manufacturing of the marketed product. Hence, development and post-marketing activities are heavily interrelated. Inputs derived from this life cycle stage can then be used as prior knowledge to design, develop and risk-assess new or modified products and processes later on in the product life cycle.

Expanding the risk management system to virtually include all quality-relevant aspects of pharmaceutical manufacturing and quality management would necessitate more or less far-reaching organisational adaptions and changes. Hence, it is important to be aware of the current state of understanding of risk management among staff and the current level of organisational integration (see Table 29). This can be used as gap analysis to plan further organisational integration activities (e.g., implementation of risk management procedures and activities taking into account relevant findings of the gap analysis, modification of the company's culture).

[265] ICH (2009), p. 16.
[266] Muzzio et al. (2008), p. 119.
[267] Adam et al. (2010), p. 106.

Table 29: Maturation of the risk management process[268]

Risk Maturity Level	Risk Processes	Attitude	Behaviour	Skills and Knowledge
Skepticism	No formal processes	"Accidents will happen"	'Fear of blame' culture	Unconscious incompetence
Awareness	Isolated use of stand-alone processes	Suspended belief	Reactive, 'fire fighting'	Conscious incompetence
Understanding and application	Extended use of combined processes	Passive acceptance	Compliance thinking	Conscious competence
Embedding and integration	Risk management embedded in the business	Active engagement	Risk-based decision making	Unconscious competence
Robust risk management	Frequent risk review and improvement	Champion	Innovative and appropriate risk management	Expert

Another possibility to assess the organisational environment with regard to a potentially existing risk culture is to ask the following questions[269]:

- Does an employee know what to do when he or she identifies a significant potential problem?
- In the case senior management identifies a significant potential problem, how is it dealt with?
- Is it determined what constitutes a "significant" event?
- Who determines which resolution approach will be applied?

If the response to three or more of these questions is something like "It depends on a case-by-case basis", then the organisation has no existing risk culture.

As can be seen in Table 29 an important aspect when rolling out risk management to the whole organisation is to take into account the skills and attitude of staff, e.g., with regard to risk awareness and risk perception. To obtain a long-term common understanding of these aspects and to get a fully effective risk management, anchoring risk perspectivism in the company's culture is of upmost importance. Generally, for successful integration of risk management into a company's quality system (and beyond) the organisation must ensure that individuals engaged in risk management activities understand the value of risk management, are adequately trained, and are familiar with risk management tools and the overall risk management process[270]. The training aspect with regard to risk management procedures, tools and the overall risk management process can easily be realised by updating the existing employee training programs to teach the relevant skills. Raschiatore[270] suggests a multilayer approach to training:

- high-level risk management training for the general employee population;
- focused policy, procedure and tool-based training for employees being part of risk management circles;
- special facilitator-level training for those employees, who have been designated as risk subject matter experts.

[268] Long (2013), p. 69.
[269] Pritchard (2007)
[270] Raschiatore (2013), p. 292.

The former aspect, i.e. ensuring a common view on the value of risk management, is more difficult to realise as it has to be reflected in the company's culture. As a first step towards building a risk culture, it is critical to share the basic understanding of relevant terms (i.e. the glossary) with all employees, including decision makers and other stakeholders and reach a common agreement of using these terms by defining them in a way that makes sense to all involved[271].

Another important factor with regard to the organisation's risk culture is to minimise the subjectivity in the organisation's risk decision making. For this, it is required to better understand how employees and other stakeholders perceive risk and how aware they are with regard to potential risks. It is clear that risk is perceived not only by technical parameters and probabilistic numbers, but also in a psychological, social and cultural context. Hence, individual, social and organisational cultural characteristics have to be taken into account in dealing and working with risk[272]. The same is valid for risk acceptance, as it is also not only related to technical estimates of risk and benefits but also to a subjective dimension, e.g., voluntariness[273]. Psychological research on risk perception has been dominated by the so-called psychometric paradigm[274] and it is referenced to the relevant literature (e.g., the work of Sjöberg[275]). As it is not possible to completely influence or direct individual risk perception of each employee, it is important that at least the overall risk management approach should take into account the resulting bias by introducing, e.g., a risk board as part of a new organisational culture. Relevant risks can be discussed within this board and different perspectives and psychological, social and cultural background of people involved would result in a more or less constant judgement approach towards risks.

The next possible step in a further evolution of risk management in the pharmaceutical industry is the expansion of the risk-based approach to virtually address all relevant business risks, not only limited to risks to product quality. This corporate risk assessment and treatment can be regarded as holistic enterprise risk management (ERM), a topic that has received increasing interest in recent years in the business environment[276]. Enterprise risk management can be defined as a process which enables industries of all sectors to assess, control, exploit, finance and monitor risks from all sources for the purpose of increasing the organisation's short and long term value to its stakeholders[277]. Monahan[278] provides two additional definitions for ERM: (1) ERM deals with uncertainty for the organisation, and (2) ERM is a methodology for managing risks associated with strategic objectives of an organisation. In comparison to traditional risk management, where individual risk categories or groups are separately managed in risk "silos", enterprise risk management enables companies to treat a wide array of risks in an integrated, enterprise-wide fashion[276]. This holistic risk management approach benefits firms by decreasing earnings and stock price volatility, reducing external capital costs, increasing capital efficiency and creating synergies between different risk management activities[279].

[271] Verma (2009), p. 30.
[272] Schmidt (2004)
[273] Starr (1969), p. 1232.
[274] Sjöberg et al. (2004), p. 13.
[275] Sjöberg (2000), p. 3.
[276] Hoyt et al. (2011), p. 795.
[277] D'Arcy (2001), p. 2.
[278] Monahan et al. (2008), p. 11.
[279] Beasley et al. (2008), p. 311.

Basically, enterprise risk management differentiates between financial risks, operational risks and strategic risks, where financial risks deal with potential losses due to changes in financial markets, operational risks cover various situations, including risks to quality, product development, or customer satisfaction, and strategic risks include, for instance, factors like technological innovation, customer preferences or future regulatory requirements[280].

But why should it be valuable for the pharmaceutical industry to strive to expand its risk management activities even to the overall corporate level to include not only risks to quality and therefore to the health of the patient but also other threads that may result in harm to the whole company and could therefore endanger stability and future growth of the organisation? To survive in the long term, companies have recently started to realise, that they must do more than relying on future returns from new potential blockbuster products; they must face current problems and address risk in a new way, and hence, pharmaceutical companies have to adjust their business models to make a more intelligent approach to risk, leading to significant transformation of these companies[281].

According to a recent survey among leading pharmaceutical companies performed by Shafiei et al.[282] four main factors influence the on-going transformation of the pharmaceutical industry: Fully integrated pharma network, personalised medicine, translational research, and pervasive computing. Each factor is associated with specific risks for the pharmaceutical organisation, with the business and regulatory environment playing a major role in the on-going transformation[282]. With regard to transformation-induced quality risks, the highest importance is given to due diligence, product transfer, and product characterisation activities, followed by technology validation and multidisciplinary regulatory knowledge[282]. According to an outlook performed by Ernst & Young principal future business risks and uncertainties according to Table 30 have been identified.

Table 30: General future business risks of the pharmaceutical industry[283]

Description of future key risks
Intense competition around branded products
Costly and highly uncertain nature of R&D
Competition from lower-priced generic products
Patent loss or expiration in the near future
Unexpected development related to safety or efficacy of products
Pipeline productivity and competition – ability to continuously develop or replace products
Pricing and access pressures
Current and future product liability claims
Regulatory environment: - Potential exposure to government price controls - Ability to obtain and maintain approval for products - Potential non-compliance issues and scrutiny from regulators - Adverse effect from changes in laws and regulations
High dependency of revenues, cash flows and earnings on protections given by patents
Manufacturing and supply-chain difficulties
Reliance on third-party and outsourcing arrangements

[280] D'Arcy (2001), p. 2.
[281] Deloitte (2009), p. 5.
[282] Shafiei et al. (2013), p. 229
[283] Ernst & Young (2013)

According to a Deloitte survey, executives identified the areas of pricing and sales, marketing, regulatory affairs, talent management and R&D as those areas where risk will rise most sharply in the next 10 years (see Figure 27). The area of pricing and sales is a key concern in the development of strategic risk, taking into account the increasing amount of cost-conscious customers and reimbursement strategies of national health systems. A new product would not success if development would be too costly and the health system is not willing to pay, as no paramount increase of efficacy and/or safety in comparison to an already existing product can be seen (here, we would have a strong link to risk-based approaches during research and development). Regulatory affairs are another focal point where risk is expected to rise, as drug regulatory agencies continue to implement even stricter rules and guidelines to ensure products are safe and efficacious. Strategies for addressing the development risk during R&D activities are an important aspect to mitigate exposure to internal company risks. Risk mitigation in this area can be performed well by the above-discussed QbD-approach. E.g., a specific strategy could be to develop many products that are not settled in the high price sector, but taken together can still produce a healthy profit margin and reduce the development risk, instead of hoping for the breakthrough of another blockbuster product. Regarding talent management, it is obvious that also in the future, the success of the pharmaceutical industry will continue to be dependent on the ability to attract and retain talent. Currently, many talented individuals are searching for the company offering the greatest short-term rewards, or where the company is implementing a transformational strategy. Future talents will not only rely on their skills in the field of R&D, but as the industry transforms, more diversified skills such as regulatory and government relations and the ability to work with other parties across the whole company will become more important.

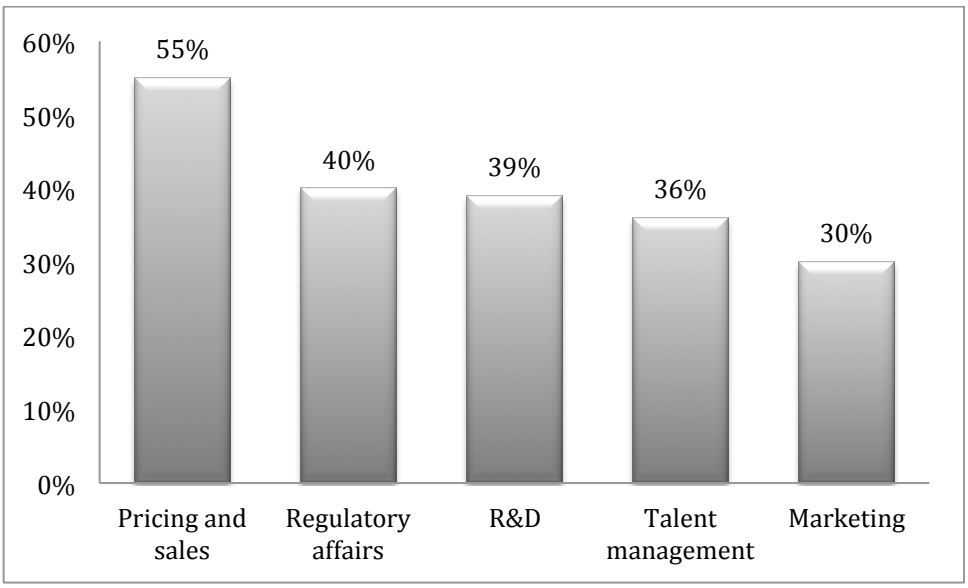

Figure 27: Supposed change of risk level between 2009 and 2015 in Western Europe[284]

It was demonstrated above, that beside quality risks, other risks exist that are most relevant for the long-term existence of pharmaceutical companies. However, quality risks play a major role, as the product success and the whole regulation activities with regard to the

[284] Deloitte (2009), p. 7.

pharmaceutical sector focus on patient health and efficacious medicine. It is clear that individual risk groups of different segments of a pharmaceutical company cannot be treated separately, as strong interdependencies exist, e.g. between quality risks and more general business risks, like risks caused by inadequate talent management that may affect product quality, time-to-market or specific compliance issues. Therefore, the ultimate approach for pharmaceutical companies towards risk should be realised by the means of an integrated enterprise risk management, taking into account quality risks and all other risks the pharmaceutical sector will face in the near and mid-term future.

6 Conclusion and outlook

This master thesis focused on the implementation of risk management into existing quality systems as a need to assure future regulatory compliance and to prepare the pharmaceutical industry for various future opportunities and threats. In the case risk management has already been implemented in some systems, it was merely focused on relevant core processes, i.e. R&D, production and quality assurance.

A sound quality management system can be regarded as a valuable primer and point of departure for risk management activities. The pharmaceutical industry has a long-lasting tradition with regard to quality management, hence lacked until now a more structured and systematic approach that can be realised by integration of risk management into existing quality systems.

Based on the above explanations it can be concluded, that with respect to risk, the pharmaceutical industry will face various potential threats in the near and mid-term future. These challenges will mainly require the companies' high ability to plan and implement adequate mitigation strategies to control the associated risks and to enable a further stable growth and a constant increase of profitability and stakeholder value.

Risk-based approaches in general can be seen as well suited for managing these upcoming challenges. Risks appear on different levels of an organisation, may come from outside or are internally made, and affect specific aspects or the business of the whole organisation. Therefore, it is important to have a system that holistically addresses all kinds of risk by the means of an integrated approach. Hence, strategies for the management of the present and upcoming risks should be built into the processes at different levels, e.g. starting with processes that govern the whole organisational activities to processes for individual quality systems. A profound enterprise risk management system can be regarded as suitable to face these future challenges.

According to a global risk management study[285], there are six main challenges for a risk management system within an organisation in the next years: (1) reducing costs, (2) aligning with the overall business strategy, (3) implementing regulatory demands, (4) improving risk management and modelling, (5) data management, and (6) developing a risk culture.

Therefore, when realising a sound risk management strategy the pharmaceutical industry has to face the following two aspects:

(a) Stepwise companywide integration of risk-based approaches, starting with the quality systems and gradually expanding risk management with regard to other relevant systems and development of an adequate risk culture.
(b) Constantly review and improve the already existing risk management system with regard to costs, overall business strategy and regulatory demands.

The key message is that in order to ensure future stability and profitability of the pharmaceutical sector, all relevant risks have to be considered in an integrative approach. That means that also non-quality risks would have to be covered by a company-wide risk management system. The ability to relate different risks from several areas would result in more efficient and effective risk mitigation strategies. This is the overall aim of enterprise business management.

[285] Accenture (2011), p. 9.

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