

# Risk-Based Compliance Handbook

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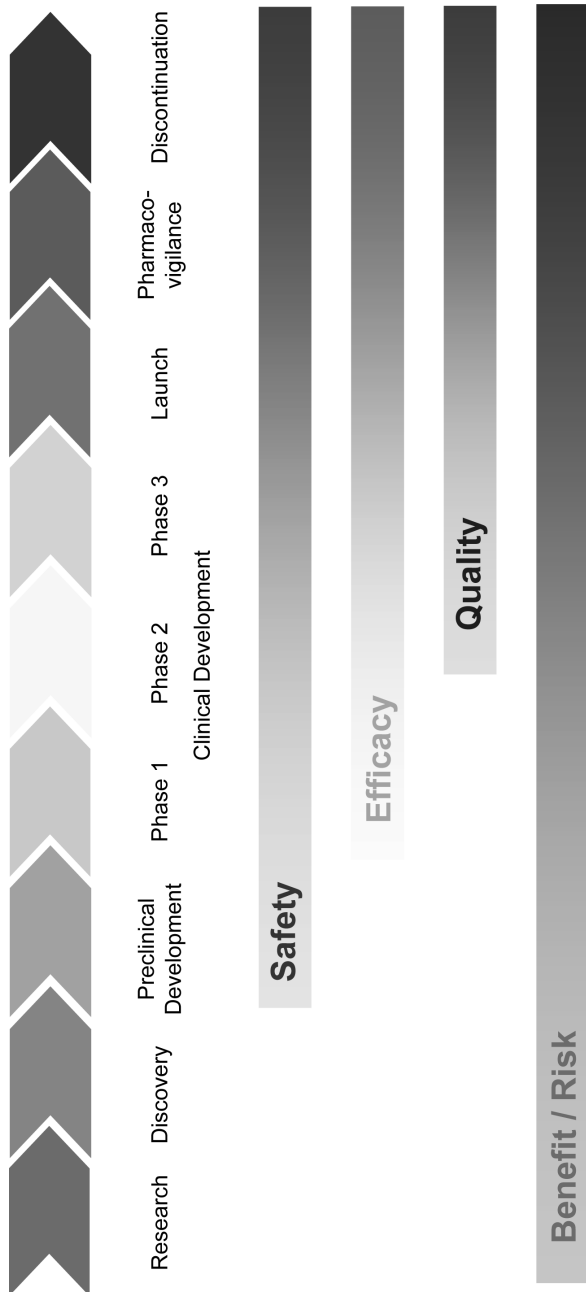
## INTRODUCTION

Paracelsus famously stated that all things are poison and not without poison; that only the dose makes a thing not a poison (*“Alle Ding sind Gift und nichts ohn Gift; allein die Dosis macht das ein Ding kein Gift ist”*) (Handbook of Pesticide Toxicology, 2001; [www.wikipedia](http://www.wikipedia)). In this statement he highlighted the benefits and risks of medicines. This ambivalence still troubles the pharmaceutical industry to this day. Drugs billed as “blockbusters” have failed to show efficacy after launch, or have had to be recalled because of safety issues. Over the past decade, 26 major drugs, with severe side effects, were recalled in the US. These include blockbusters like Pfizer’s pain-killer Bextra in 2005 (global sales of \$1.3 billion prior to recall), Merck’s pain-killer Vioxx in 2004 (\$2.55 billion), Bayer’s heart drug Baycol in 2001 (\$1 billion), Warner-Lambert’s anti-diabetic Rezulin (\$2 billion) and Johnson & Johnson’s anti-heartburn Propulsid (\$1 billion), the last two in 2000 ([www.timesofindia](http://www.timesofindia)). Drugs in Phase III clinical trials have not confirmed the expected safety and efficacy ([www.drugresearcher](http://www.drugresearcher)) and new drug applications have failed to gain approval from the regulatory authorities despite successful outcomes of the clinical trials ([www.emea.europa](http://www.emea.europa); [www.oncolink.com](http://www.oncolink.com)). These failures are tremendously costly, and are a somewhat unexpected result given the many sophisticated drug development models deployed by the pharmaceutical industry.

Even for successfully marketed drugs there is high risk associated with planned or unplanned changes to manufacture, analysis or distribution, as changes may alter the drug, and thus its safety and efficacy. Technical knowledge gained

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Figure 1.1



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over the years may not be documented in sufficient detail or may not be readily available to permit a thorough scientific appraisal of a change. The issue of same or similar becomes a hot debate (far from resolution) with bio(techno)logical drug products ([www.bioprocessintl.com](http://www.bioprocessintl.com)).

These few examples already help in illustrating the importance for appropriate and adequate benefit/risk management processes and methodologies that cover the entire drug lifecycle (see Figure 1.1).

A literature review reveals a plethora of material on specific and particular aspects of risk management. However, no current publication addresses the entire drug lifecycle from a benefit/risk perspective. This book aims to provide the reader with an overview of the available and typically applied methodologies for risk management, always viewed from a compliance (with the applicable regulations for health care products, in particular pharmaceutical drug products) perspective. The information is based on current regulatory guidance, personal communication with industry, health care associations and regulatory agency representatives, and selective literature reviews. The result is a compilation of industry best practices and current trends in benefit/risk management. By relating these methods and processes to the drug lifecycle and by addressing persistent industry issues, gaps and shortcomings of the currently available toolbox for benefit/risk management will become more apparent and easier to detect.

Although the term “risk management” is more prevalent than “benefit/risk management”, in the end it is always a matter of weighing up the benefits against the risk — just as Paracelsus pointed out some 500 years ago. What has really changed since are, of course, the requirements for compliance with the applicable regulations. The applicable regulations are generally referred to as good practices: good clinical practice (GCP), good laboratory practice (GLP), good manufacturing practice (GMP), good distribution practice (GDP) and good pharmacovigilance practice (GPhVP) ([www.mhra.gov.uk](http://www.mhra.gov.uk)). Compliance is not something absolute or precisely defined. On the contrary, it is dependent upon circumstances and interpretation, and thus always the result of a benefit/risk analysis.

Why this book and why now? A great number of training courses are offered on the subject of risk management, and more importantly on the new paradigm of a risk-based approach to regulatory compliance. This concept will be described and discussed in much detail later in this book. There are a large number of articles in publications targeting the healthcare industry covering risk management related topics. Despite of all these activities and all the information available, large parts of the healthcare industry are either unaware, reluctant to embrace or confused as to the best approach for adopting and implementing these concepts. The problem, it seems, is in part information overload, and in part missing the context with

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regards to the drug lifecycle. Therefore, the authors deem it an appropriate time to present the discerning reader with this publication.

This book does not describe new methods or processes; what it does is to present an overview and a critical discussion of these in relation to the drug lifecycle, with the constant aim of achieving compliance. For those familiar with the healthcare industry it is a known fact that the goal of achieving compliance is in permanent conflict with the need for marketing in the shortest possible time and producing at the lowest possible cost. To enable management to make the right decisions at the right time it is not only essential to have the appropriate processes and methodologies in place, but also to be in a position to extract data and information from these that can be presented and communicated in an intelligible and useful manner. As much of the general public, and sometimes even the regulators, struggle to comprehend the language and terminology of the industry technical expert, it is of paramount importance to find ways in which to “translate” technical speak into common English. The technical experts need to deliver the benefit/risk information in a way that can be understood by both technical and commercial staff. The best benefit/risk management activity will invariably fail if communication is compromised.

## ICH Q9 QUALITY RISK MANAGEMENT

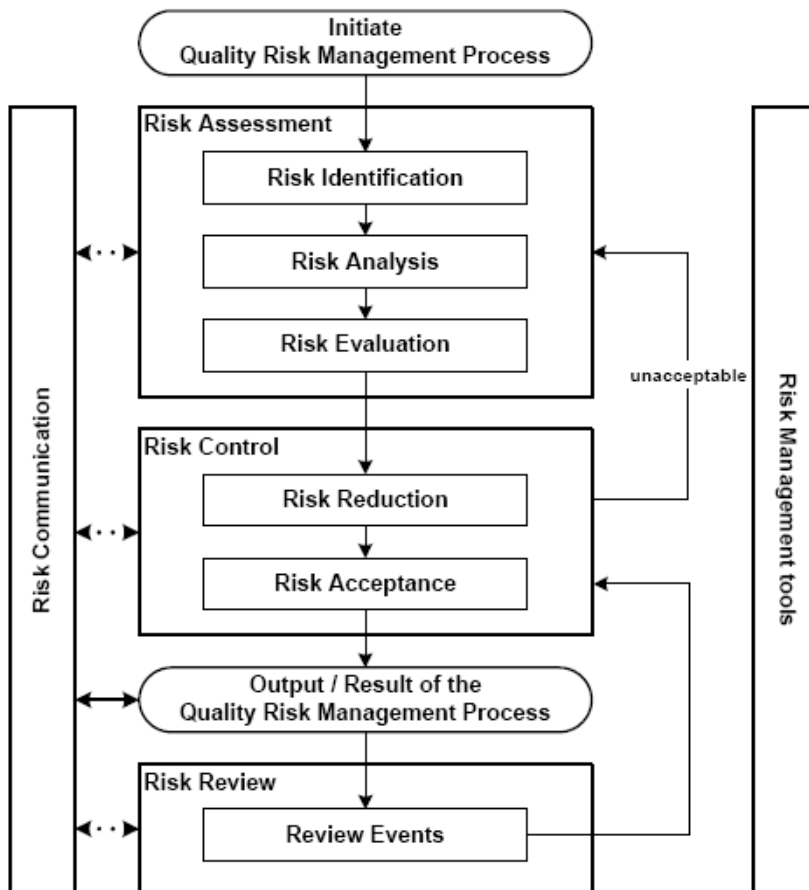
Risk assessment isn't just a regulatory strategy. It's a way for human beings to cope with the world and its uncertainties

(Clinton, 2003)

The sheer importance given to ICH Q9 is expressed by the conversion of the ICH guidance document into Annex 20 of the European Good Manufacturing Practices on 14 February 2008 (*ec.europa.eu*) by the European Commission. The document had an operational deadline of 1 March 2008, despite the insistence by the regulators that it is *not mandatory*. Nonetheless, this addition also required a revision of the introduction (*ec.europa.eu*) and an amendment of chapter 1 (*ec.europa.eu*) “Quality Management” of EudraLex (*ec.europa.eu*), The Rules Governing Medicinal Products in the European Union, and inclusion of a paragraph on quality risk management:

- 1.5 Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.
- 1.6 The quality risk management system should ensure that 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 the level of effort, formality and

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**Figure 1.2**


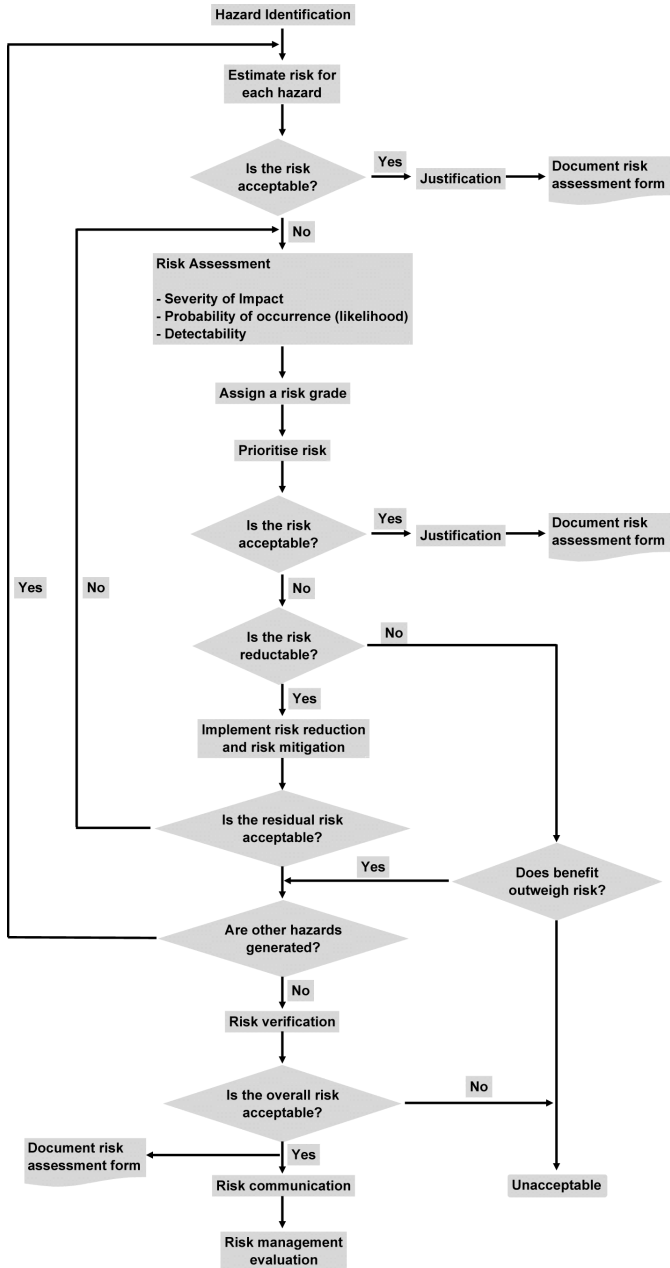
documentation of the quality risk management process is commensurate with the level of risk.

This poses quite a conundrum for industry — whether to adopt and comply, or to ignore. The following chapters in this book address risk management in the context of compliance and good business practices, thereby presenting arguments for and against the adoption of ICH Q9 in all and every instance or circumstance.

ICH Q9 achieves one eminently important goal by defining on a globally accepted level the elements that make up (quality) risk management (illustrated in Figure 1.2).

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*Risk-Based Compliance Handbook***Figure I.3**

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Too many equate risk assessment with risk management, when clearly this is not the case. This is now the framework from which process or product specific flavours of the methodology may be developed. ICH Q9 standardises where all others (e.g., ISO ([www.iso.org](http://www.iso.org))) have failed. Although the document lists in Annex I several risk management methodologies, these are merely there for reference and are not aligned to the drug lifecycle.

The flowchart in Figure 1.2 can be expanded to allow for reduced documentation effort for certain risks. For example, going for a walk when rain is forecast may mean getting wet. That can be an acceptable risk and does not require a lengthy risk assessment. The flowchart illustrated in Figure 1.3 contains all these steps.

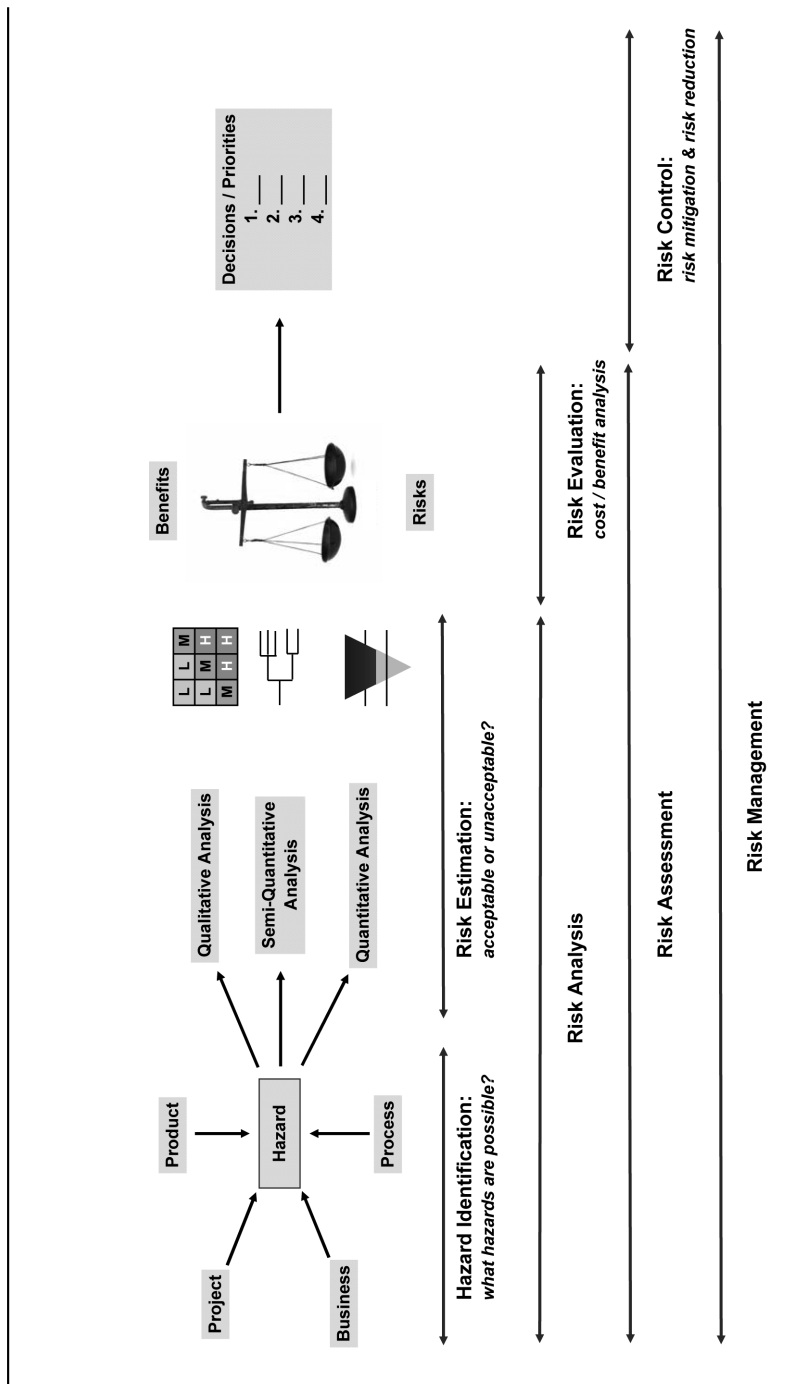
## TERMINOLOGY

As not all readers may be fully acquainted with the terminology used in risk management, some definitions are given here, taken from ISO 14971 ([www.iso.org](http://www.iso.org)) and ICH Q9 ([www.ich.org](http://www.ich.org)).

Harm	Physical injury and/or damage to the health of people (including the damage that can occur from loss of product quality, or availability) or damage to property or the environment.
Hazard	A possible source of harm.
Risk	A combination of the probability of occurrence of harm and the severity of that harm. This has three primary components — a hazard, the probability of the hazard occurring (likelihood) and the potential impact of that hazard (severity).
Residual risk	Risks remaining after protective measures have been taken.
Risk analysis	The estimation of the risk associated with the identified hazards.
Risk assessment	A systematic process of organising information to support a risk decision to be made within a risk management process. This consists of identifying (risk analysis), estimating and evaluating (risk evaluation) the nature and severity emanating from a risk.

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Figure 1.4





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Risk management	The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk. The overall and continuing process of minimising risks throughout a process, product, project or system's life cycle to optimise its benefit risk balance.
Risk communication	The sharing of information about risk and risk management between the decision maker and other stakeholders.
Risk control	The process through which decisions are reached and implemented for reducing risks to, or maintaining risks within, specified limits.

These steps and the associated risk management phases are shown in Figure 1.4.

Risks are often grouped by their impact on a particular aspect of the industrial environment as shown in the following example. Entries may either cause a risk to product quality, for example, and thus to the patient, or they may themselves be at risk.

- Healthcare compliance risks, e.g.,
  - finished pharmaceutical product quality
  - quality control laboratory analysis results
  - patients and consumers safety.
- Personnel risks, e.g.,
  - safety
  - skills
  - health
  - training.
- Methodology risks, e.g.,
  - manufacturing processes

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- cleaning processes
- packaging.
- Environmental risks, e.g.,
  - heating, ventilation, air conditioning (HVAC)
  - environmental protection
  - temperature
  - humidity
  - energy.
- Raw materials risks, e.g.,
  - specifications
  - use
  - composition
  - suppliers
  - delayed release.
- Machinery risks, e.g.,
  - calibration
  - maintenance
  - productivity.
- Business risks, e.g.,
  - corporate reputation
  - project execution risks
  - brand recognition

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- integrity
- cost.

Companies will look beyond compliance risk as there is no sense in having a compliant process that causes an unacceptable risk to the environment or the operator.

## RISK QUANTIFICATION

Not every risk can be quantified, as in the case where there is no quantitative methodology available (see Chapter 7 on R&D) or data cannot be quantified, and it is then acceptable to have qualitative assessments performed. Risk quantification should be kept simple, as almost invariably only high risk issues will be addressed, given limitations on resources. Table 1.1 provides an overview over several possible ways to quantify risks.

## PROBABILITY OF OCCURRENCE OF HARM

As risk is the combination of the probability of occurrence of harm and the severity of that harm, the ways this can be expressed, or put into values has to be addressed. (Some publications use the term harm, others the term hazard, ICH Q9 uses them interchangeably.)

It is not unusual to find risk management teams spending more time arguing on the “precise” quantification of a specific risk than actually managing the risk. Equally taxing can be the determination of the likelihood of occurrence. Listed below are examples for classifying and determining probability.

- Low or 1: improbable — the probability of the risk is perceived to be unlikely.
- Medium or 2: occasional — the probability of the risk is perceived to be likely.
- High or 3: frequent — the probability of the risk is perceived to be highly likely.

Or

- Very common:  $\geq 1$  in 10
- Common:  $>1$  in 100 and  $<1$  in 10

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**Table I.1**

		Risk Quantification									
		Low			Medium			High			
Different types of classification	Qualitative	1			4						9
		3			6						9
	Quantitative	A			B						C
		1	2	3	4	5	6	7	8	9	10
		1			4		7				10

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**Table 1.2**

<b>MIL-STD 882D</b>	<b>ISO 14971:2000</b>	<b>FDA Guidance</b>
Catastrophic	Catastrophic	Major
	Serious	Major
Critical	Critical	Major
Marginal	Marginal	Moderate
Negligible	Negligible	Minor

- Uncommon:  $\geq 1$  in 1,000 and  $< 1$  in 100
  - Rare: 1 in 10,000 and  $< 1$  in 1,000.
- Or (Standard Practice for System Safety, 2000)
- Frequent: likely to occur often ( $X > 10^{-1}$ )
  - Probable: will occur several times in the life of the system ( $10^{-1} > X > 10^{-2}$ )
  - Occasional: likely to occur sometime in the life of the system ( $10^{-2} > X > 10^{-3}$ )
  - Remote: unlikely but possible to occur in the life of the system ( $10^{-3} > X > 10^{-6}$ )
  - Improbable: so unlikely, it can be assumed occurrence may not be experienced ( $X < 10^{-6}$ )

Note: ISO 14971:20079 also defines a probability level of “incredible”, which seems to obsolete itself.

## HAZARD (HARM) SEVERITY

The next step in the risk management process is determining the severity of the impact. Severity is a measure of the possible consequences of a hazard. Severity levels from three different sources ([www.ehcca.com](http://www.ehcca.com)) are compared in Table 1.2.

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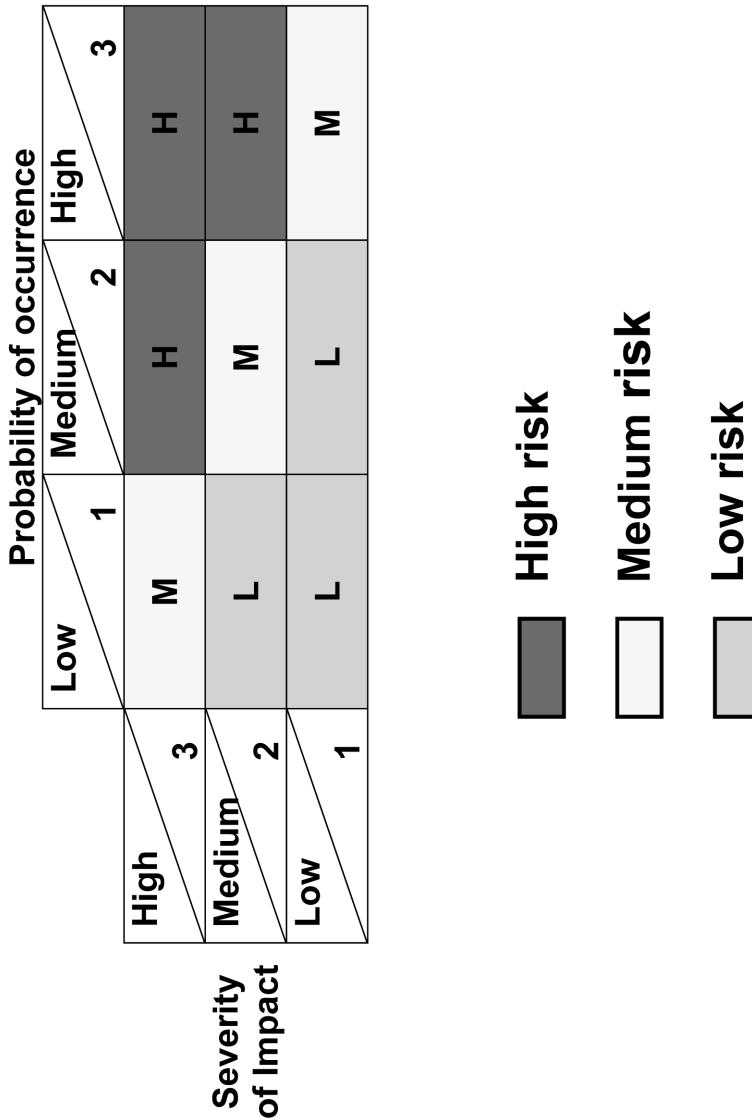


Figure I.5

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Another possibility is to classify severity as follows.

- Low or 1: expected to have a minor negative impact — the damage would not be expected to have a long term detrimental effect.
- Medium or 2: expected to have a moderate impact — the impact could be expected to have short- to medium-term detrimental effects.
- High or 3: expected to have a very significant negative impact — the impact could be expected to have significant long-term effects and potentially catastrophic short-term effects.

## HAZARD DETECTABILITY

Detectability is the ability to discover or determine the existence, presence, or fact of a hazard. Processes that improve the detectability of hazards and quality risks might also be used as part of a risk control strategy. The probability of a risk being detected can be estimated as follows.

- Low or 1: detection of the fault condition is perceived to be unlikely.
- Medium or 2: detection of the fault condition is perceived to be reasonably likely.
- High or 3: detection of the fault condition is perceived to be highly likely.

## RISK EVALUATION

A variety of methods may be used to combine the likelihood estimate with the severity rating and the detectability. These may be multiplied together to obtain a numeric estimate of risk. The risk grade, also sometimes called a risk priority number (RPN), is calculated as:

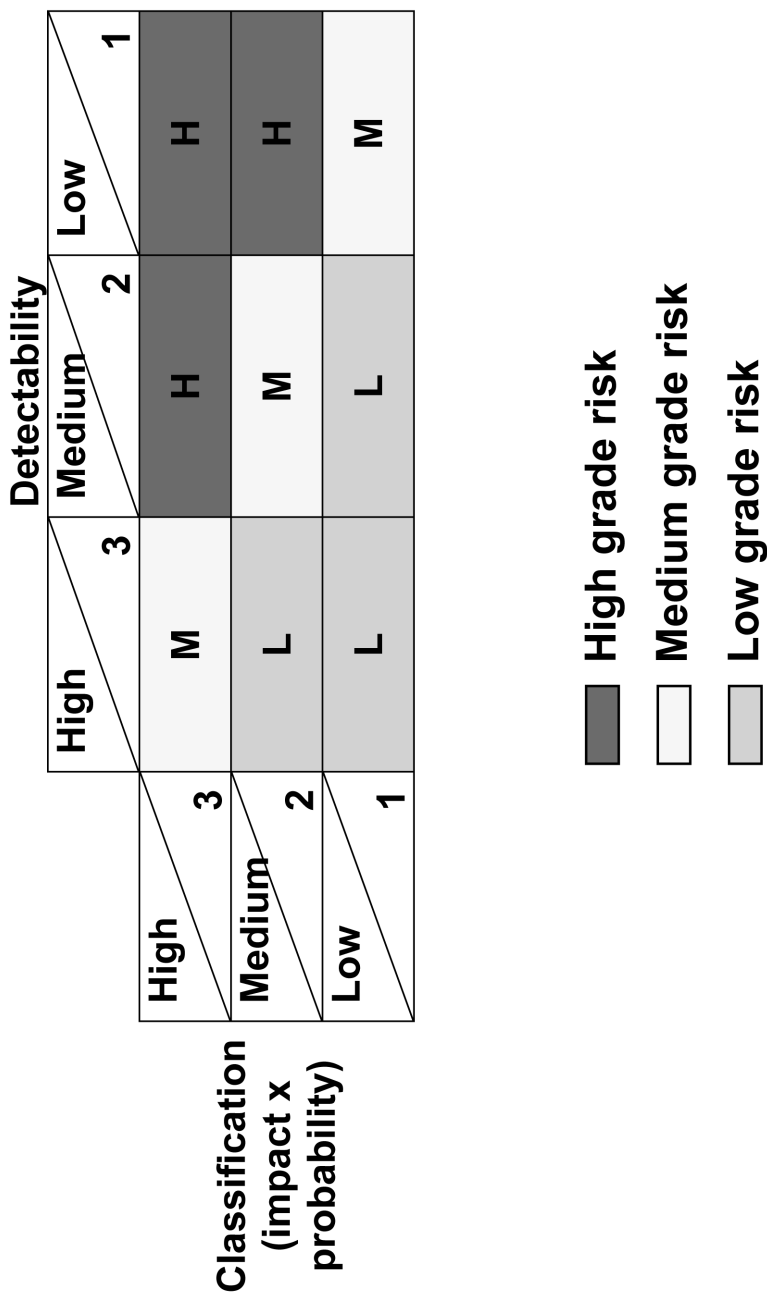
$$\text{RPN} = \text{probability of occurrence} \times \text{severity of impact} \times \text{detectability}$$

Depending on the values selected during the hazard identification process, this will yield a specific number or a qualitative description (e.g., medium). Figures 1.5 and 1.6 give an example for the visualisation of this concept.

The risk classification from Figure 1.5 is correlated with the detectability for yielding a risk priority number, which is then used to determine whether risk reduction and/or risk mitigation is needed.

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Figure I.6





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Another aspect of addressing risk significance is in the business planning context, where in the context of risk, the significance is described as a function of time ([www.symantec.com](http://www.symantec.com)).

- Long-term (years) — risks resulting from global events, and laws and legislation.
- Medium-term (months) — risks resulting from market forces.
- Short-term (days) — risks resulting from interactions with third parties (e.g., customers).
- Operational (hours or minutes) — risks arising from the normal operational environment.

In the healthcare industry the long-term risks are likely to be the most critical, having the highest potential to cause serious damage.

## RISK MITIGATION AND RISK REDUCTION

Each identified hazard needs to be assessed as to whether the associated risk is negligible, acceptable or unacceptable. For unacceptable risks, the mitigation strategy should define the corrective, correction and preventive actions to help modify the risk levels and bring it down to an acceptable risk level.

- Risk mitigation — the focus is on the reduction of the severity of impact of harm.
- Risk reduction — the focus is on the reduction of probability of occurrence and detectability of harm. Measures are then implemented to minimise the risk.
- Corrective action ([www.iso.org](http://www.iso.org)) — action taken to eliminate the causes of an existing non-conformity, defect or other undesirable situation in order to prevent recurrence.
- Correction action — action taken to repair, rework, or adjust and relate to the disposition of an existing nonconformity.
- Preventive action — action taken to eliminate the cause of a potential non-conformity, defect, or other undesirable situation in order to prevent occurrence.

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**Table 1.3**

	<b>Ease of implementation</b>	<b>Efficacy of operation</b>	<b>Cheapness of implementation</b>	<b>Overall</b>
<b>Detection/ Prevention</b>	Poor	Good	Poor	<b>Poor</b>
<b>Fixing</b>	Average	Average	Average	<b>Average</b>
<b>Management</b>	Good	Poor	Good	<b>Good</b>

Risks in the areas labelled L for low in Figure 1.6 are generally judged as broadly acceptable to all parties and do not require risk reduction. Those labelled M represent an area of undesirable risks. However, these can be tolerable if risk reduction is impracticable or if its cost is disproportionate compared to the improvement gained. In this zone, the balance of cost versus benefit is the key. A written rationale justifying the decision is needed and consideration given to increased monitoring to ensure any occurrence of the failure is detected. Finally, those areas assessed as H represent an area of high risk. These risks are generally judged as intolerable so that risk reduction measures must be implemented.

Once any risk mitigation or reduction measures have been put in place, the assessment has to be repeated in order to verify that the outcome is acceptable as assumed.

The relative values of the control measures, can take into consideration, for example ([www.symantec.com](http://www.symantec.com)):

- ease of implementation
- efficacy of operation
- cheapness of implementation.

Table 1.3 provides an example assessment.

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## **RISK ACCEPTANCE AND RISK REVIEW**

Usually quality assurance is required to verify that the measures put in place are in accordance with the internal quality system, rules and regulations, and that they have achieved their purpose. In addition, the involved parties need to verify and confirm the effectiveness of the risk management process.

The business environment is rarely static for long, and the applicable regulatory framework is also subject to change. Therefore, the necessity, frequency and methodology for the review of past risk assessments should be detailed in an internal document, such as a standard operating procedure (SOP).

## **RISK COMMUNICATION**

Risk communication is an essential activity in ensuring an effective risk management process throughout the entire product lifecycle. It is one way of evaluating the effectiveness of the risk management. Therefore, it is essential to ensure that everyone appreciates the importance of risk management and risk assessments and that all have a good and comprehensive understanding of the process.

A company should define a suitable program for communication of risk messages to the target audience and ensure that these have been received and understood. Management has to encourage all staff to adopt risk reduction behaviour. The program should define who, how, why, and how often messages need be delivered to the intended targets, including regulatory authorities. Communication need not be carried out for each and every risk acceptance.

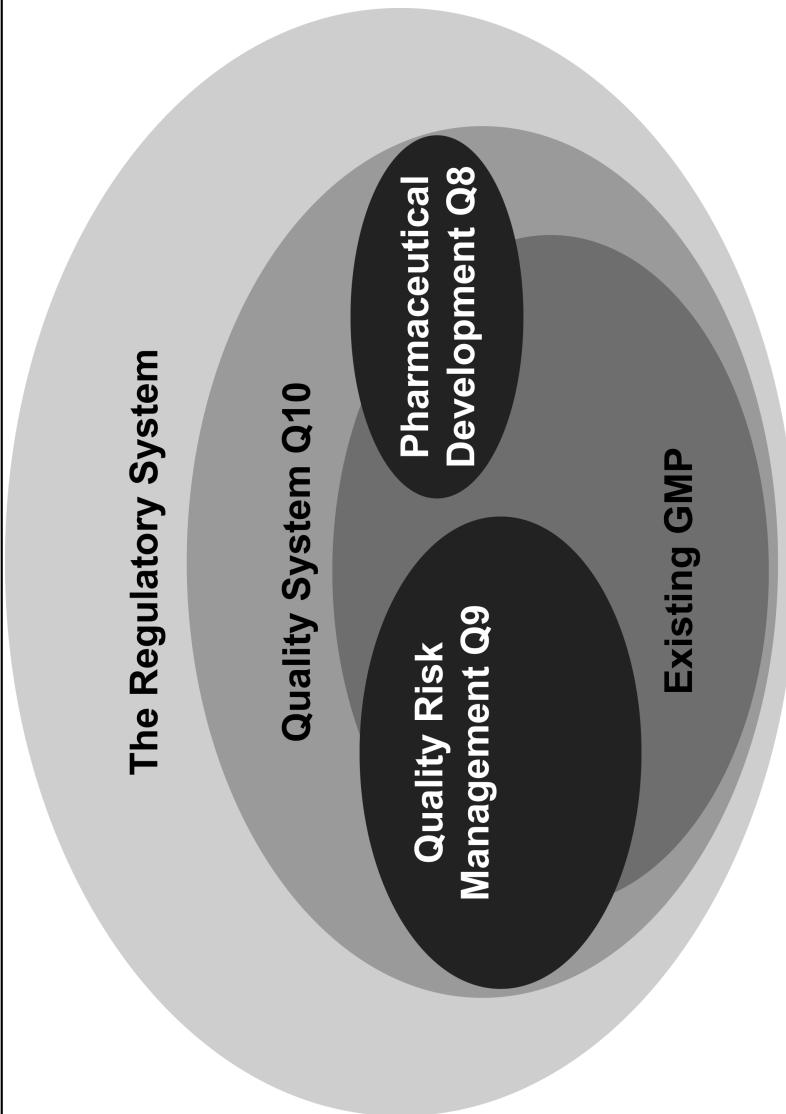
## **ICH Q8, Q9 AND Q10**

Risk management as described in ICH Q9 ([www.ich.org](http://www.ich.org)) is a concept that can be developed as a stand-alone item. However, the full benefit of the new approaches to pharmaceutical quality will be best obtained by implementing the concepts in ICH Q8 Pharmaceutical Development, ICH Q9 Quality Risk Management and ICH Q10 Pharmaceutical Quality System together (PDA, 2008).

Whereas the ICH Q8 and Q9 guidelines have been finalised and adopted by member states, ICH Q10 is currently at step 2 of the ICH review and adoption process.

The ICH Q8 guideline is intended to provide guidance on the contents of Section 3.2.P2 (Pharmaceutical Development) for drug products as defined in the

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**Figure I.7**

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scope of Module 3 of the Common Technical Document. The guideline does not apply to contents of submissions for drug products during the clinical research stages of drug development. However the principles in this guideline should be considered during these stages. This guideline might also be appropriate for other types of products, and to determine its applicability for a particular type of product, applicants should consult with the appropriate regulatory authorities.

An annex to ICH Q8 was released on 1 November 2007 for consultation. This provides further clarification of key concepts outlined in the core guideline. In addition, this annex describes the principles of quality by design (QbD). The annex is not intended to establish new standards. However, it shows how concepts and tools (e.g., design space) outlined in the parent Q8 document could be put into practice by the applicant for all dosage forms. Where a company chooses to apply quality by design and quality risk management (Q9: Quality Risk Management), linked to an appropriate pharmaceutical quality system, then opportunities arise to enhance science- and risk-based regulatory approaches (see Q10: Pharmaceutical Quality System).

Whereas the ICH Q9 guideline provides principles and examples of tools for quality risk management that can be applied to *all* aspects of pharmaceutical quality, including development, manufacturing, distribution, and the inspection and submission/review processes *throughout the lifecycle* of drug substances and drug (medicinal) products, biological and biotechnological products, including the use of raw materials, solvents, excipients, packaging and labeling materials, the ICH Q8 guideline is much more limited in scope.

The ICH Q10 Pharmaceutical Quality System guideline, which was released for consultation under Step 2 of the ICH process on 9 May 2007, applies to pharmaceutical drug substances and drug products, including biotechnology and biological products, throughout the product lifecycle. The elements of Q10 should be applied in a manner appropriate and proportionate to each of the product lifecycle stages, recognising the differences among, and the different goals of, each stage.

Despite the differences in scope and applicability between ICH Q8 and the Q9 and Q10 guidelines, the regulators emphasise the integration of these three guidelines into one integrated concept (shown in Figure 1.7) (as presented at several conferences by various regulatory agency members who helped developed the guidelines).

It becomes immediately apparent that these guidelines go beyond what is required for GMP compliance. This should bring with it a number of benefits for industry and of course the patients. As with all new and generally untested concepts it will take a while for industry to accept, adopt and apply them.

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This integrated approach calls for innovation in science and the way compliance is achieved, based on benefit/risk assessments. These are good intentions, and provided both the industry and the authorities have equally strong scientific and compliance knowledge this could indeed fundamentally change the healthcare industry.

Let us now take you on a journey following the drug lifecycle, where we address the many facets of benefit and risk from the perspective of all those involved in the process, all of whom work towards one common goal: to deliver a safe and efficacious product to the patients in compliance with the healthcare regulations.

## REFERENCES

Cap Uldriks, CDRH, Using Risk Management to Defend Reporting Decisions to the FDA, [www.ehcca.com/presentations/devicecongress2/uldriks\\_a.pdf](http://www.ehcca.com/presentations/devicecongress2/uldriks_a.pdf)

*Handbook of Pesticide Toxicology* (2001) Academic Press

<http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/>

[http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/2008\\_02\\_12\\_gmp\\_annex20.pdf](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/2008_02_12_gmp_annex20.pdf)

[http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/2008\\_02\\_12\\_introduction\\_gmp.pdf](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/2008_02_12_introduction_gmp.pdf)

[http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/2008\\_02\\_14\\_gmp-part1-chapter1\\_q9.pdf](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/2008_02_14_gmp-part1-chapter1_q9.pdf)

<http://en.wikipedia.org/wiki/Paracelsus>

<http://www.bioprocessintl.com/popups/articles.asp?id=30120074>

<http://www.bioprocessintl.com/popups/articles.asp?id=50120073>

<http://www.drugresearcher.com/news/ng.asp?n=74564-novo-nordisk-genentech-stroke-blood-clot-novoseven>

<http://www.emea.europa.eu/htms/human/opinion/opinion.htm>

<http://www.oncolink.com/library/article.cfm?c=2&s=76&id=775>

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*[http://timesofindia.indiatimes.com/India/Drug\\_majors\\_reel\\_as\\_blockbusters\\_fail/articleshow/2205768.cms](http://timesofindia.indiatimes.com/India/Drug_majors_reel_as_blockbusters_fail/articleshow/2205768.cms)*

ISO 8402, *[www.iso.org](http://www.iso.org)*

PDA Extra Report (2008) QRM & Regulatory Inspections, 28 February, Vol. 2, No. 2

Standard Practice for System Safety, MIL-STD-882D (2000) Department of Defense, February 10, Appendix A, Table A-2, page 19,  
*[www.safetycenter.navy.mil/instructions/osh/milstd882d.pdf](http://www.safetycenter.navy.mil/instructions/osh/milstd882d.pdf)*

Symantec (2006) Integrated IT risk management, *[www.symantec.com](http://www.symantec.com)*

*[www.ich.org](http://www.ich.org)*

*[www.iso.org](http://www.iso.org)*

*[www.mhra.gov.uk](http://www.mhra.gov.uk)*



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