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Steps Beyond Risk Assessment in QRM: RBDM, The next horizon

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STEPS BEYOND RISK ASSESSMENT IN QRM: *RBDM, THE NEXT HORIZON*

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ABSTRACT

The topic of **Risk-based Decision Making (RBDM)** was highlighted as one of these areas requiring clarification in the International Committee on Harmonisation (ICH) concept paper for the revision of Q9. This paper examines 5 key areas on RBDM identified in the concept paper, focusing on: What good risk-based decision making actually means, How QRM may improve decision-making and How risk-based decisions might be achieved. This was executed by reviewing peer-reviewed published research literature and examining best practices in other industries, with a view to initiating a dialogue which could help advance the questions posed. Based on this analysis, a list of **21 attributes** commonly applied to RBDM were identified. These criteria were sorted under the headers of Governance, Process (each QRM and KM) and People.

INTRODUCTION

In November 2020, the International Committee on Harmonisation (ICH) published a concept paper [1] highlighting 'areas for improvement' in the application of ICH Q9: Quality Risk Management (QRM) [2] and proposing four areas that should be addressed with an update to the guidance1. The topic of Risk-based Decision Making (RBDM) was highlighted as one of these areas requiring clarification. The concept paper states that:

[1] In this paper, the forthcoming update is referred to as ICH Q9 (R1).

'while there are references in ICH Q9 to decision- making, there is a lack of clarity on what good risk-based decision making actually means, how QRM may improve decision-making, or how risk-based decisions might be achieved. There is a breadth of peer-reviewed research in this area, but the level of visibility (and uptake) of that research within the pharmaceutical industry may be improved. It would also be useful to address the expected benefits of investing in risk-based decision-making activities.'

Reflecting on the quote and breaking it down to its component parts, the authors have examined the questions posed in the comment.:

'while there are references in ICH Q9 to decision- making, there is a lack of clarity on ..

What good risk-based decision making actually means?

How QRM may improve decision-making?

How risk-based decisions might be achieved?

The quote then continues with the following observations:

'There is a breadth of peer-reviewed research in this area, but the level of visibility (and uptake) of that research within the pharmaceutical industry may be improved.

It would also be useful to address the expected benefits of investing in risk-based decision-making activities'

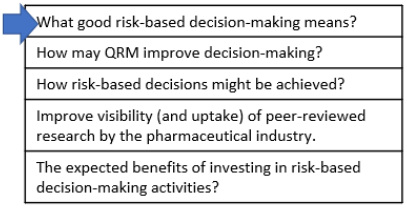
This paper attempts to address these topics by reviewing peer-reviewed published research literature and examining best practices in other industries, with a view to initiating a dialogue which could help advance the questions posed. Exploring these areas has provided some resolution, some key learnings, and has identified next steps towards clarifying RBDM.

In the course of the research, the authors have identified potential key attributes of RBDM, on which a best practice framework for the Pharmaceutical Sector may be designed. They also observed that while the wide adoption of ICH Q9 principles to date has advanced technical understanding of risk and addressed the 'RB' element of RBDM, to fully advance the effectiveness of QRM within the Pharmaceutical Quality System (PQS), applying scientific understanding to the 'DM' element of RBDM is still lagging. The ultimate objective of this ongoing research is to identify a 'best practice' approach to RBDM, that will enable an organisation to improve its capability in this element of QRM and make decisions which are better informed, supported by science and evidence, and recognize and minimize human bias and other influence. It is hoped that this paper will initiate a dialogue which will help advance the journey from emphasis on Risk Assessment to achieving effective RBDM.

1. 'WHAT GOOD RISK-BASED DECISION MAKING ACTUALLY MEANS'?

The ICH Q9 (R1) concept paper notes that:

> *'while there are references in ICH Q9 to decision- making, there is a lack of clarity on what good risk-based decision making actually means,'*



It is the authors' view that a possible reason for the lack of clarity with respect to RBDM, may be that it was not addressed in the original publication of ICH Q9 in 2005. In fact, that document noted that decision nodes (or 'diamonds' denoting the decision-making symbol) were not shown in the diagram because:

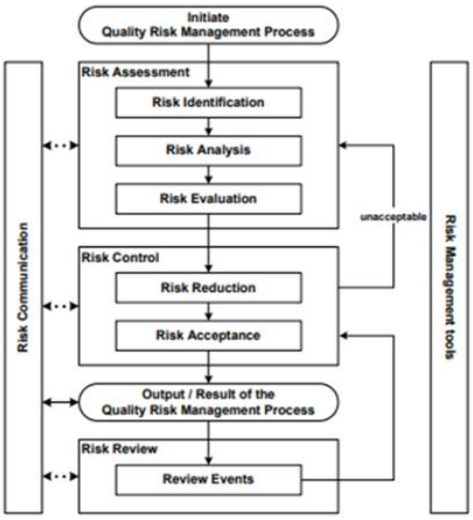


Figure 1: Quality Risk Management Process Diagram

> *'decisions can occur at any point in the process. These decisions might be to return to the previous step and seek further information, to adjust the risk models or even to terminate the risk management process based upon information that supports such a decision.'*

On reviewing and analysing the large body of research conducted into both risk management and decision theory since 2005, the authors propose that this statement could be considered an over-simplification of the role of decision-making in a risk management processes. While substantial understanding has been developed in risk assessment and the associated techniques, the commonly used tools do not clearly address the complexity of the ***decision making*** involved in the communication, control, and management of the risks identified.[3]

There are, in fact, many decisions made *within* the QRM process. These decisions include the selection of appropriate tools for hazard and risk analysis, the appropriate risk rating approach, the level of risk acceptance applied, and the acceptability of risk control measures. Any of these decisions, if not well made, have the potential to impact the control of risk, and ultimately the quality of the product. Throughout the ICH Q9 document (see Table 1), these decisions are encouraged to be **'informed'** and **'science-based'**.

Table 1: References to Decision Making in ICH Q9

1	*'Quality risk management supports a scientific and practical approach to decision-making.'*
2	*'Effective quality risk management system can facilitate better and **more informed** decisions.'*
3	*'Quality risk management should include systematic processes designed to coordinate, facilitate and improve **science-based** decision making with respect to risk.'*
4	*'Decision makers might use different processes, including benefit-cost analysis, for understanding the optimal level of risk control.*
5	*'It specifically provides guidance on the principles and some of the tools of quality risk management that can enable more **effective and consistent** risk-based decisions, both by regulators and industry, regarding the quality of drug substances and drug (medicinal) products across the product lifecycle. It is not intended to create any new expectations beyond the current regulatory requirements.'*

While these references from ICH Q9 give guidance to the expectations of RBDM, they **do not clearly define the term.** To ascertain a preliminary insight into the 'current state' regarding a definition of RBDM in the pharmaceutical sector, a short informal survey of five leading global pharmaceutical operations determined that none had a documented definition of RBDM in their respective Pharmaceutical Quality Systems (PQS). Without such a definition, it is difficult to have clarity of purpose or mature standardised approaches. This suggests that the ICH observation in terms of seeking clarity with respect to RBDM has substance and is worthy of further research.

Therefore, as suggested by ICH in the ICH Q9(R1) concept paper, the researchers turned to other industry sectors, including those regarded as High Reliability Organisations (HROs)[2], to seek a definition for RBDM. A total of 16 organisations were reviewed (illustrated in Fig 2, and detailed in Appendix 1), selected on the basis that each had a standardised Risk Management System, which included guidance on decision-making.

[2] The term HRO originates in the work performed (1989-1996) by Todd LaPorte, Gene Rochlin, and Karlene Roberts of the University of California into the common characteristics of organisations that, despite working in highly complex and hazardous environments, operate without accidents. Included in the original study were nuclear aircraft carriers, commercial aviation, and nuclear power operations

Figure 2: Sectors/Organisations researched for definition of RBDM

It was determined that despite, in cases, detailed advice on how to approach RBDM, only 4 had an explicit definition related to decision-making. (Table 2)

Specifically, only one agency, the US Coast Guard, provided a definition of RBDM. NASA and the Nuclear sector provided a definition for a similar term - Risk *Informed* Decision Making (RIDM). Whether these terms represent different decisions or represent different approaches to the same decisions, is an analysis for a to be performed by the authors in a future paper. But for now, the researchers are simply focused on any clarity that these *definitions* may offer as a learning to the pharmaceutical industry.

Table 2: Sectors/Organisations with a documented definition of RBDM

SECTOR	DEFINITION
US Coast Guard *Quick-reference Guide to Risk-based Decision Making (RBDM): A Step-by-step Example of the RBDM Process in the Field*	Risk-based decision making is a **process** that organizes information about the possibility for one or more unwanted outcomes to occur into a broad, orderly **structure** that helps decision makers make more **informed** management choices." More simply stated, RBDM asks the following 1. What can go wrong? 2. How likely are the potential problems to occur? 3. How severe might the potential problems be? 4. Is the risk of potential problems tolerable? What can/should be done to lessen the risk?
International Atomic Energy Agency *Considerations on Performing Integrated Risk Informed Decision Making* *IAEA-TECDOC-1909 (2020)*	Integrated Risk Informed Decisions Making (IRIDM) process: a decision-making **process** that applies to safety issues and takes account of many relevant factors in a **systematic** and **holistic** manner. Specifically, in the IRIDM process, risk considerations are explicitly addressed in integrating and balancing the decision, together with other factors (such as good engineering practice, sound organizational and administrative arrangements, **knowledge** that has been derived from experience, costs, radiation doses for personnel, etc.). It can be used for a wide range of licensee or regulatory issues that have safety implications for any type of nuclear facility.
International Nuclear Safety Group *A Framework for an Integrated Risk Informed Decision Making Process* *INSAG-25 (2011)*	Integrated Risk Informed Decision Making (IRIDM) is a **systematic process** aimed at the integration of the major considerations influencing nuclear power plant safety. The main goal of IRIDM is to ensure that any decision affecting nuclear safety is optimized without unduly limiting the conduct of operation of the nuclear power plant. It underpins nuclear safety decisions and ensures **consistency** with the safety goals of the Member State.

SECTOR	DEFINITION
NASA *Risk-Informed Decision-Making Handbook* **NASA/SP-2010-576** **Version 1.0** **April 2010**	The RIDM **process** addresses the risk-informed selection of decision alternatives to assure effective approaches to achieving objectives. NOTE: Risk-informed decision making is distinguished from risk-based decision making in that RIDM is a fundamentally deliberative **process** that uses a diverse set of performance measures, along with other considerations, to inform decision making. The RIDM process acknowledges the role that human judgment plays in decisions, and that technical information cannot be the sole basis for decision making. This is not only because of inevitable gaps in the technical information, but also because decision making is an inherently subjective, values-based enterprise. In the face of complex decision making involving multiple competing objectives, the cumulative wisdom provided by experienced personnel is essential for integrating technical and nontechnical factors to produce sound decisions.

While definitions vary, each refer to decision making as a **'process'** and use terms such as **'systematic'** and **'informed'**. This highlights that:

- Decision making may be a process within a *process*, i.e., a part of QRM, but a distinct process itself – perhaps with its own attributes, 'tool kit', and audit trail.

- Decision-making needs to be *systematic*, i.e., following a fixed plan or structure. This will assist with consistency, another key attribute mentioned.

- Decisions should be *informed*. This highlights the importance of linking QRM and RBDM with the other key enabler of the PQS, suggested by *ICH Q10: Pharmaceutical Quality System*, Knowledge Management (KM). [4]

However, at this point, it may be worth noting two further considerations, when abstracting learnings from these sectors:

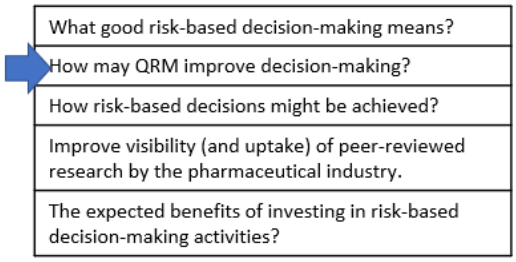
- While there may be a benefit from understanding how other risk conscious industries define and approach RBDM, it must be considered in the context of the operational application of the risk management process. For example, the US Coast Guard applies risk management in the operational environment of rescue, response, and surveillance. The learnings may not translate directly into a different operational environment, such as commercial pharmaceutical manufacturing operations.

- Both NASA and the Nuclear sectors recognise that, apart from the **'technical'** information provided by risk assessment, there are also **'non-technical'** factors at play in the decisions made within the entire risk management process, including regulations and standards (e.g., good engineering practice, organizational and administrative arrangements, experience,

costs, etc.). NASA notes the role that '*human judgment plays in decisions, and that technical information cannot be the sole basis for decision making.*'

It is noteworthy, that the lack of a formal definition of RBDM is not confined to the pharmaceutical industry and, perhaps, is not a barrier to enhanced understanding of what RBDM means. Therefore, the authors did not attempt to craft a definition but rather attempted to seek an understanding the key attributes of RBDM. This research is presented in section 4 of this paper, but before focusing on it, we first explore the how QRM may improve decision-making.

2. 'HOW QRM MAY IMPROVE DECISION-MAKING'



The published literature on decision-making and, indeed, on decision-making with respect to risk is extensive – far too extensive to summarise in this paper. It includes emerging evidence that, while risk analysis has become a technical and routine process, RBDM includes a non-technical, deliberative, and judicious component. This academic thread [3] has raised many considerations, including some that are also raised in the ICH Q9(R1) revision concept paper, namely:

- Subjectivity
- Formality

And other considerations that the authors are adding based on this review of RBDM

- Complexity
- Uncertainty
- Ambiguity
- Science-Based

The next sections take a deeper look at these considerations and potential mitigations to overcome some are presented. While for others, further research is needed before solutions can be suggested.

2.1. SUBJECTIVITY

The ICH Q9(R1) concept paper expresses a concern in relation to '*high levels of subjectivity*' in risk assessments and in QRM outputs, noting:

> *'the reasons for this can include highly subjective risk scoring methods and differences in how risks are assessed and how hazards, risk, and harms are perceived by different stakeholders. This can lead to varying levels of effectiveness in the management of risks. While subjectivity cannot be completely eliminated from risk assessment and QRM activities, it may be controlled using well recognised strategies, including addressing bias and behavioural factors.'*

The choice of tools and risk scoring approaches in QRM are themselves decisions and represent RBDM. These decisions are subject to a myriad of biases, heuristics, viewpoints, preferences, priorities, and pressures. Table 3 details some of the heuristics and biases that our research colleagues, O'Donnell [5], and Ramnarine [6], have previously discussed. The influence of many of these could be reduced by more structured decision-making processes, informed by evidence and knowledge.

Ramnarine notes that:

> *'the key to reducing subjectivity in decision-making is to increase the amount of information, data and fact-based knowledge available on which to base decisions, and to develop effective tools in order to accurately interpret that information, data and knowledge.'*

This is sage advice and echoes the basis of classical Operations Research, which advocates the core role of objectivity:

> *'Its distinctive approach is to develop a scientific model of the system, incorporating measurements of factors such as change and risk, with which to predict and compare the outcomes of alternative decisions, strategies, or controls. The purpose is to help management determine its policy and actions scientifically".* [7]

However, the ICH concept paper notes that subjectivity, to some degree, may be unavoidable. This is a view proposed by William W Lowrance [8], a noted author in health research ethics, who pointed out that estimates of risk, whether made by scientists or lay people, cannot escape containing some elements of subjectivity.

> *'the very defining of the questions, and into the designing of the experiments used in assembling evidence, and then into the weighing of the social importance of the risk.'*

Table 3: Summary of Heuristics impacting QRM as examined by *O'Donnell and **Ramnarine

Heuristic	Influence
Adjustment/ Adjustment*	Being overly influenced by the first approximation
Availability bias*	overestimating the likelihood of an event because it happened recently
Knowledge bias**	selecting the option one knows most about
Present bias**	preferring options with quick pay-back
Recency bias**	placing greater weight on recent events
Representativeness*	Inferring from a small behaviour, what will occur in the large
Status quo bias**	tendency to keeping things the same

The discipline of Normative Decision Theory [9] attempts to establish a set of guiding principles for decision-making. The intent is to overcome the subjectivity of the decision maker and to develop an

optimal standard or method for decision-making, driven by an agreed set of values. Normative Decision Theory attempts to address what we *should* do. It is an area of research that is of keen interest to mathematicians, statisticians, and computer models.

However, identifying a reliable method for decision-making has not been an easy exercise. In 1989, two leading scientists performed an elegant experiment by presenting the same evidence to four recognised decision-making models[3]. All the methods examined, when fed with the same information, yielded different results. In essence, in the absence of empirical evidence in support of the best decision-making method, the decision maker must make their first subjective decision and select the 'best' tool. This is called the '*decision makers paradox.'* [10].

The debate between the advocates of structured objective decision making and those arguing the unavoidability of subjectivity continues. [11] As it stands, it may even be appropriate for the decision maker to balance the logic of pure evidence, with Cartesian Doubt[4] or a sceptical eye. Notwithstanding this dilemma, an appropriate level of formality in decision-making must serve to reduce the influence of subjectivity, while assisting the decision-maker in understanding the preferences of self, and of all other stakeholders to the decision outcome.

The influence of subjectivity in QRM can be difficult to assess. In part, this is because the justification for decisions is seldom documented in the QRM record. Consequently, an independent reviewer, often with the benefit of hindsight, is judging the decision by the outcome and, with what may also be an element of subjectivity, with perceptions of the decision-makers preferences. A line of sight to a structured decision-making process may give transparency and clarity to decisions with sub-optimal outcomes and demonstrate that they were rational and responsible. This is a focus area of future research by the authors.

While subjectivity in both risk analysis and risk management may be unavoidable - ultimately, a question the decision-maker should consider is, whether the assessment made, is an adequate basis for the risk control decision in hand? As argued here, this too is a judgement, susceptible to the same subjectivity, heuristics, preferences, and biases as the assessment itself. The application of an appropriate level of formality and documenting decision rationales would assist in the evaluation of the objectivity of the decision-making process.

2.2. FORMALITY

[3] The methods examined were Multi-Criteria Decision Analysis (MCDA); Multi Criteria Decision Making (MCDM); the Weighted Sum Model; and the Analytical Hierarchy Process (AHP).
[4] The philosophical idea proposed by Descartes that the world outside the self is subject to uncertainty

The ICH Q9(R1) Concept paper states:

> *Lack of understanding as to what constitutes formality in QRM work - this area has the potential to be further developed for deeper understanding to lead to a more effective application of QRM principles and better execution of QRM activities. There has been significant confusion and uncertainty in the industry and among regulators as to what constitutes formality in QRM work, and how generally to interpret this principle. It would be useful to clarify what is expected in terms of formality and that there is flexibility in how much formality may be applied in relation to QRM activities, while emphasizing that robust risk management should always be the overarching goal of QRM.*

The concept of formality in QRM processes has been explored recently by O'Donnell et al [12]. The authors concluded that formality may be a continuum and offered several potential definitions. While the authors did not specifically explore formality in the context of decision making, they did note that the 2010 WHO Guideline on QRM [13] stated that

> *'the procedures for risk-based decisions and formality of approach should be commensurate with the level of patient risk'*

And that:

> *'critical issues should have been addressed with appropriate high urgency and formality and risk-based decisions made by staff with appropriate authority.'*

Other than these references, there is little clarity on expected formality with respect to RBDM. The authors have previously discussed formality with respect to decision-making in the QRM process. [14] We advocated consideration of the criteria used by NASA, i.e., that formal decision-making processes should be applied when decisions are complex, uncertain, have multiple attributes, and where the stakes are high. These criteria could form a basis for an appropriate approach to formality in RBDM.

Our research into decision-making with respect to risk identifies further considerations, not specifically recognised in the ICH Q9(R1) Concept Paper. These areas have been discussed with respect to QRM [15][16][17] and the role of RBDM and, for completeness, are also included here.

2.3. COMPLEXITY

The analysis of risk, with the commonly used risk assessment tools, generally requires the decomposition of a system into basic elements. These basic components are then analysed, often in considerable detail, to understand the fundamental potential for hazards. This narrow scope, and the one-factor-at-a-time approach to analysis, can oversimplify the characterisation of the same hazards in complex settings. It can also result in a reductive and oversimplified risk communication to the decision-maker. This is not a new problem - in 1947, the American Economist Herbert A. Simon

published *Administrative Behaviour* [18], a work which eventually led him to receiving the Nobel Prize in Economics in 1978. In this work, Simon introduced the concept of *'bounded rationality'*– an idea that when making decisions, reason is limited by the cognitive limitations of the decision-maker, imperfect information, and time constraints.

Building on the concept, the esteemed sociologist Amitai Etzioni in a 2001 paper called *'The Humble Decision-Maker'* [19] proposed that rational decision making was almost impossible in a modern management environment, given the volume of information and the complexity. He noted that decision-makers were commonly pressed to make decisions with only partial information and, occasionally, even less certainty about the reliability of this information. As Etzioni observed:

> *'With computers, our capacity to collect and semi-process information has grown, but information is not the same as knowledge. The production of knowledge is analogous to the manufacture of any other product. We begin with the raw material of facts (of which we often have a more than adequate supply). We pre-treat these by means of classification, tabulation, summary, and so on, and then proceed to the assembly of correlations and comparisons. But the final product, conclusions, does not simply roll off the production line. Indeed, without powerful overarching explanatory schemes (or theories), whatever knowledge there is in the mountain of data we daily amass is often invisible.'*

Our research colleagues, Lipa et al, have extensively discussed the role of Knowledge Management (KM) in reducing uncertainty in QRM[20][21] . KM is recognised as a twin enabler of PQS decision-making, along with QRM, and may have a significant role in both reducing uncertainty and navigating complexity. Lipa et al have suggested intertwining and integrating these enablers to enhance process understanding in decision-making. (Fig 4)

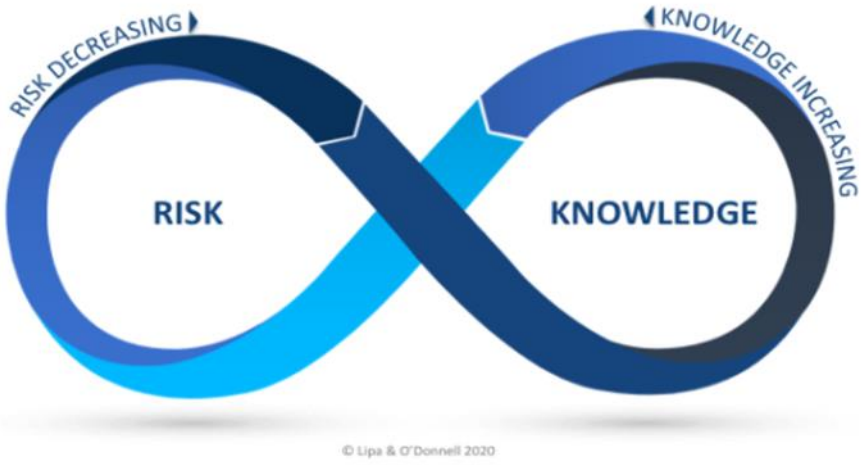


Figure 4: Risk Knowledge Infinity Cycle proposed by Lipa, O'Donnell, and Greene.

Modern pharmaceutical operations are complex and the ability to coherently access and analyse large amounts of information has become more challenging. Digital processes are now part of every aspect of the supply chain and operations. As operations become more global and computer systems form the basis of communication, the ability to maintain an overview is reduced and employees became more siloed. According to the Harvard Business Review [22] fewer than 44% of employees say they know where to find the information they need for their day-to-day work. The paper also indicates that only 25% of 'knowledge workers' receive effective training in information analysis and use.

In a PQS, tasks such as investigations are enabled and accelerated by access to the right data and suitable analytical tools. Currently, complaint investigations can take up to 30 days, as paper records and electronic data are accessed, reviewed, and analysed. Modern data mining techniques provide opportunities to enable and enhance these processes. Therefore, data literacy is an essential competence within modern organisations. The need for data analytics in big data environments is growing.

However, the skills of the data miners and those of the data users – or decision-makers - are different. One skill set does not necessarily understand the needs of the other. There are underlying risks if data provided to a decision-maker is incomplete, inaccurate, or unreliable. Data Integrity practices and the application of the ALCOA+ [5] principles in operations have demonstrated the need to proactively manage the quality of data.

> *'Complexity can quickly overwhelm a decision-maker, making it nearly impossible to guarantee that each critical component of the decision is appropriately considered in the analysis* [23]
> Clemen & Reilly

The pharmaceutical decision maker is likely operating in a globalised, technical, regulated, and dynamic environment, with the potential to rapidly impact risk controls. A further consideration are the escalation processes that are often prevalent in PQS elements. Often the ultimate approver of a decision ranks high in the organisation, and potentially further from the details of the problem in hand. Formal decision-making processes typically offer structure to the information supplied to decision-makers and provide higher assurance that they are informed.

[5] The ALCOA+ Principles are the Data Integrity Principles applied within the pharmaceutical industry. The acronym stands for Attributable, Legible, Contemporaneous, Original and Accurate.

2.4. UNCERTAINTY

The confusion between risk, variability, and uncertainty has been studied by economists, mathematicians, statisticians, psychologists, and biologists, since the distinction was first disentangled in 1921, by an American economist Frank Knight. [24] Risk, he argued, was measurable. Risk exists when the outcome of a decision is unknown, but the probability is measurable. Uncertainty, on the other hand, applies when the decision-maker does not know all the information and therefore *cannot* determine the probability of each potential outcome.

Risk is defined in ICH Q9 as

> *'the combination of the probability of occurrence of harm and the severity of that harm' (ISO/IEC Guide 51)*

and it notes that

> *'Uncertainty is due to combination of incomplete knowledge about a process and its expected or unexpected variability. Typical sources of uncertainty include gaps in knowledge gaps in pharmaceutical science and process understanding, sources of harm (e.g., failure modes of a process, sources of variability), and probability of detection of problems.'*

The challenge of managing uncertainty remains to this day. In 1992, an eminent risk management scholar, Frank Warton, [25] warned that

> *'Failures to cope with uncertainty in the management of technological risk abound. Their causes include overconfidence in scientific knowledge, the underestimation of the probability or consequences of failure, not allowing for the possibility of human error, and plain irresponsibility concerning the potential risk to others.'*

In relation to QRM, this topic was discussed by O'Donnell [5], who noted

> *'there is widespread agreement that one of the core principles underpinning effective risk management is the principle that risk management explicitly addresses uncertainty—that it explicitly takes account of uncertainty, the nature of that uncertainty, and how it can be addressed'*

Ramnarine [6] reminds the decision-maker that

> *'Uncertainty is defined as a lack of assurance due to insufficient data. Uncertainly can also impact outcomes of a QRM effort. It is therefore important to have sufficient data in order to reduce uncertainty in risk management, which can also help with reducing subjectivity and bias.'*

Research has shown that uncertainty itself is complicated. [26][3]. ISO 31010:2019 Risk Management, Risk Assessment Techniques [27] discusses uncertainty noting that it is a term that has many

underlying causes, including uncertainty that results from a lack of knowledge, but also the uncertainty that may result from the intrinsic variability that may be within a process (or measurement). The former may be reduced through the accumulation of knowledge. The latter can potentially be controlled by further measurement. These are the **evidential uncertainties** that should concern the risk assessor.

For the risk-based decision-maker, it may be important to also consider **outcome uncertainty**. Often in risk management, a judgement is required to determine whether the level of outcome uncertainty of a given situation is acceptable. The key word here is 'judgement'. Despite good analysis, the decision-maker may still need to make a value judgement on whether the situation is acceptable or requires further data/analysis/modelling, broader safety margins, or whether a different choice is warranted.

Therefore, ISO 31010 refers to '***decision uncertainty'***, which it calls the uncertainty associated with value systems, professional judgment, company values and societal norm. The guidance gives examples of uncertainty as:

- Uncertainty as to the truth of assumptions, including presumptions of how people may act or behave.
- Validity in the assumptions on which a decision is to be based.
- Uncertainty in the validity or accuracy of models established to make predictions of the future.
- Events, including changes of circumstances or condition, whose occurrence, character, or consequences are uncertain.
- Uncertainty associated with disruptive events.
- Uncertain outcomes of systematic issues that may have wide ranging impacts that cannot be easily defined.
- Lack of Knowledge that arises when uncertainty is recognised but not fully understood.
- Unpredictability.
- Uncertainty arising from the limitations of the human mind – for example, in the understanding of complex data, predicting situations with long term consequences or making bias free judgements.

As suggested by ICH Q9(R1), there is a breath of peer reviewed research on the topic of the management of uncertainty in decision making. It is too broad to be summarised here.

2.5. AMBIGUITY

In 2002, Klinke and Renn, from the Centre of Technology Assessment in Baden-Wurttemberg [3], suggested *ambiguity* as an additional challenge to the management of risk. They argued that

ambiguity arises from different interpretations of facts, or from the different application of rules to similar facts.

Ambiguity cannot be resolved by further data or measurement, as it relates to the value judgement placed on that evidence. Ambiguity is not the same as subjectivity, where different conscious or unconscious biases are applied to a fact. With ambiguity, different *meanings* are ascribed to the same fact. Ambiguity has the potential to affect RBDM, by creating misunderstandings and divergence.

The argument is well illustrated in a 2002 research report, published by the UK Health and Safety Executive (HSE)[28], which states:

> *The HSE's attempts to reduce risks to levels that are ALARP (As Low As Reasonably Practicable) encounter the difficulty that "low", "reasonable", and "practicable" are what Habermas[6] has called empty words, i.e. words that different people fill with different meanings*

A 2015 study of ambiguity in risk assessment [29], identified many sources of ambiguity in risk management including language, perspectives and values, culture, relevance of information, and attitude – all of which also influence the decision-maker. They proposed a definition of ambiguity in the context of engineering risk assessments as:

> *'the existence of multiple interpretations concerning the basis, content, and implications of risk information.'*

Concerns from ambiguity and inconsistent risk language were highlighted by these researchers previously. [30]. With increased complexity and reliance on system integration in pharmaceutical operations it is essential that decision-making is not compromised by ambiguity in language or process.

2.6. 'SCIENCE-BASED'

Although, those attributes discussed above are the most noted attributes in the literature with respect to RBDM, ICH Q9 encourages decisions to be *'science-based'*, a term which the authors propose should include:

- The use of proven, systematic, empirical methods.
- Outcomes are informed by rigorous and reliable data and knowledge
- Accurate measurements over a significant number of observations
- Evidence is peer reviewed and approved.

[6] Contemporary German Philosopher

However, in reality 'good science' may be less evident when 'voting' type techniques, commonly used in QRM practices within the pharmaceutical sector, are used. These approaches are qualitative in nature and rely heavily on the judgment and experience of the participants, as depicted by Coburn and Weddle in shown in figure 5 below. [31]

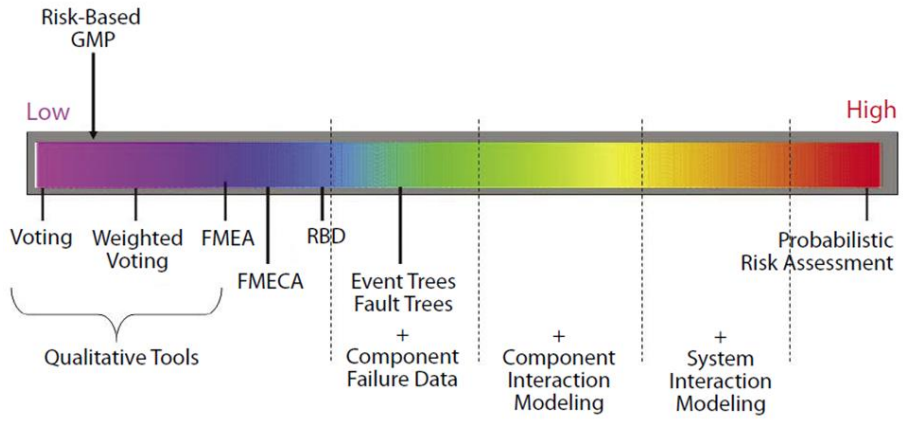


Figure 5: Risk Analysis Spectrum as illustrated by Coburn & Weddle

Commonly, there are inconsistent interpretations to the application of 'high', medium' and 'low' rankings, leading to inconsistent outcomes. Risk Controls are applied that claim to convert 'high' ranking risks into 'medium' ones, whereas, in reality, the change to risk is minimal and speculative. These approaches may also rely heavily on applied knowledge or experiences, which may be very tacit[7] in nature.

Even where the QRM process and the application of accepted methods, may be 'compliant' and rule based, the information used, and the judgement applied, can lead to unreliable and inconsistent outcomes. As noted by Dr O'Donnell[8]:

> *'the industry has probably reached a plateau in its QRM learning, (with a) stagnation and lack of innovation with respect to QRM tools'* [17]

An enhanced use of quantitative data and probabilistic methods as depicted by Coburn and Weddle (Fig 5), to support QRM decisions, would improve the scientific reliability of the decisions made and bring them closer to the 'science-based' ambition of ICH Q9. However, there are both challenges and obstacles to the application of more sophisticated assessment methods.

[7] Based on personal and professional experience

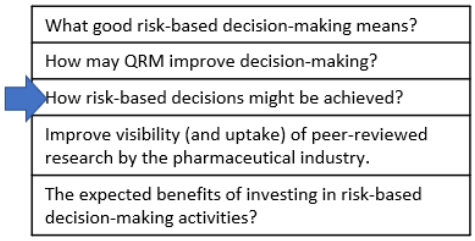
[8] previously mentioned in this article elation to his research, Dr O'Donnell is also of the Irish Health Products Regulatory authority (HPRA) and is the rapporteur of the Expert Working Group tasked with revising ICH Q9. This quote was expressed in the context of his role as a regulator.

It is the authors experience that the lack of reliable data when making decisions is a fundamental gap in the decision-making process. There is a growing realisation within the pharmaceutical industry that the records within the 'traditional-type' quality system – with the focus on witness and compliance – may not capture the data required for informed risk analysis. Furthermore, the actual rate of occurrence of failure modes may be difficult to calculate as it may be scattered and recorded across disconnected paper-based records, generating a mammoth task of search and retrieve. Even then, historical data may not equate to the probability of future occurrence, when factors such as e.g., equipment aging, are considered.

Notwithstanding these challenges, the pharmaceutical industry is moving to digital transformation, and consequently is progressing towards a more rigorous approach and implementation of real time digital data collection and analysis systems which facilitate improved understanding of process controls, including the causal factors of failure and disruption. The authors believe that these advances should enable more scientific, and data driven risk analysis, which, in turn, should result in improved decision-making about risk and risk control, thus resulting in better risk management outcomes.

3. 'HOW RISK-BASED DECISIONS MIGHT BE ACHIEVED'

Having established, though our literature review of risk-based decision making as detailed in section 3, decision theory recognises that RBDM is both technical and behavioural. [3][25]. Data driven risk analysis could be viewed as the measurable component of risk management (technical component). While the decisions about risks are judgements, made currently by humans[9] (non-technical component).



The non-technical component requires that the tools of risk analysis be blended with structured decision-making tools, to avoid susceptibility to the impacts of errors of judgement, prioritisations, stresses, and the ambiguities that affect all human endeavour in our operations.

To understand how other sectors have approached both these technical and non-technical components of decision-making within risk management processes, the authors reviewed the various handbooks, manuals, standards, and guidance on RBDM from the sources illustrated in Fig 2 (and detailed in Appendix 1). Based on this analysis, we formulated a list of **21 attributes** commonly applied to RBDM (Fig 6). These criteria were sorted under the headers of Governance, Process (each QRM and KM) and People. These categorisations were chosen to align with the 'Pillars of Knowledge

[9] The pharmaceutical industry has not reached the point of Artificial Intelligence yet.

Management' utilised by KM practitioners and referenced in the ISPE[10] *Good Practice Guide to Knowledge Management in the Pharmaceutical Industry.* [32]

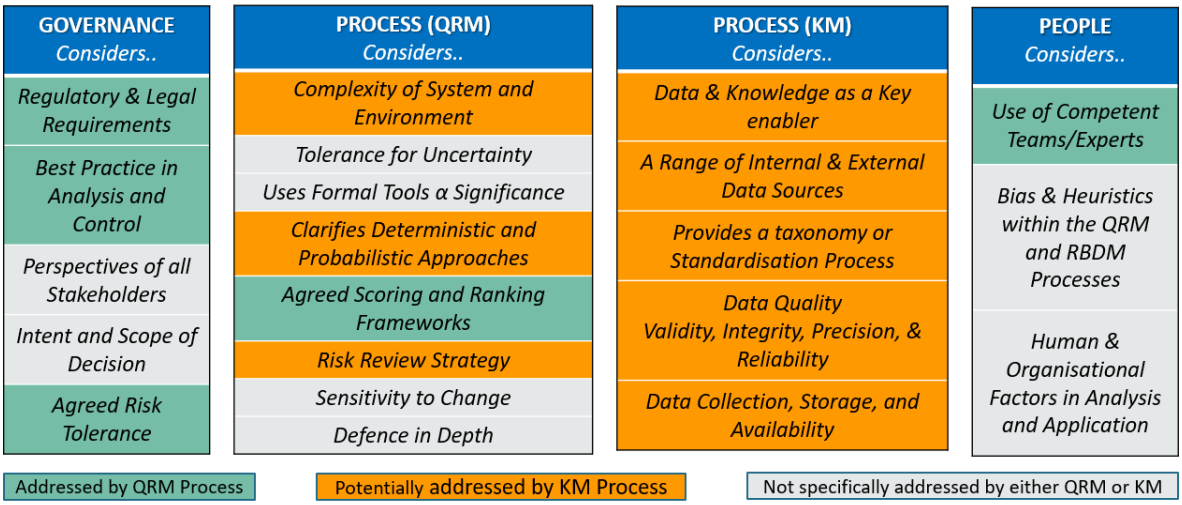


Figure 6: Compilation of 21 RBDM attributes from reviewed sources.

Examining these attributes in more detail, the authors suggest that those shaded in green (5 attributes) are delivered by the 'technical component' of QRM, i.e., the hazard and risk analysis steps. There remain opportunities to improve this component. These are addressed in the ICH Q9(R1) concept paper and will, presumably, be enhanced with the first draft of ICH Q9(R1), expected to be published early in 2022.

The attributes highlighted in orange (7 attributes) are those, in the view of the authors, that could potentially be addressed by a mature KM process. This further highlights the integral roles of QRM and KM in informing RBDM and endorses the authors belief that KM is a critical element of an effective PQS[20][33][32]. This research is ongoing within the TU Dublin PRST (Pharmaceutical Regulatory Science Team) and the clarity, from this analysis, on the potential value of KM to RBDM will contribute to the future direction of this research.

A key insight from analysing these attributes is that **other sectors consider 8 further attributes in their RBDM guidance**. These attributes should also be addressed by the pharmaceutical industry if the pain points of QRM are to be fully addressed and the influence of QRM on RBDM delivered. Addressing these attributes could include:

- Use of decision making **'processes'** to ensure that the needs of ALL stakeholders, including regulatory stakeholders, are addressed when making decisions about the control or

[10] International Society of Pharmaceutical Engineers.

acceptability of risk. This may be particularly important when the RBDM is addressing risks that are complex, uncertain, have multiple attributes, and where the stakes are high.

- A **connection** between the **risk assessments** performed and the intent and scope of the **risk decision** in hand. Within the PQS, risk assessments are often performed as broad information sources (e.g., process or equipment FMEA[11]) and may not offer a complete technical solution to the risk question in hand. [34]

- Understanding the **tolerance for uncertainty** in RBDM. [35]

- Using Structured **Knowledge Management** processes to **inform** the decision-maker.

- Recognising the **factors or changes that might significantly impact the output of RBDM.** The use of additional technical tools such as Scenario Analysis, Monte Carlo simulations, or Probabilistic Risk Analysis may be helpful to the decision maker in certain contexts.

- Understanding the **causal factors of risk control**, through technical tools such as fault tree analysis or FMEA, allowing the identification of early signals and feedback/feedforward controls that may prevent unwanted outcomes. The emerging discipline of Reliability Engineering in pharmaceutical manufacturing operations has much to contribute to the 'defence in depth' approach.

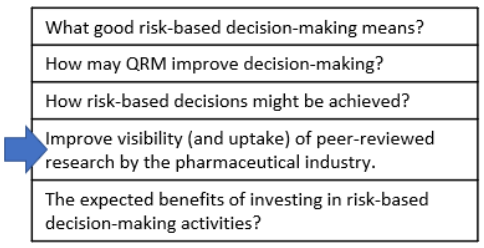
- **Systematic RBDM process**es that ensure that decision making throughout the QRM process is consistent and objective, controlling subjectivity, heuristics and biases from the non-technical element of RBDM.

- **The objective** of RBDM should be to **devise informed rule-based approaches** that can be applied consistently and effectively in operations, removing human and organisational influences.

The effective RBDM decision-maker has a complex task. They must align technical analysis with the intent and scope of the Risk Management Process and assure integrity, reliability, resilience, agility, responsiveness, and appropriateness in the decision-making process. Addressing all 21 of these attributes may be required to assure the preferred and optimal outcome. The authors suggest that this may be the missing link to fully effective QRM.

[11] Failure Modes and Effects Analysis

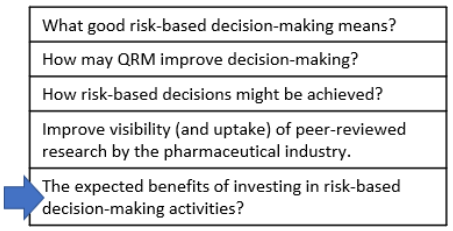
4. UPTAKE AND VISIBILITY OF PEER-REVIEWED RESEARCH ON RBDM



In 2010, as part of its Critical Path Initiative, FDA published a framework for advancing its regulatory science objectives [36]. To support this mission, FDA planned to recruit '*outstanding scientists*', to collaborate with other government agencies, and to commission research to inform the scientific decision making of the agency. FDA have established Centres of Excellence in Regulatory Science and Innovation (CERSI) in collaboration with John Hopkins University, UCSF-Stanford, University of Maryland, Georgetown University, and Yale-Mayo Clinic, to enable the *'rigorous science-based assessment of innovative technologies while balancing risk vs. benefit'*. [37]The FDA Quality Metrics [38] initiative has seen collaborations with both Xavier University and St Gallen University [39], noting that the PRST has contributed to the output of the latter (A summary of this proposed research is presented as a separate paper in this edition of Level 3 journal).

These collaborations have recognised the role for academic research, together with regulators and industry in informing future direction and policy. The topic of RBDM will also benefit from a collaborative approach, ensuing that regulatory revisions, such as ICH Q9(R1), are informed by the best available science. This research hopes to develop and contribute to both the regulators and industry's understanding of best practice, with respect to RBDM.

5. THE 'EXPECTED BENEFITS OF INVESTING IN RISK-BASED DECISION-MAKING ACTIVITIES'



In our review of other sectors, the US Coast Guard most succinctly defined the benefits of RBDM, when it stated that BBDM offers: [40]

> *'1. A common decision-making process that your peers and superiors will already understand and expect*
>
> *2. Decisions that you can more easily defend because of the process you followed and the stakeholders you involved*
>
> *3. Better decisions in cases where systematic consideration of risk reveals information that leads to different decisions*
>
> *The first two benefits are important but hard to quantify. The third benefit can save live'*

The expected benefits of leading practice in RBDM are, perhaps, well expressed by the original references to it in the current ICH Q9 (Table 1). These references aspire to a ***'scientific and practical approach to decision-making.'*** Our initial research suggests that this requires a recognition of both the 'technical' and 'non-technical' contributions of both QRM and KM to RBDM and, when required, additional RBDM tools and formality. ICH Q9 recognises this when it states, *'Effective quality risk management system can facilitate* ***better and more informed decisions.'***

Furthermore, ICH Q9 recognised that *'Quality risk management should include* ***systematic processes*** *designed to coordinate, facilitate and improve science-based decision making with respect to risk.*' Perhaps, to date, the emphasis has been on improving the systematic nature of the technical elements that contribute to QRM and the time is now right for the 'next horizon', which is to address the non-technical elements of RBDM.

Perhaps the most important benefit is to *'enable more* ***effective and consistent risk-based decisions****, both by regulators and industry, regarding the quality of drug substances and drug (medicinal) products across the product lifecycle.*' (ICH Q9)

We are also reminded of the observation by Dr O'Donnell (quoted in section 3.6 above)

> *'the industry has probably reached a plateau in its QRM learning, (with a) stagnation and lack of innovation with respect to QRM tools'* [17]

The industry has before it the opportunity to overcome this plateau, with the release of ICH Q9(R1) and the associated training assets. These should assist the next steps, toward improved QRM effectivity, realising the benefits of ICH Q10 [4] and its associated objectives, and assist in delivering the best possible outcomes for patients. The authors recommend advancement of this research to develop an informed and systematic process to RBDM. The authors, through research into scientific approaches to decision-making, RBDM and best practice, are committed to the development of '*innovation with respect to QRM tools.'*

6. APPENDIX 1 – TABLE OF SECTORS/ORGANISATIONS REVIEWED FOR INSIGHTS INTO RBDM

SECTOR	REFERENCE
Aerospace (NASA)	S3001: Guidelines for Risk Management Ver G (2017) (NASA)
Blood Banking	Risk Based Decision Making for Blood Safety Alliance of Blood Operators (2014)
Civil Aviation	Risk Based Decision Making Principles Standardization Workgroup of the Safety Management International Collaboration Group (SM ICG) for International Aviation (2013)
Coast Guard	Quick-reference Guide to Risk-based Decision Making (RBDM):A Step-by-step Example of the RBDM Process in the Field US Coast Guard
Energy	US Department of Energy Risk Management Guide DOE G 413.3-7A (2011)
Enterprise	ISO 31000:2018 Risk Management Guidelines
Environment	Science and Decisions: Advancing Risk Assessment (2009): National Research Council EPA
Finance	Committee of Sponsoring Organisations (COSO) Enterprise Risk Management: An Integrated Framework (2017)
	HM Treasury The Orange Book: Management of Risk – Principles and Concepts (UK, 2020)
General	ISO Guide 73:2009 Risk Management Vocabulary
Medical Device	ISO 14971:2019 Medical devices — Application of Risk Management to Medical Devices
Medicinal Products	European Medicines Agency Benefit-risk methodology project Work package 4 report: Benefit-risk tools and processes (2012)
Nuclear Industry	Considerations on Performing Integrated Risk Informed Decision Making IAEA-TECDOC-1909 (2020) International Atomic Energy Agency
	A Framework for an Integrated Risk Informed Decision-Making Process *INSAG-25 (2011)* International Nuclear Safety Group
Project Management	Guide to Project Risk Management Body of Knowledge (PMBoKÆ)
Safety (Workplace)	UK Health & safety *Reducing Risks, Protecting People, NSE's Decision Making Process (2001)*

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