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IMPROVING RISK BASED DECISION MAKING EFFECTIVENESS: INSIGHTS FROM OTHER INDUSTRIES

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ABSTRACT

The Pharmaceutical Regulatory Science Team (PRST), founded in 2005, carries out research into strategies to address the challenges and opportunities of implementing science and risk-based decision making and manufacturing approaches. Since its inception, the PRST has continued to progress research on quality risk management (QRM), knowledge management (KM) operational excellence (OpEx), post-approval change management (PAC, and PAC 1VQ), quality metrics and related topics covered by ICH Quality Guidelines.

Recently the focus of the PRST has been on Risk-Based Decision Making (RBDM) and as such has written a series of 4 papers on strategies to improve RBDM effectiveness. This, the first of these papers, explores the existing published research into Risk-Based Decision Making and how the topic is addressed in other high-risk industries. Learnings from this research has identified 21 essential attributes of effective RBDM, which are presented in the final section of this paper.

1. INTRODUCTION AND CONTEXT SETTING

Increasingly in the 21st century, global regulatory oversight of the pharmaceutical industry has adopted a risk-based approach. (FDA, 2007) Complying with basic Good Manufacturing Practice (GMP) is now seen as a minimum standard of control and there is an increasing expectation to implement continuous improvement and innovation as an additional means to control product safety, reduce patient risk, and assure supply. (Cavazzoni, 2021)

Central to this ambition is a collaboration amongst global regulatory agencies, through organisations such as the *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use* (ICH). ICH have published a number of guidance documents, including *ICH Q10: Pharmaceutical Quality Systems.* (ICH, 2008)

ICH Q10 introduces the Pharmaceutical Quality system (PQS) as a system that governs all stages of the pharmaceutical product lifecycle, noting that the GMP requirements do not *explicitly* address all stages of the lifecycle. Product development and aspects of technology transfer, in particular, are not subject to the same GMP controls as other stages in the lifecycle. The ICH Q10 document, therefore, described an intent to:

> *'Encourage the use of science and **risk-based approaches** at each lifecycle stage, thereby promoting continual improvement across the entire product lifecycle.'* ***(ICH Q10)***

ICH also published *ICH Q9: Quality Risk Management* (ICH, 2005), which stated that:

> *'An effective quality risk management approach can further ensure the high quality of the drug (medicinal) product to the patient by providing **a proactive** means to **identify and control potential quality issues** during development and manufacturing.*

Additionally, use of quality risk management ***can improve the decision making*** *if a quality problem arises.*

Effective quality risk management ***can facilitate better and more informed decisions,*** *can provide regulators with greater assurance of a company's ability to deal with potential risks and can beneficially affect the extent and level of direct regulatory oversight.'*[1] ***(ICH Q9)***

However, the anticipated increase in *'proactivity'* expressed in the original ICH Q9 objectives was not realised, with some observers noting that there is an *'innovation crisis'*, particularly in pharmaceutical manufacturing technology (Fleming, 2018)(Laermann-Nguyen et al., 2021). Indeed, since the publication of ICH Q9 and ICH Q10, there remain many challenges and obstacles to updating and improving manufacturing operations. This is noted in the 2019 Drug Shortage Report (FDA, 2019), where upon analysing the persistent issue with drug shortages, the United States Food and Drug Administration (FDA) noted that quality, unlike cost, is not a competitive advantage in the marketplace and that this dynamic may encourage manufacturers to reduce costs by minimizing investment in quality.

'Manufacturers are more likely to keep costs down by minimizing investments in manufacturing quality, which eventually leads to quality problems, triggering supply disruptions and shortages' ***(FDA, 2019)***

While scientific excellence is the foundation of the pharmaceutical industry, the appetite to change established products, processes, or technologies is low. Complex regulatory post-approval change processes lead to long lead times for facility or supply chain upgrades, acting as a deterrence to change. (FDA, 2019) (Vinther & Ramnarine, 2019) The current situation does not align with the intent of Quality Risk Management (QRM), as predicted in the FDA's strategic plan, *Pharmaceutical GMP for the 21st Century: A Risk Based Approach* (FDA, 2006), which stated:

'Modern quality systems, when coupled with manufacturing process and product knowledge and the use of ***effective risk management practices****, can handle many types of changes to facilities, equipment, and processes without the need for prior approval regulatory submissions. Manufacturers with a robust quality system and appropriate process knowledge can implement many types of improvements.'* ***(FDA, 2006)***

To address some of the challenges with implementing QRM, ICH established an Expert Working Group to revise ICH Q9. A concept paper identified four areas of improvement to be addressed by the revision, one of which was **Risk-Based Decision-Making (RBDM)**. (ICH EWG, 2020) The concept paper stated:

'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*

[1] Bold print not in the original document. Where used in the paper, it is added by the authors for emphasis.

address the expected benefits of investing in risk-based decision-making activities'. ***(ICHQ9 (R1) Concept Paper, 2020****)*

The Pharmaceutical Regulatory Science Team (PRST) founded in 2005, carries out research into strategies to address the challenges and opportunities of implementing Science and Risk based decision making and manufacturing approaches. Since its inception, the PRST has continued to progress research on quality risk management (QRM), knowledge management (KM) operational excellence (OpEx), post-approval change management (PAC, and PAC 1VQ), quality metrics and related topics covered by ICH Quality Guidelines.

This paper is the first of a series written by PRST, focused on improving RBDM effectiveness, in support of the objectives of the ICH Q9(R1) concept paper. This first paper will explore the existing research into Risk-Based Decision-Making, as suggested by the ICH Q9(R1) 2020 concept paper.

Additional papers in this series are presented graphically in figure 1 and include:

- Paper 2: Improving RBDM Effectiveness – A Case for Key Decision Review Points (KDRPs) in Quality Risk Management.
- Paper 3: Improving RBDM Effectiveness – Determining the Level of Formality.
- Paper 4: Improving RBDM Effectiveness – Addressing Uncertainty.

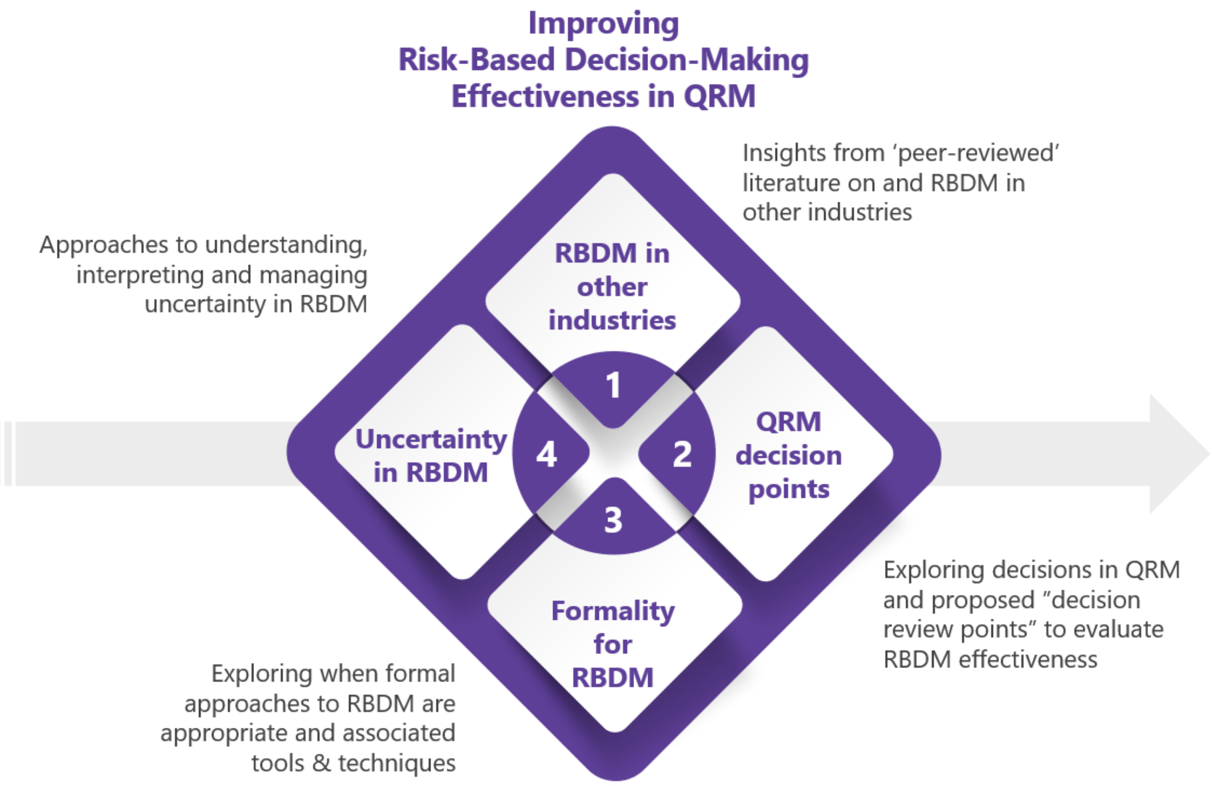

Figure 1: Series of papers on Improving RBDM Effectiveness in QRM

This series of papers builds upon previously published work by the authors on the topics of QRM and on Knowledge Management (KM). Research by the PRST established a strong and iterative connection between

QRM and KM (M. Lipa et al., 2020) and recent research by the group explores how that interconnection impacts upon RBDM. (Martin Lipa et al., 2022)

This first paper reviews published literature on RBDM and explores its application within QRM processes, as described in the updated QRM guidance, referred to as ICH Q9(R1) (ICH, 2023). The review includes how RBDM is addressed in other industries is also carried out. In addition, the authors conducted a review of relevant decision science literature and the insights gained are shared in this series of papers.

2. RISK-BASED DECISION-MAKING – SEEKING A COMMON DEFINITION

This review commenced by seeking a definition of RBDM. RBDM is a term used in many industries in connection with decision-making. However, a thorough review of published literature did not reveal a universally recognised definition for the term. In fact, it was found that the term is used with different meanings in different contexts.

A recent collaboration between the Ohio State University College's US Centre for Foodborne Illness Research and Prevention, the College of Public Health, and the Translational Data Analytics Institute, published the results of a scoping study on all available literature referencing RBDM in the food, agricultural, environmental, and medical literature. (Morgan et al., 2021) From an initial return of 2,552 unique peer reviewed publications published from 1983-2020, the researchers noted an increase in the publications referencing the term (Figure 2) and identified that the term was used in many contexts with different meanings. The most used contexts were:

- When considering risk acceptability and the trade-offs between risk and other factors.
- When establishing priorities for the allocation of resources
- As an approach to more effective stakeholder engagement

The study did not, however, find a common definition and concluded that the term has a wide application and, therefore, should be qualified with the decision context.

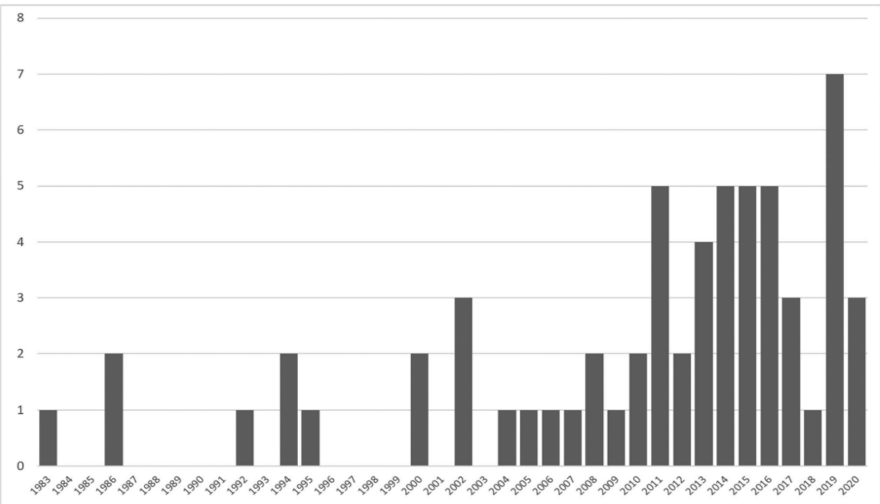

Figure 2: Publications mentioning RBDM (Morgan et al)

As mentioned previously, the concept paper for ICH Q9(R1) noted that there is a *'breadth'* of peer reviewed literature on the topic of RBDM. However, the authors have found that the use of the term is highly contextual and, therefore, caution that consideration of any research or studies on RBDM, must be evaluated with respect to its comparability and applicability to the use of RBDM in QRM processes within pharmaceutical manufacturing operations.

Furthermore, in more recent times, the closely related term ***'risk informed decision making' (RIDM)*** has become commonplace also. A review of the literature has found that RIDM is invoked for key decisions, and it is the preferred term (and process) in industries with highly sophisticated risk management strategies, e.g., the aerospace industry.

A broad distinction between the two terms is given by Charles Yoe, in his 2019 book *Principles of Risk Analysis, Decision Making Under Uncertainty* (Yoe, 2019)

> *Risk is an important decision-making criterion. When risk is the **only** criterion, decisions are **risk-based.** When risk is an influential member of a set of decision criteria, decisions are **risk-informed**.*
>
> *In **risk-based decision making**, risk estimates and risk narratives form the basis for decisions. Unacceptable levels of risk trigger action. By contrast**, risk-informed decision-making** trades off levels of risk with other criteria to arrive at a decision. **(Yoe, 2019)***

A similar more detailed distinction is offered by Zio, a leading academic in the area of reliability, safety, and critical risk (Zio & Pedroni, 2012) who proposes that:

> *'A **risk-based decision-making (RBDM)** process provides a defensible basis for making decisions and helps to identify the greatest risks and prioritize efforts to minimize or eliminate them. It is based primarily on a narrow set of model-based risk metrics, and generally does not lead much space for interpretation. Considerations of cost, feasibility and stakeholder concerns are generally not a part of risk-based decision-making, which is typically conducted by technical experts, without public consultation or stakeholder involvement.*

While in contrast, Zio defines RIDM as:

> *'A **risk-informed decision-making (RIDM)** process is a deliberative process that uses a set of performance measures, together with other considerations, to "inform" decision-making. The RIDM process acknowledges that human judgment has a relevant role in decisions, and that technical information cannot be the unique basis for decision-making. This is because of inevitable gaps in the technical information, and also because decision-making is an intrinsically subjective, value-based task. In tackling complex decision-making problems involving multiple, competing objectives, the cumulative knowledge provided by experienced personnel is essential for integrating technical and non-technical elements to produce dependable decisions'.*

Consequently, it emerges that a meaningful understanding of the term RBDM is not a simple matter of '*looking over there'* and exploring the use and application of the term in other sectors. A clear and definitive understanding of RBDM may be more elusive than just benchmarking against other sectors. There is a level of interrogation and interpretation required to extract the learning and insights from other sectors that may be of use in the context of enhancing RBDM within QRM in pharmaceutical operations.

3. RISK-BASED DECISION-MAKING IN QRM – WHERE ARE THE DECISION NODES?

In realising that context is important to assure a meaningful comparison with other industry definitions, the authors turned their attention to refining and clarifying the context with respect to RBDM in pharmaceutical QRM. This was somewhat challenging as both the original and the revised guidelines, illustrated the QRM process without decision nodes (Figure 3), commenting that:

> *'Decision nodes are not shown in the diagram ... because decisions can occur at any point in the process.'* ***(ICH Q9(R1))***

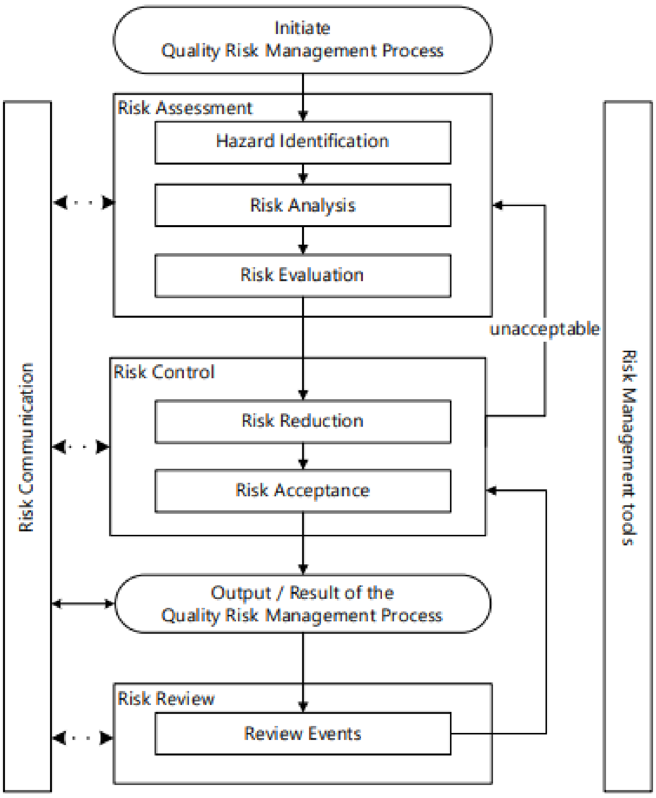

Figure 3: The QRM Process Model from ICH Q9 (R1)

The inference is that a risk management process is a cumulation of decision-making *within* the process. Such decisions might include:

- The identification of the risks or hazards to be analysed.
- The selection of appropriate tools for analysis.
- The selection of a risk assessment team.
- The risk raking approach to be applied.
- The scoring of risks.
- The level of risk tolerance applied.

- The acceptability of risk control measures.

ICH Q9(R1) also states that the document:

> *'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.'* ***(ICH Q9(R1))***

This suggests that the term RBDM may be used in the context of QRM and the evaluation of risk but may also be used in the context of decisions made with respect to the quality of the product. However, the latter are, more accurately, decisions that are *informed by* QRM.

Further exploration that there are potentially *two* decision contexts and intents invoked when using the term RBDM in the pharmaceutical context, the authors noted that *both* ICH Q9 and ICH Q10 acknowledge that one of the objectives for adopting the risk-based approach is to make more *'informed decisions.'*

Technically, some of these decisions are based on a technical assessment of risk and others may require *deliberation* beyond the technical analysis. A change management decision, for example, may involve balancing the (technical) evaluation from QRM with other (deliberative) considerations such as the expected *benefits* of the change. This additional deliberation involves, in some cases, multiple stakeholders. This scenario is closer to the concept of RIDM offered by Yoe, Zio, and others such as NASA. (Office of Safety & Mission Assurance NASA, 2010) The distinction is important when developing guidance for these decision types.

The authors ponder if, in fact, ICH Q9(R1) may be referring to RBDM in the narrower, and more commonly applied context of the term, that is to the *technical analysis* of risk. This premise may be supported by the inclusion of a definition of RBDM in the revised ICH Q9(R1), which defined it as:

> *'An approach or process that considers knowledge about risks relevant to the decision and whether risks are at an acceptable level.'* **ICH Q9 (R1)**

Consequently, the authors, throughout this series of papers reflect on RBDM in this context, i.e., with respect to the technical analysis of risk. Recognizing that, in reality, a QRM process may extend along the full product lifecycle and hence may occur over years or decades, Paper 2 of this series addresses the need to review these technical approaches throughout the QRM process, to assure consistency and accuracy in RBDM. Paper 2 explores the introduction of key decision review points in the ICH Q9 QRM process. (A Case for Risk Decision Review Points (KDRPS) in the Quality Risk Management Process, 2023)

4. RISK BASED DECISION MAKING – INSIGHTS FROM DECISION SCIENCE

No review of RBDM would be complete without exploring decision science. The study of decision-making is the focus of many disciplines, including mathematics, sociology, psychology, economics, political science, and business management. It has attracted the interest of minds for centuries from Herodotus (500BC), Pascal, de Fermat, and Bernoulli (17^{th} Century), Bayes, and Laplace (18th Century). Because the volume of scientific publications on decision-making is vast and spans many centuries and specialities, this review focuses on current thinking and on research that particularly addresses decision-making about risk.

It was an American public administrator, in a book entitled *The Functions of an Executive* (Barnard, 1938), who first highlighted that organisational decision-making may differ from personal decision-making. Later in 1966, the Stanford Professor Ronald Howard coined the term *'decision analysis'* in reference to the formal process of decision-making.(Howard, 1966). Howard defined a decision as:

> *'An irrevocable allocation of resources – irrevocable in the sense that it would be extremely costly to go back'.* ***(Howard 1966)***

With this definition, Howard differentiated decision-making *as an executed action*, from decision-making as a state of mind. Searching for a logical process in the face of uncertainty, Howard also drew a distinction between a good decision and a good outcome as follows:

> *'A good decision is a logical decision, one based on the uncertainties, values, and preferences of the decision maker. A good outcome is one that is profitable or otherwise highly valued. In short, a good outcome is one that we would wish would happen.'* ***(Howard, 1996)***

Howard noted that *'pending the invention of true clairvoyance'*, the pursuit of good outcomes was best achieved by the pursuit of good decision-making. He described a decision-making model which recognised that the decision-maker needs to establish options, that each option is subject to variability and that the decision-maker needs to understand the sensitivity of each outcome to these variables. A further interesting feature of Howard's early decision-making model is that the decision-maker may choose, because of the analysis, to seek further knowledge in an attempt to reduce uncertainty. Thus, the link between seeking knowledge and decision-making under uncertainty was established.

Howard recognised the role of uncertainty and that the decision-maker needs to understand the uncertainty associated with the most '*crucial'* variables, i.e., those that most influence the decision outcome.

He also noted that the *preferences* of the decision-maker play a significant role in the choices made – one decision-maker may prefer the certainty of a known outcome while another may tolerate some uncertainty if a real benefit can be gained. These choices reflect the risk tolerance of the decision-maker. Given that risk management is often an interdisciplinary group activity and that there are many stakeholders to the outcome of the process, disparate *risk tolerance* may be a significant influence on outcome. It should be noted that decision-makers can also vary in their tolerance of uncertainty, which indeed may vary significantly between different cultures. (Hofstede, 2001)

Charles Vlek, of the University of Groningen (Vlek, 1984), a contemporary academic in the field of environmental risk management, noted that:

> *'Decisions can be evaluated by process as well as by outcome'* ***(Vlek, 1984)***

Vlek proposed that good decision-makers, by applying good process, will make more good decisions than bad. Calibration against the pattern of their outcomes is a telling indicator. Furthermore, he stated that:

> *'Novel and complex decisions wrought with uncertainty about the (long-term) consequences cannot but rely on process criteria'.* ***(Vlek, 1984)***

Reflecting on these contributions from decision science, the authors suggest that by considering decision analysis as a science which complements risk science, some of the challenges the decision-maker encounters when faced with uncertainty may be addressed.

This opinion is supported by the academic Vicki Bier (Bier, 2020) who noted that:

> *'Decision analysis and risk analysis largely grew up together, as "siblings"— forging their own paths through life, but influenced by each other in positive ways, and coming together in different ways over the years'.* ***Bier (2020)***

Considering this interconnection of risk science with decision science, two early leaders in the field of decision science, Keeney and Raiffa, published the manuscript for a proposed book entitled *Decision Analysis with Multiple Conflicting Objectives, Preferences and Value Trade-offs.* (Keeney & Raiffa, 1976) Even in the preface of the working manuscript, they admitted that if the title were to reflect the contents, the book should be called *On Cardinal Utility Analysis with Multiple Conflicting Objectives: The Case of Individual Decision Making Under Uncertainty from the Prescriptive Point of View—with Special Emphasis on Applications but with a Little Theory Thrown-In for Spice'.* Both titles reflect the complexity of the ideas that the authors were trying to convey. A key point of the publication was that the responsible decision-maker thinks hard about ***uncertainty*** and ***preferences*** when making decisions about risk, particularly in complex contexts.

In a separate publication and reinforcing the argument for decision-making processes (Keeney, 1984), Keeney described decision analysis as:

> *'A formalization of common sense for decision problems which are too complex for informal use of common sense.' (Keeney 1984)*

4.1. BOUNDED RATIONALITY

Just as Voltaire observed that common sense is *'not so common'*, the American economist Herbert A Simon observed that decision makers were not always rational. In 1947, Simon published *Administrative Behaviour* (Simon, 1947), a work which eventually led him to receiving the 1978 Nobel Prize in Economics. In this work, Simon introduced the concept of *'bounded rationality'* to explain that when making decisions, reason is constrained by the cognitive limitations of the decision-maker, imperfect information, and time constraints.

This contradicted the prevailing theory of the time, that of *'Economic Man'* (Homo Economicus), a term whose origins are debated, including speculation that it originated with the familiar name of Pareto some 80 years previously. Economic Man was commonly described as a rational being, making informed decisions designed to achieve his goals at minimal cost. This was the popular view of mathematicians, a discipline where the possible outcomes of a decision are measured using probability. This approach was reinforced with the 1944 publication of the first ground-breaking work on Game Theory by von Neumann and Morgenstern (von Neumann & Morgenstern, 1944). Game theory operates on the premise of *'rational agents'* i.e., that a decision-maker, be it a person or software, will always consider the data and analysis presented and select the optimal option. However, Simon argued that, in reality, this was not always the case.

The idea that decision-makers would behave irrationally led to an explosion of research into both the heuristics[2] of decision-making and the importance of a having a decision-making framework or model to control and avoid the worst consequences of irrational decision-making. A key contribution to the area was made by another set of Nobel Prize winners[3] (2002), Daniel Kahneman and Amos Tversky, who proposed a theory on the psychology of choice - **Prospect Theory** - in 1979. (Kahneman & Tversky, 1979) Prospect Theory, also known as the Loss Aversion Theory, states that decision-makers value losses and gains differently. It poses the concept that a decision-maker 'feels' losses more keenly than gains, that this loss is relative to some *'reference point'* and that this reference point varies from situation-to-situation or person-to-person.

The French economist, Maurice Allais suggested decision-makers place more value on outcomes that are certain, relative to outcomes that are merely probable. This bias is referred to as the *'certainty effect'*[4]. (Allais, 1953) That people are *'irrational'* when faced with uncertainty is well recognized.

The numerous biases and heuristics, consciously and unconsciously, influencing the decision-maker and contributing to decision-making irrationality was further developed by Kahneman and Tversky and are well summarised in the 2012 best-selling book *Thinking Fast and Slow*. (Kahneman, 2012) Many of these mental shortcuts, if not managed, can contribute to errors and misjudgements about risk and the impact of risk.

4.2. PROBABILITY

In the context of QRM the observation, also made by Kahneman & Tversky, that people are poor at discriminating ***probabilities*** is noteworthy. Typically, individuals will place an over optimistic weight on outcomes with lower possibilities. If an event seems unlikely, no matter how catastrophic, the decision maker is overly attuned to the improbability of the event. (Kahneman & Tversky, 1979) However, this may be moderated if the decision-maker has *directly* experienced the rare event (a survivor of an airplane crash will regard it as less improbable). (Camilleri & Newell, 2013) More recently, arguments have been made that when rare events are presented as a possibility, the mere mention of them attracts our attention, captivates the imagination as a novelty, leading to over-weighting of the probability. (Erev et al., 2008)

While the scientific debate continues, the reality is that although the analyst can calculate the ***probability*** of each outcome presented to the decision-maker – it does not follow that the decision-maker will assign the appropriate weighting. These are troublesome heuristics and should be acknowledged and addressed if risk assessments are to be translated into good decisions.

The correct interpretation of risk and probability, in analysed data, is not a given and decision-makers can display incompetence in this regard. (Bruine de Bruin et al., 2020) Research shows that in addition to lived experience, cognitive, motivational, and emotional factors may all influence the decision-makers willingness to apply rational cognitive processes to the data presented. The more complex the data and the analysis, the more *'bounded'* is our rationality. Although the analysis of risk and risk data may predict the potential

[2] Heuristics are 'mental shortcuts' used to make decisions.

[3] Although the Nobel prize was awarded for the work of both scientists, at the time of the award Tversky was deceased and Nobel Prizes are not awarded posthumously.

[4] Also called the Allais Paradox.

outcomes of decision options and choices, it does not necessarily follow that this is how decisions will be made. (Slovic & Fischhoff, 1988)

4.3. UNCERTAINTY

High uncertainty is probably the most problematic decision-making scenario. Indeed, it is possible that the risk IS the uncertainty.[5] To further complicate matters, the source of that uncertainty may vary. It may be due to:

1. High variability or potential randomness in the data, which makes prediction of future outcomes difficult (aleatory uncertainty);

2. A lack of data and knowledge (epistemic uncertainty).

ICH Q9(R1) defines it as:

> *The term "uncertainty" in quality risk management means* ***lack of knowledge*** *about hazards, harms and, consequently, their associated risks.* ***(ICH Q9(R1))***

It is clear when making decisions involving risk and when outcomes have the potential to cause harm, uncertainty is undesirable. The optimal solution is to delay the decision until more reliable data, information, and knowledge is available. However, while product lifecycles are getting shorter, the discovery-to-approval phases are still averaging 10.5 years, which represents a protracted knowledge development process. (The Biotechnology Innovation Organisation et al., 2021) It is not practical or reasonable to wait. The development of knowledge of products, processes, and materials must proceed in parallel with the management of risk and uncertainty. Additionally, until the knowledge collected is beyond dispute, there may be multiple interpretations of the knowledge that is available *(ambiguity)*.

It is also true that, in complex settings, some risks will remain unknown for extended periods, i.e. ignorance. This includes sources of error, material influences, system/system, or system/human interactions, etc. A further complication is that knowledge developed some time ago, for example in the earlier stages of a product lifecycle, may suffer from *'knowledge decay'*, in terms of recall and access (Thorndike, 1914), and '*information decay'* in terms of relevance to a technologically advancing horizon. (Geertsema & Lu, 2021). A typical example of the latter is that early data may be generated by methods or instruments not considered *'modern'* a decade later.

Deciding upon a course of action to control a risk when there are many unknowns and uncertainties is difficult and many risks may remain uncertain for a long time. Chris Whipple of Purdue University (Whipple, 1986) expressed the problem as follows:

> *'Estimating the magnitude of risks that cannot be measured directly, frequently requires the use of assumptions that cannot be tested empirically.*

[5] This is how it is expressed in the ISO 31000 Risk Management standard, which defines risk as *'the effect of uncertainty on objectives*.'

Not only are such risks uncertain, but often the uncertainty cannot be characterized by a probability distribution. Although such distributions are useful for describing some uncertainties, they are often not feasible in risk assessment.

Sometimes there is no reasonable method even to assign weights to the plausibility of alternative assumptions. Methods have been developed to elicit subjective descriptions of uncertainty; these, however, raise the question of whose estimates to accept.'
(Whipple, 1986)

As highlighted by Whipple, introducing methods to understand and address uncertainty often introduces the interconnected hazard of subjectivity.

Understanding how to evaluate uncertainty is a critical competency to decision making about risk. In ICH Q9 (R1), uncertainty is identified as one of the factors to be considered when making decisions with respect to risk and when applying a level of formality to that decision-making:

The level of uncertainty that is associated with the area being risk assessed informs how much formality may be required to manage potential risks. ***(ICH Q9(R1), 2023)***

The technical understanding of risk is typically developed by risk analysis. When data is limited, this is often achieved by taking a probability approach or by modelling the problem. These approaches must consider, and not unreasonably add to, the state of uncertainty.

Finally, it has been established that decision making under uncertainty may lean on different mental abilities and competencies than those used for evidence-based decision-making. These concepts are discussed in more detail in paper 4 of this series (Addressing Uncertainty, 2023)

5. RISK-BASED DECISION MAKING – EXPLORING APPLICATION IN OTHER KEY INDUSTRIES

Finally, in order to complete a review on RBDM, the authors turned to other industries, including those regarded as High Reliability Organisations (HROs)[6], to seek a definition for RBDM. A total of 16 organisations were reviewed (illustrated in Figure 4), selected on the basis that each had a standardised Risk Management System, which included guidance on decision-making.

[6] 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.

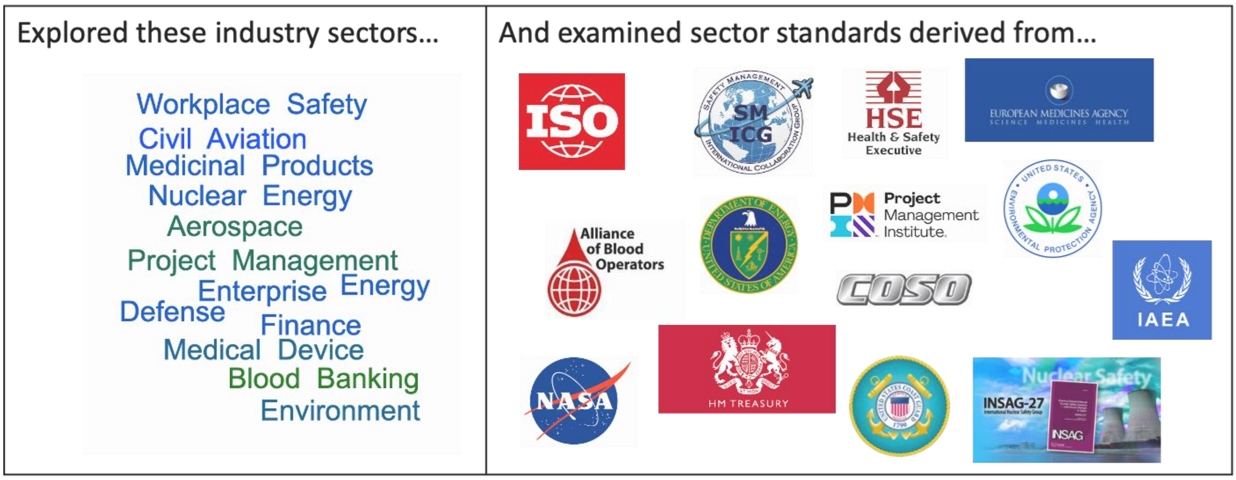

Figure 4: An illustrative list of the industries explored for insights into RBDM.

Details of this review have previously been published by the authors in a paper entitled: *Steps Beyond Risk Assessment in QRM: RBDM, the next horizon.* (Mulholland et al., 2021). The review helped identify 21 critical attributes of good decision-making, which were categorised as:

- A robust QRM Process
- Use of the best available knowledge
- Application of good governance and consideration of human factors

These attributes are presented in Figure 5 and demonstrate, once again, the value placed on knowledge as an enabler of good risk management. The 10 characteristics of a robust QRM process and its role in supporting RBDM, will be further developed in future work.

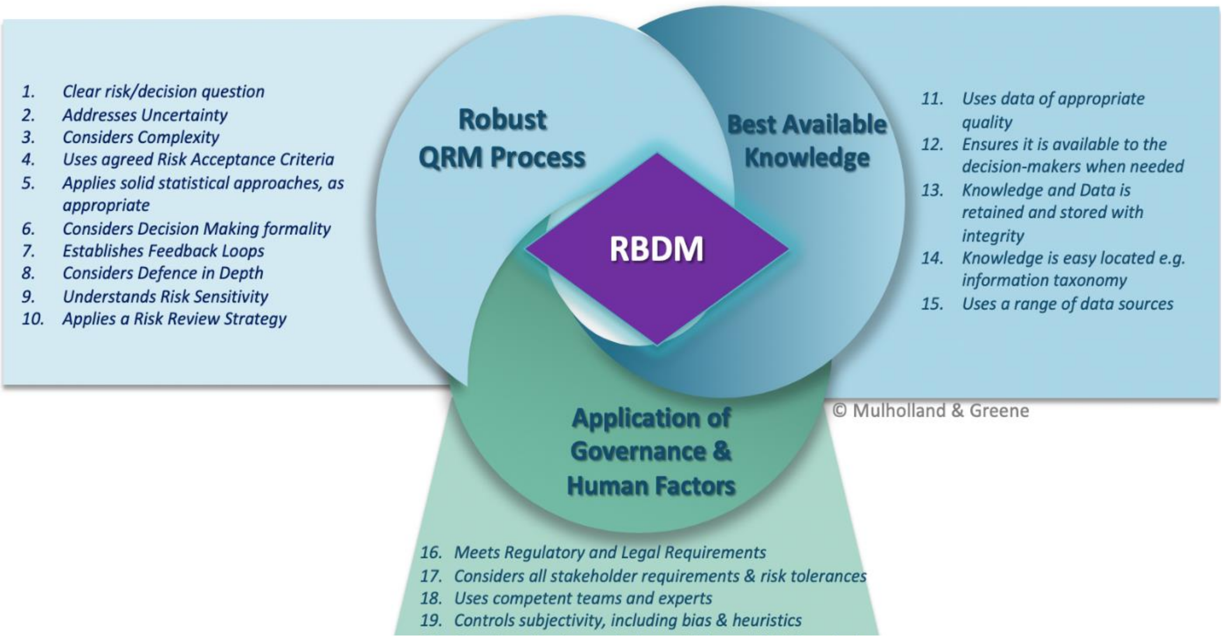

Figure 5: 21 Essential Attributes of good Risk Based Decision Making

6. CONCLUSION

When the ICH Q9(R1) expert working group decided to consider RBDM as one of the a focus areas for an enhanced approach to QRM, the concept document highlighted the availability of a '*breadth of peer-reviewed research in this area'* in support of this improvement. This paper outlines some of the research conducted to support the objective of making it visible to the pharmaceutical industry.

Among the insights gleaned, the authors identified that the term 'risk-based decision-making' is not universally defined and that it may have different meanings in different contexts. The authors note that this must be considered when reviewing applications in other industries or environments.

The authors have interpreted RBDM as applying to those related to the *technical* analysis of risk and the acceptance of risk based on *technical* criteria. This aligns with the definition in ICH Q9(R1) when it refers to knowledge about risk at all stages in the QRM process. Through this lens, the authors harvested best practices from other industries, and compiled a list of 21 attributes of *'good'* RBDM. This study confirmed the central role of knowledge and knowledge management in supporting QRM and RBDM, particularly over elongated product lifecycles.

Also, of importance is the recognition that decision-makers do not always act rationally when making decisions. Even with the best information available, a range of heuristics and biases, both conscious and unconscious, can still come in to play. This confirms that the advocacy of both formality and the control of subjectivity in ICH Q9(R1) is well founded.

Research also suggests that the decision-makers rationality is further challenged when there is a significant level of uncertainty. Uncertainty can invite subjectivity, as experts grapple with interpreting limited data to predict risk outcomes. ICH Q9(R1) also highlights uncertainty as a hazard in complex RBDM and this research confirms that this requires conscious management.

In summary, research suggests three safeguards against irrationality and error in RBDM:

1) The application of **formality** to the RBDM process. This is in addition to the application of formality to the QRM process in general, including formal risk analysis. There are many tools available to enhance the rigour applied to RBDM, thus avoiding the worst hazards of uncertainty and subjectivity. These are discussed further in paper 3 of this series (Determining the Level of Formality, 2023)

2) The development of supporting KM processes to assure that the best knowledge is available to support RBDM, recognising that, along elongated product development lifecycles, knowledge may not easily flow to the decision-maker and may lose its currency.

3) Recognition that the evaluation and interpretation of limited data, inviting the application of predictive approaches to the analysis of risk, requires different capabilities and competencies than that of evidence-based decision-making. This is explored further in paper 4 of this series. (Addressing Uncertainty, 2023)

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