Level 3

Volume 15 | Issue 2 Article 18

2020

# Quality Risk Management: Seeking the Diamonds: Making the Case for Improved Formality in QRM Decision-making

Valerie Mulholland
*Technological University Dublin*

Anne Greene
*Technological University Dublin*, anne.greene@tudublin.ie



## Recommended Citation

Mulholland, Valerie and Greene, Anne (2020) "Quality Risk Management: Seeking the Diamonds: Making the Case for Improved Formality in QRM Decision-making," *Level 3*: Vol. 15: Iss. 2, Article 18.
doi:https://doi.org/10.21427/yfw0-hy89
Available at: https://arrow.tudublin.ie/level3/vol15/iss2/18

# Quality Risk Management – *Seeking the Diamonds*
# Making the Case for Improved formality in QRM decision-making

## Author

**Valerie Mulholland, PhD Researcher, PRST, TU Dublin**

## Abstract

In November 2020, a newly formed working group of the ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) published a concept paper [1] outlining the considerations for an update to *ICH Q9: Quality Risk Management* [2]. In the concept paper, the expert group identified four areas for improvement with respect to the current application of Quality Risk Management (QRM). One of the areas identified as problematic was a *'lack of clarity in risk-based decision making'*. The paper described a *'lack of clarity on what good risk-based decision-making means'*. This paper looks at risk-based decision-making and, in particular, whether higher level of formality in decision-making would improve the effectiveness of both QRM and KM within key elements Pharmceutical Quality System (PQS).

## Introduction

In 1921, at a presentation to the American Society of Mechanical Engineers, Frank & Lilian Gilbreth presented the first structured method for documenting process flows [3]. The husband-and-wife team were both Industrial Engineers and, indeed, were the pioneers of *'time in motion studies'* – the forerunner of standardised work practices. To this day, process flow diagrams are used in many industries to detail, analyse, and visualise the key steps in a process. While there are some variations in notation, commonly a task is represented as a rectangular box and a decision is a diamond. The diamond denotes the point in the process when more than one option is available, and a decision is required.

In 2005, the pharmaceutical guidance on Quality Risk Management (QRM) – *ICH Q9: Quality Risk Management* [2] – was published. It included a flow diagram to illustrate the proposed risk management process (Fig 1). The lack of decision nodes was notable. The text of the document pointed out that this was because decisions could occur *anywhere* in the process.

Risk Management is a tool to support decision-making. The objective of QRM, according to ICH Q9, is to *'improve science-based decision making'* within the Pharmaceutical Quality

System (PQS). QRM informs the process owner of the hazards that must be managed, whether the level of control applied is adequate or not, and whether action is required.

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'* *ICH Q9*

However, QRM is also itself a continuum of contributary decisions - from the selection of the appropriate risk analysis tools used to identify and rank hazards, to the risk ranking scores applied, to the actions required to control the hazard, or to whether applied controls are adequate, etc. All these contributory decisions cumulate within the risk management process and contribute to the effectiveness of the outcome. It should be noted that the ICH Q9 revision concept paper listed, as another concern, the high level of subjectivity applied in risk assessments resulting, perhaps, in a lack of effectiveness when addressing risks. In the view of this author (with considerable auditing experience), the provenance of some of these decisions are not always clear e.g. why a certain risk analysis tool was selected, how the risk ranking scheme was decided, how individual ranks were assigned, how a particular risk control was deemed to be the most appropriate, how uncertain this decision was and whether it should be further monitored. When controlling critical quality attributes, the output of these contributary decisions can be significant.

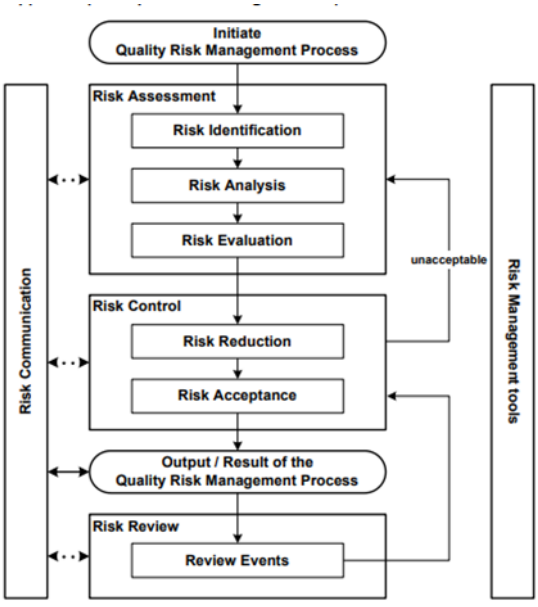


*Figure 1: QRM Process Diagram - ICH Q9*



https://arrow.tudublin.ie/level3/vol15/iss2/18
DOI: https://doi.org/10.21427/yfw0-hy89

Therefore, QRM is both an input to decision-making and an output of several contributory decisions - both of which are important in terms of the objectives of a QRM programme. However, ICH Q9 provides little guidance in relation to decision-making or the level of formality required.

There are many, many (hundreds? thousands?) decisions made every day in a typical pharmaceutical operation. Decisions are made every time a person does something characterised by the words- review, approve, evaluate, determine, check - and so on. These are common words in PQS documentation and represent the output of decisions at all levels. However, this paper is focused on the more impactful of those decisions. It focuses on the decisions that QRM contributes to informing, rather than the contributary decisions that inform QRM. This paper considers how QRM, and indeed its twin enabler Knowledge Management (KM), support the significant decision-making nodes (or diamonds) within the PQS and whether this would be better evidenced by using formal decision-making processes.

## What is a Decision?

There are many definitions of a decision. The Oxford Dictionary includes *'a conclusion or resolution reached after consideration*' and *'the action or process of deciding something or of resolving a question'.* In his book *Why Decisions Fail: Avoiding the Blunders and Traps That Lead to Decision Debacles* [4], the Ohio State University Professor Paul C Nutt, an expert in the field of strategic management and decision-making, described decision-making '*as taking place when a person in authority identifies an important issue and carries out a process to make a choice that produces outcomes with consequences'.* This is a useful description for the purpose of this reflection.

The Stanford Professor Ronald Howard first coined the term *'decision analysis'* in 1966 [5] and he defined a decision as *'an irrevocable allocation of resources – irrevocable in the sense that it would be extremely costly to go back'*. While this seems a dramatic definition – it does highlight the high level of commitment that some decisions require and the need to be certain of the outcome.

There are decisions within the PQS that are quite impactful and somewhat *'irrevocable'*, such as deciding which equipment to purchase, what set-points, specifications, or controls to apply; which supplier to use; whether to release a batch with an issue; what validation strategy to adopt; whether a process is in control; whether to outsource a GMP activity; or whether a change to a process step or test method is appropriate, etc. Decisions of this importance may have consequences if incorrect. Turning back may also be a very difficult

option. These are the type of decisions that this paper is concerned with, because they may have a significant impact on product quality.

When considering these types of decisions, one ponders: Should a level of formality be required when making decisions of this importance, such that the process of decision-making is both rigorous and transparent? What if some of the information that informed the decision is uncertain or unreliable, should the rationale be recorded? Does the current level of formal documentation in these systems (change control documentation, batch manufacturing and control records, validation protocols and reports) adequately explain the decision made? Should not the decision itself be documented, explained and justified? Formal processes with supporting documentation can provide evidence on how these decisions were made, given the knowledge and information available at the time.

While significant decisions are often made with a large body of evidence (knowledge) supporting the selected option, they can also be made in novel and new contexts with a worrying lack of direct or reliable evidence to support the outcome (risk) of the decision. These decisions are often examined in regulatory audit. They require explanation and often also require transparency and credibility. The level of formality applied to the decision-making, in these situations, can assist with these explanations. These are the 'diamonds' within the PQS.

**Critical Decision Making in a Pharmaceutical Quality System**

Another ICH Guidance, *ICH Q10: Pharmaceutical Quality System* [6] highlights the elements of the PQS where critical and strategic decisions are made. Decisions in these PQS elements are important and should be evidence-based, i.e., supported with appropriate data. Decisions on high-risk elements of the operation should, ideally, be as certain as possible. However, on occasion these decisions can be more uncertain and are then considered risk-based decisions. In this case, the uncertainties should be understood and managed. The PQS elements highlighted in ICH Q10 are elements are illustrated (Fig 2).



https://arrow.tudublin.ie/level3/vol15/iss2/18
DOI: https://doi.org/10.21427/yfw0-hy89

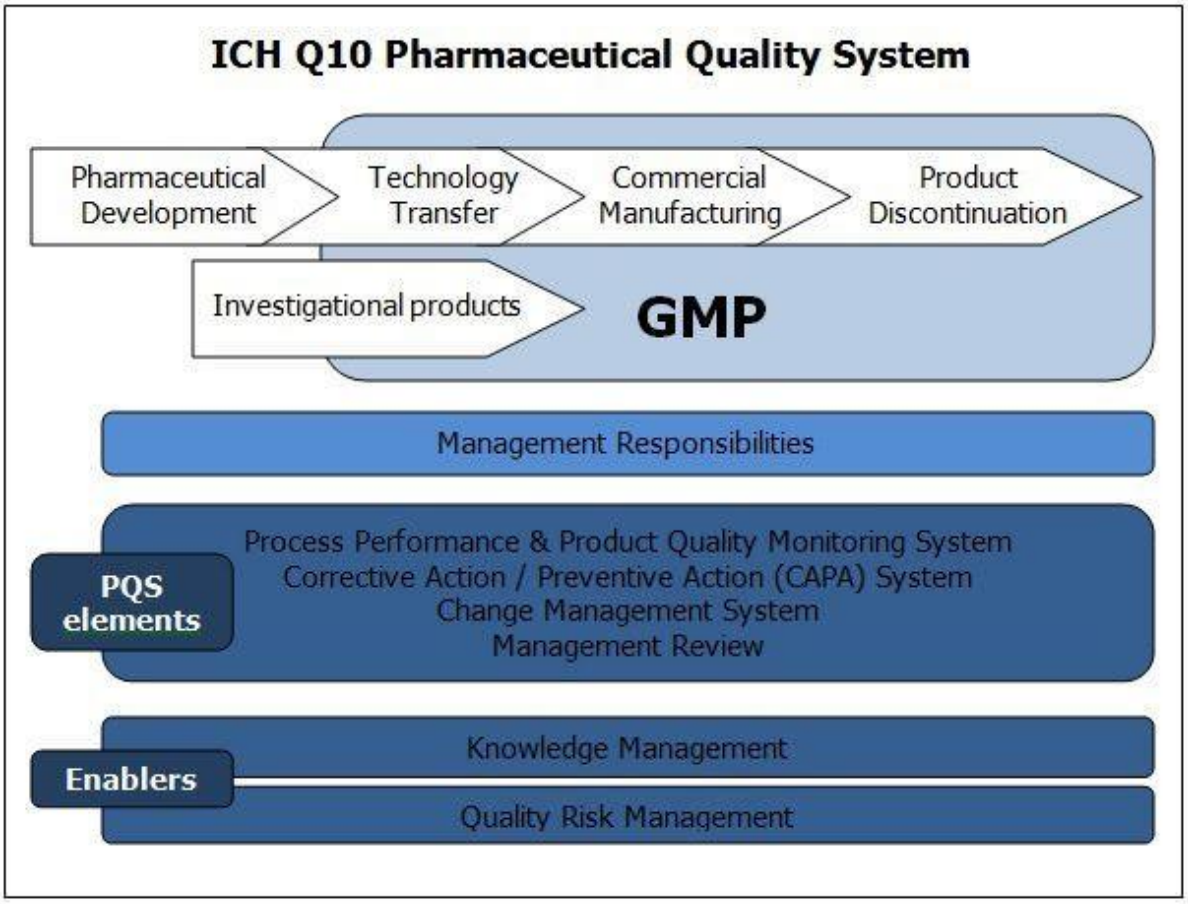


***Figure 2: ICH Q10 Pharmaceutical Quality System Model***

These elements are where the 'diamonds' lie – the decisions that significantly require the support of both QRM and KM. Examples are considered for each element:

- **Process Performance and Product Quality Monitoring (PP&PQM)**
  Impactful decisions are made when deciding on process equipment, process settings, testing and detection methods, or validation strategies. Containment, contamination, and cross contamination represent some of the risks that need to be understood and controlled. With established processes, there is typically a large body of knowledge (Knowledge Management) to inform these decisions. Such decisions are evidence based and this evidence is normally underpinned by good science. Occasionally novel processes, novel applications of processes, or novel products may result in a less certain knowledge base and the consequent need to analyse options using a risk-based approach.
  Early in the pharmaceutical product lifecycle, for example in product or process development, much may still be unknown or uncertain about the variability of processes, the causes of these variabilities, or the relationships between variables. The relationship between the critical to quality attributes of the product and process controls may be theoretical or assumed from prior knowledge. As the process development cycle progresses, this understanding is developed through modelling, experimentation, and measurement. However, product development and process design or construction are often conducted concurrently, and decisions may need to be made on process specifications, equipment procurement, control systems, etc before the supporting information is fully evolved. These now become risk-based decisions as the supporting knowledge is incomplete.

As an added complication, the decision-makers in these phases of the product life cycle are typically not the same people who manage the subsequent operation, nor those who justify and explain these decisions to regulatory authorities. Capturing the logic of these decisions within the Knowledge Management (KM) system is an important objective.

- **Change Management**

  Deciding whether to implement a change, while ensuring that there are no unintended consequences, can represent a significant decision in the PQS. Commonly, these decisions are based on accumulated evidence. For example, a decision to reduce sampling frequency or sampling points is typically based on analysing the reliability of existing evidence.

  However, ICH Q10 also advocates continuous improvement and innovation. True innovation often requires novel approaches. Innovative changes may lack direct evidence and can, therefore, represent decisions under uncertainty (risk). Such decisions are often made by a team with diverse expertise to ensure that all relevant information (knowledge) is considered. Change control processes typically require a high level of documentation recording the considerations in support of the change proposal. However, they often do not offer a complete perspective on the alternate considerations.

  These types of decisions may benefit from a formal systematic approach to assure that the value of the proposal, and all the alternative approaches, and supporting the evidence for each option is understood. This adds a clarity as to why the particular option was chosen, while providing evidence that alternatives were analysed and considered. It can also show that the values and objectives of the operation e.g., product quality was central to these considerations and that any risks were identified, monitored, and managed.

  This type of approach is particularly useful if the expected benefits of the change are not realised or if the decision has unintended consequences. What was known and understood at the time of the decision can help manage the hindsight bias that is often prevalent when reviewing such decisions.

- **Corrective & Preventive Action (CAPA).**

  Corrective actions are typically applied after an issue is detected. Issues that have an impact on supply can introduce another decision influencing factor – urgency. The need to act quickly can introduce an entire set of heuristics[1] and competing viewpoints into the decision-making process. If the issue has impacted product quality or a process control that influences product quality, then care is required to assess the available information and options in an objective way. Formal decision-making processes or tools can assist in the endeavour, balancing the competing objectives of urgency and accuracy, while ensuring that the decision is transparent and evidential.

  ICH Q9 strongly advocated the use of formal root cause analysis tools. While this author is not aware of any direct empirical evidence that the use of formal tools has improved the outcome and resolution of issues, her experience as an auditor concludes that it has certainly made it easier to review the comprehensiveness of the investigative process and to determine the influencing factors.

  ICH Q10 also encourages preventive actions and continual improvement. These are actions that reduce the *potential* for an unwanted event to occur or to improve a control. Deciding how to act in order to correct or improve processes governed by the PQS, without

[1] Heuristics are the strategies derived from previous experiences with similar problems. These strategies depend on using readily accessible, though loosely applicable, information to solve problems.



https://arrow.tudublin.ie/level3/vol15/iss2/18
DOI: https://doi.org/10.21427/yfw0-hy89

compromising the existing control, can require thoughtful and considered decision-making to determine the most appropriate course of action.

- **Management Review.**
  Management Review provides oversight of the PQS and is the forum for providing assurance that process performance and product quality is managed. Management must have confidence in the accuracy and reliability of the information reviewed, i.e. that it is reliable and that any decisions made are informed.
  This is a particularly important consideration given the modern management trend towards data visualisation. As organisations strive to get greater clarity on complex operations, there is a growing reliance on the reductive treatments of data as trends, graphs, charts, dashboards and other 'business intelligence' tools. Management Review is occasionally prone to concluding the state of control based on concise presentations of complex data or issues, sometimes without reference to the significance of the information in terms of reliability or context. While data visualisation is an important clarifying concept, the decision-maker is in danger of making subjective decisions despite the wealth of data available. While a little knowledge is a dangerous thing, a picture that paints a thousand words without the supporting detail may present an equal hazard.

These elements depend on the twin enablers - KM and QRM - to inform decision-making. QRM and KM inform decision making in different ways. Knowledge, information, or data offers the decision-maker a level of certainty and confidence when deciding. When much is known and understood, the KM system assures that the information is available, shared, and disseminated. It supports the decision with a weight of evidence, introducing objectivity into the process and, consequentially, the outcome. In an ideal world – information will be gathered to support all the alternatives. This information will be analysed, evaluated and assessed against the objectives of the decision makers. The best option will be obvious and will be selected. The enablers are inversely related, as knowledge grows risk decreases. [7]. (Fig 3) [8]. The journey from QRM to KM based decision-making should be mapped by a growing body of knowledge and an associated confidence in the accuracy of that information.

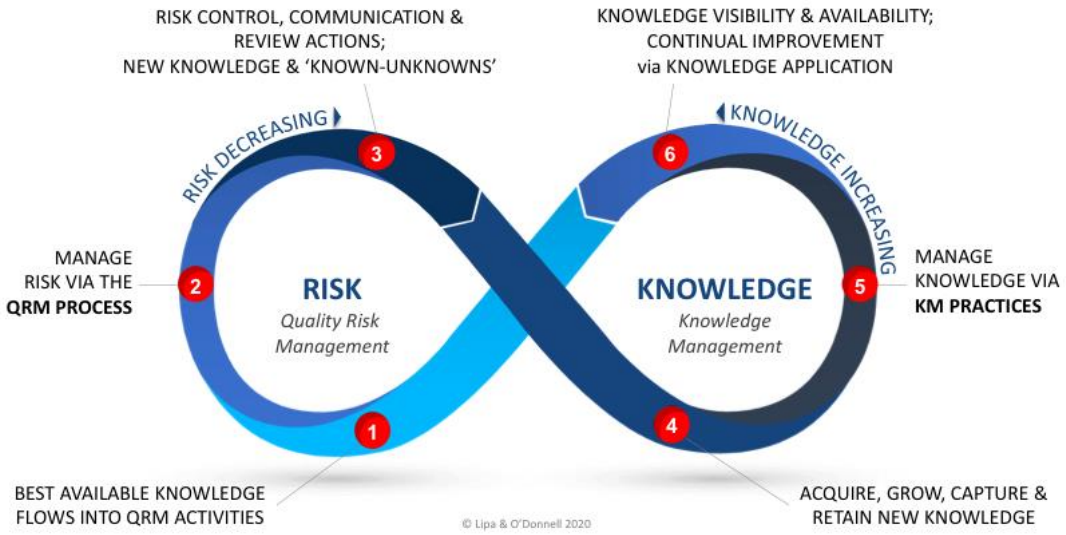


***Figure 3: Risk Knowledge Infinity Cycle as applied to ICH Q10 [8]***

However, many decisions are not made in ideal worlds – in reality, information may be sketchy, inadequate or unreliable, options may be limited, or constrained by time, resources or capacity – all of which mean that the ideal option does not clearly present itself and that some risk or uncertainty underpins each option. When less is known or understood, the QRM process helps the decision-maker. It can provide the tools to evaluate the limited information available, to predict potential outcomes, and to estimate the uncertainty associated with those outcomes.

In 1921, the Chicago based economist Frank H. Knight [9] distinguished between risk and uncertainty. Risk, he argued, was measurable. Risk exists when the outcome of a decision is unknown, but the chance of each outcome is measurable (probability). When throwing a dice, for example, the outcome is unknown – but the chances of throwing a six is measurable (1/6). When performing a risk assessment within the PQS, we analyse the various risks and assign a probability to their occurrence. Uncertainty applies when the decision-maker does not have information and therefore cannot determine the probability of each outcome.

When decisions are made under uncertainty, the accuracy of the outcome must be confirmed by subsequent (rather than predictive) measurement. The requirement to establish the effectivity of implemented CAPA actions or changes are driven by this requirement. The uncertain elements of the process or controls are identified and are then monitored and



https://arrow.tudublin.ie/level3/vol15/iss2/18
DOI: https://doi.org/10.21427/yfw0-hy89

measured and become understood. Information transforms uncertainty into knowledge. It is important that companies and regulators alike can identify and confirm that any uncertain outcomes of a required decision are verified to be appropriate, effective and correct.

*'Decision making is an art, only until the person understands the science'*

***Pearl Zhu, Decision Master: The Art and Science of Decision Making*** [10]

**What is a Good Decision?**

A simple answer might be that it is the one that results in a good outcome. However, good outcomes may also be achieved by good luck [11], and not necessarily reflect the wisdom of the decision-maker. Likewise, good decision-making does not prevent the possibility of a poor outcome. (*However, it must improve the chances that that will not happen.)*

Another explanation of a good decision might be that looking back, and given the information available at the time, the decision-maker would make the same decision. Hindsight is a powerful informer. The challenge with both explanations is that the decision-maker must wait to see if they were correct. While outcomes are the ultimate decider of the correctness of a decision, they can be a lagging measure.

Poor decisions invite a justifiable analysis of the options and information available at the time of the decision, highlighting the advantage of *transparency* in decision-making and the ability to demonstrate how decisions were made. Impactful decisions, particularly if complex and uncertain, may lead to poor outcomes irrespective of the thought and formality applied. Adjudicating the quality of decision-making by the *process*, rather than the outcome may be a more informative exercise. Demonstrating what was known at the time and the reliability of the information available to the decision-maker can be critical to defending poor outcomes.

When the decision has the potential to impact product quality or patient safety and there are uncertainties with the applied option, then indicators or monitors must be applied to signal, at the earliest possible opportunity, if the decision was incorrect or inappropriate. Pharmaceutical regulators have recently highlighted the increasing numbers of defective product on the market [12] . Whether this is connected to poor decision-making within these processes (or poor monitoring and control), is difficult to determine. It has resulted, however, to some discussion on the effectiveness of QRM and whether decisions relating to quality are adequately informed. [13]

A lack of formality in decision-making does not assist in the defence or understanding of these decisions. The previously mentioned concept paper on the perceived problems with the application of QRM notes that the industry struggles with formality and what is expected. A recently published survey of 12 pharmaceutical companies and 11 regulatory agencies noted that most operations *'had a system in place to enable documentation of major decisions, however, systems are used primarily to document outcomes rather than the process, while information from documentation is not always used, and feedback loops are not in place*' [14].

The previously mentioned Professor Howard, one of the founders of the discipline of decision analysis, developed a 'Decision Hierarchy' (Fig 4) [15] highlighting that when decisions are important or complex, then a rigorous approach should be adopted. Proven and formal decision-making processes or tools encourage consideration of the problem, the information and options available, and the uncertainties involved. They also provide a justification and record of how and why a decision was made. That there should be a high level of formality applied to important decisions within the PQS, is consistent with the QRM principles presented in ICH Q9:

- *The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient, and*
- *The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk*.

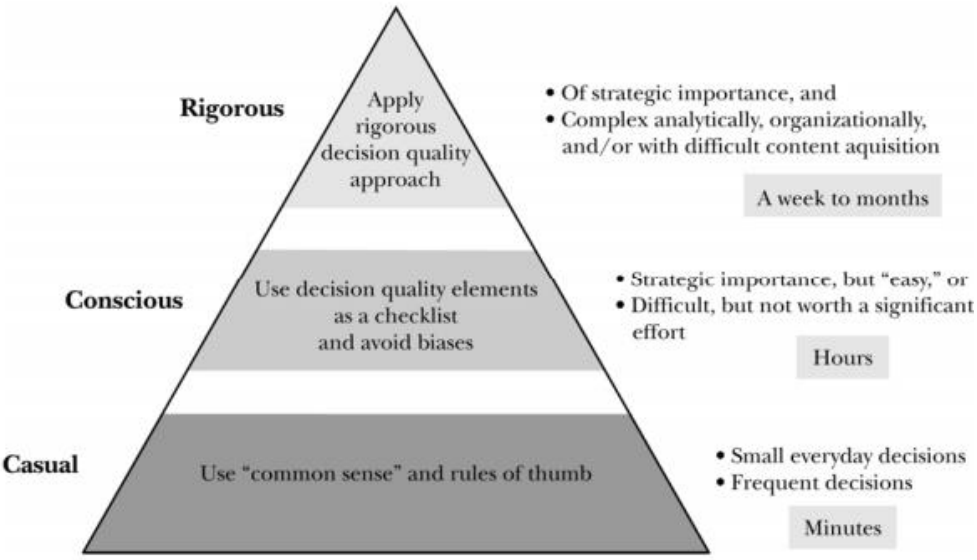


***Figure 4: The Decision Hierarchy (Howard, 2000)***



https://arrow.tudublin.ie/level3/vol15/iss2/18
DOI: https://doi.org/10.21427/yfw0-hy89

**Why formalise decision-making?**

Decisiveness is a quality that we have come to admire in leaders. It inspires those around them. As a result, leaders often have a bias for action and making quick decisions, occasionally ignoring data, expertise, or details that was available at the time.

Haste in decision-making can, in complex and critical situations, overlook important detail. Yet decisions are commonly time sensitive. To assure that all relevant information is captured and considered, and its reliability and significance understood, and that gaps in information are equally understood, formalising the decision-making can contribute. The industry has already seen the benefit of formalising root cause analysis (author's view) and the discipline and transparency it has delivered, even in time sensitive situations – formalising decision-making should have a similar effect.

These time-dependent situations are fraught with heuristics, including our human unwillingness to process large volumes of data. Complex problems require energy to resolve. Bounded rationality[2] is not uncommon when the information required to best inform a decision is too challenging to absorb, perhaps due to the complexity of the information, the ability of the information holder to communicate it, the ability of the decision maker to comprehend it, or the time and attention that can be spared to considering it [16]. Whatever the information constraints, the decision-maker consciously or unconsciously decides that the effort is excessive, and that the problem or solution does not require that level of rational attention. Heavy workloads often drive this approach.

Pharmaceutical manufacturing involves increasingly complex operations, with many processes, systems, controls, data, materials, conditions, variables, and relationships. Operations have moved from assuring process control by relying on personnel following procedures, to reliance on an elaborate interweave of people, computerised systems, automation, and data - all monitoring process variables.

Relationships among variables can be just as impactful as any variable in isolation. Much QRM is assessed one-factor-at-a-time, when sophisticated modelling may be required to fully understand these relationships. When issues present themselves or change is desirable, the

[2] Bounded rationality is the idea that rationality is limited, when individuals make decisions, by the tractability of the decision problem, the cognitive limitations of the mind, and the time available to make the decision.

underpinning information may not be simple or complete. Information can also be dynamic and change the understanding of the problem. It is not uncommon to note in regulatory audits that the problem statements of issues (defined early in the process) are not ultimately reflective of the assigned root cause (s), indicating that enhances understanding of the issue evolved as more complete information emerged.

As discussed, modern pharmaceutical operations are complex and the ability to coherently access and analyse a lot 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 [17] , 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. However, formulating data into knowledge and digital intelligence is a challenge. The need for data analytics in big data environments is growing. However, the skills of the data miners and those of the data users 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+ [3]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* [18]. Clemen & Reilly

A further consideration is the escalation processes that are often prevalent in PQS elements. Often the ultimate approver of a decision is high in the organisation and potentially further

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



https://arrow.tudublin.ie/level3/vol15/iss2/18
DOI: https://doi.org/10.21427/yfw0-hy89

from the detail of the problem. Formal decision-making processes typically offer structure to the information supplied to decision-makers and provide higher assurance that they are informed.

A 2015 study by the Project Management Institute [19] discovered that 47% of unsuccessful projects were impacted by poor decision-making. While this represented a small percent of overall projects, it was enough to encourage the organisation to prepare and publish *A Guide to the Project Management Body of Knowledge (PMBOK® Guide)* [20] detailing a formal 5-step framework to improve the effectiveness of decision-making. They noted a 74% improvement in outcomes when a formal decision-making process was in place[4]. They key success factors were:

- Ensuring that decision-makers had the correct information to make decisions
- That the decision makers were aligned with the overall strategy and goals
- That the decision-makers paid adequate attention to risk management

Of interest in this conclusion is the contribution of both knowledge management and risk management to the value of decision-making. Critical to decision making is knowing what is known and understanding the reliability of what is known, knowing what is not known and the risk with the unknown (uncertainty). The interconnected relationship between knowledge and QRM is explored in a detailed literature review in a paper published recently by Lipa, O'Donnell, & Greene [7].

KM can assist in creating access pathways to the correct, relevant, and current information. QRM can provide the means to assess the validity, reliability and integrity of that information.

These challenges may not be apparent to the decision-maker. In Europe, Qualified Persons (QP) are trained to evaluate, and critique data presented. However, this is not a universal skill among PQS decision-makers. Alignment is needed to assure that the data presented to the user, the decision-maker, is comprehensive and of value. Wang and Strong [21] noted that to improve data quality, data providers need to understand what that data means to the user.

However, as mentioned previously, data complexity invites a need to visualise and reduce information to a graph or chart. People can better understand complex data when presented with it in a visual form. Therefore, it is becoming increasingly common to present complex

[4] Note: This is not the first or most notable study to demonstrate this point. It is, however, current and in an industry that interacts significantly with pharmaceutical manufacturing and its decision making.

data as a visualisation. While these are useful communication tools, this reductive approach can occasionally obscure important detail and may fail to deliver insight. The hazards in this condensed viewpoint must be considered and managed in the process of important decision-making.

Finally, there is the fact that one decision, generally, leads to another – frequently decisions are sequential. An early decision is made with the knowledge available at that time and, as a result, locks the decision maker into a course of action. The next decision choice is fated by the first. This 'Sunk Cost' concept [22] of decision commitment is occasionally exemplified in a PQS through poor quality control data. Despite evidence showing the unreliability of a committed test method, there is often a reluctance to improve the method, or to change it altogether, to a more reliable alternative. Decisions should be viewed and managed strategically, keeping the ultimate objectives in mind. However, this too, introduces complexity.

ICH Q10 is clear that it welcomes improvements of this type, although there are significant regulatory challenges with the approval complexity of post-approval changes [23].

**Should all decision-making be formal?**

In the first of a series of monographs published by this research unit (the Pharmaceutical Regulatory Science Team, TU Dublin) [24] the FDA's Gregg Claycamp highlighted the importance of controlling subjectivity in decision-making. He advocated that a structured approach created opportunities for identifying and controlling subjectivity, especially in relation to risk-based decision-making. However, he also advised that such formality was not required for all decision-making but could be limited to a small number of major decisions, where 'transparency, consistency and coherence' among multiple objectives' is required.

Formality can assist with organising the required information (or gaps) and assessing its reliability. It can assist with assessing and managing the uncertainty with outcomes. It is not required for ALL decisions - It must be recognised that formal decision-making takes time and not all decisions justify this effort. If, however, a decision is clear cut i.e., one option is clearly and obviously superior – then this level of effort is not required. If, however, there is a degree of uncertainty with the options available and the decision might change if more was known or understood – then the level of formality may be justified. Formality is useful when the consequences are important, the stakes are high, and the outcomes uncertain. A key question



https://arrow.tudublin.ie/level3/vol15/iss2/18
DOI: https://doi.org/10.21427/yfw0-hy89

used by NASA [25] when deciding whether to apply a formal decision process to a decision is *'Is there a net benefit to reducing uncertainty?'*, implying can we afford to get it wrong?

NASA typically apply four criteria to the decision to use formal processes. These are:

- **High Stakes**
  Formal process is applied when the outcome of the decision has the potential to significantly impact costs, safety, or important objectives.
  In the case of pharmaceutical manufacturing operations, a decision outcome with the potential to significantly impact product quality, patient safety, ability to supply, or regulatory compliance should consider the use of formal processes.

- **Complexity**
  If the consequences of the various options are challenging to understand without detailed analysis, then formality should be considered. There have been several approaches to assessing complexity in manufacturing environments [26] [27] and they consider factors such as human factors, machine complexity, interfaces, task complexity, process and control systems, capacity, urgency, information cues, etc.

- **Uncertainty**
  If there is a level of uncertainty associated with some of the inputs to the decision e.g. insufficient data or a lack of reliable information, such that the uncertainty affects the assessment of the alternatives, creating a risk that needs to be managed. Decision situations may involve more than one source of uncertainty. The larger the number of sources of uncertainty, the more complicated the decision [18].

- **Multiple Attributes**
  An attribute is a term in decision analysis synonymous with objective. In a typical scenario time, cost, resources, safety, quality are all potential objectives, which may on occasion compete for priority. The greater the number of attributes, the greater the need for formal analysis. Formal techniques will usually require that an attribute scale be agreed early in the process, in order to priorities or rank these competing attributes. In pharmaceutical manufacturing, quality must be a high priority – but in practical terms cannot come at ANY cost.
  Common examples include the confidence and assurance that extensive validation data can provide versus the cost of generating that assurance; the need to complete an investigation to root cause versus the need to implement a timely solution; the need to keep the cost of medicine affordable versus the expense of quality control and assurance. Modern operations balance the need for progress and innovation with protecting quality. To succeed the decision-maker need to understand these conflicts and balance the trade-offs. This can be assisted through improved decision-making.

- **Diversity of Stakeholders**
  The decision-making process also requires that the values of external 'interested parties' i.e. stakeholders are understood, prioritised and included. A stakeholder is an individual or organisation that is materially affected by the outcome of a decision. In pharmaceutical decision-making this may include regulatory authorities, clinicians, purchasers and patients (though perhaps not in that order). These stakeholders may not necessarily have the same values nor place them in the same order as the decision maker.

Developing objectives hierarchies is a key tool in structured decision-making. It develops the criteria against which alternatives will be evaluated. Therefore, criteria should be clear and unambiguous i.e. SMART (Specific, measurable, accurate, relevant, time-based).

Earlier in this paper, the author reviewed the elements of ICH Q10 and discussed how it represents the parts of the PQS where significant decision-making (or diamonds) occurs. One element is change control. A change decision may represent an economic opportunity to the organisation. The position of economic factors relative to product quality in the hierarchy of values in the organisation should assist all decision-makers make appropriate decisions

It should be noted that in a pharmaceutical lifecycle, the values of these stakeholders may also change. For example, when a product is new, a patient may place a high value on safety. As the product becomes established and measured data provides assurance of safety, this may become less important to this stakeholder and another factor, such as price, may become more significant in rank. However, for the regulatory authority, safety may continue to be a high priority. Likewise, if a new technology is used in a process, a regulatory authority may place a high initial value on reliability. As this factor is assured with real time measurement, this may become less of a priority relative to another value to this stakeholder. Acquired knowledge is a key driver of the iterative reprioritisation of values.

Finally, there are often different perspectives when looking at the same data or information. Decision makers frequently find themselves facing different opinions or perspectives on the required actions, based on the same information base. This may be because experts or advisors bring different experience or values, or it could also be due to different competencies, attitudes or risk appetite. Understanding the drivers for those interpretations can be critical to assessing the advice. Even when there is a common alignment on information, there may be diversions on the impact of even small changes on the situation.



https://arrow.tudublin.ie/level3/vol15/iss2/18
DOI: https://doi.org/10.21427/yfw0-hy89

Table 1, developed by the author, illustrates how criteria for significant decision-making within a pharmceutical manufacturing operation could be aligned with the NASA criteria and serve to develop a guideline for the application of formality in decision-making within the PQS.

| High Stakes | Complexity | Uncertainty | Multiple Objectives | Diverse Stakeholders |
|---|---|---|---|---|
| - Impacts a Critical Control Point or Key Parameter associated with a Critical to Quality Attribute<br>- Impacts a test method designed to assure product quality and safety<br>- Impacts a Regulatory Requirement or commitment<br>- Impacts ability to supply | - Involves a task/step, method recognised as complex or critical<br>- Impacts more than one process and/or control system<br>- The change has the potential to severely disrupt operations and supply if incorrect | - Alternatives are not supported by reliable accurate data<br>- Change would significantly reduce confidence in state of control | - Decision is highly coupled with another attribute e.g., time, resources<br>- A negative outcome could threaten the objective of the organisation, including product quality and patient safety | - Decision is part of a regulated system e.g., PQS<br>- Decision affects a regulatory filing<br>- Decision includes or affects a third part e.g., outsourced activity |

***Table 1: Examples of Factors affecting Decision Formality***

**What formal models could be used?**

There are a variety of models designed to support decision-making. This paper does not focus on the various methods that could be used e.g., decision trees, influence diagrams, Multi-Criteria Decision Making, or NASA's Risk Informed Decision Making. This will be the topic of future work. However, all these methods serve to document why a particular alternative was chosen above others and they serve as a **decision audit trail**.

NASA's Risk Informed Decision Making process serves as a decision audit trail and it concludes with a 'decision report'. Table 2 gives an outline of a NASA decision report to demonstrate the value of structure and formality, and to illustrate the type of information trail it could provide. This consolidation of information improves access, in the event of review or audit. It records the information and knowledge that was available to support each decision alternative and evaluates the reliability and sensitivity[5] of that information. It demonstrates how the uncertainties with options was assessed using risk analysis. It justifies the exclusion

[5] Sensitivity: How variables are affected based on changes in other variables

of some options with supporting rationale. It informs those affected by the decision outcome of the outstanding uncertainties and of the performance measures required to monitor the effectiveness of the chosen outcome.

This report can be part of the knowledge base for the organisation and be included in the knowledge management framework.

| | |
|---|---|
| **Executive Summary** | This summary describes the problem to be solved and a general overview of each of the alternatives.<br>It identifies the organizations and individuals involved in the decision-making process and summarizes the process itself, including any intermediate downselects[6].<br>It presents the selected alternative and summarizes the basis for its selection. |
| **Technical Basis for Deliberation** | This section includes the following:<br>• **Technical Summary:** This section describes the problem to be solved and a general overview of each of the alternatives.<br>• **Top-level Requirements and Expectations:** This section contains the top-level requirements and expectations identified in the early steps of the decision-making process. In cases involving diverse stakeholders, a cross reference between expectations and stakeholder may be presented.<br>• **Derivation of Performance Measures**: This section shows the derivation of performance measures for the decision e.g., the objectives hierarchy, a table mapping the performance objectives to the performance measures. When constructed scales are used, the scales are presented.<br>• **Decision Alternatives:** This section shows the compilation of feasible decision alternatives and rationales for the pruning of alternatives prior to risk analysis. Alternatives that are retained for risk analysis are described. This section also identifies any imposed constraints on the allowable performance measure values, and a map to the originating top-level requirements and/or expectations.<br>• **Risk Analysis Framework and Methods:** This section presents the overall risk analysis framework and methods used in the process. Performance parameters are identified for each alternative.<br>• **Risk Analysis Results:** This section presents the risk analysis results and includes:<br>  • **Scenario descriptions:** For each alternative, the main scenarios identified by the risk analysis are presented.<br>  • **Performance measure Probability Density Functions (pdfs)**: For each alternative, given the presence of uncertainty, the actual outcome of a particular decision alternative will be only one of a spectra of potential outcomes for that choice and will depend on the occurrence, non-occurrence, or quality of occurrence of intervening events. Therefore, risk analysts model each significant possible outcome, accounting for its probability of occurrence, in terms of the scenarios that produce it. This produces a distribution of outcomes for each alternative - probability density functions |

[6] Downselect: to narrow the field of choices, especially, to choose a supplier from candidates under consideration.



https://arrow.tudublin.ie/level3/vol15/iss2/18
DOI: https://doi.org/10.21427/yfw0-hy89

| | |
|---|---|
| | (pdfs). All scenarios are presented along with a discussion of any significant correlation.<br>• **Imposed constraint risk:** For each alternative, the risk with respect to imposed constraints is presented, along with a discussion of the significant drivers contributing to that risk.<br>• **Supporting analyses:** For each alternative, uncertainty analyses and sensitivity studies are summarized.<br>• **Risk Analysis Credibility Assessment:** This section presents the credibility assessment performed |
| **Performance Commitments:** | This section presents the performance measures, ranking and risk tolerances used to develop the performance commitments during the decision process, with accompanying rationale.<br>It tabulates the resultant performance commitments for each alternative. |
| **Deliberation:** | This section documents the issues that were deliberated during decision making process.<br>• **Organization of the deliberations:** The deliberation and decision-making structure is summarized, including any downselect decisions and proxy decision-makers.<br>• **Identification of the contending decision alternatives:** The contending alternatives are identified, and rationales given for their downselection relative to the pruned alternatives. Dissenting opinions are also included.<br>• **Pros and cons of each contending alternative:** For each contending alternative, its pros and cons are presented, along with relevant deliberation issues including dissenting opinions. This includes identifying violations of significant engineering standards, and the extent to which their intents are met by other means.<br>• **Deliberation summary material:** Briefing material, etc., from the deliberators and/or risk analysts to the decision |
| **Alternative Selection:** | This section documents the selection of an alternative<br>• **Selected alternative:** The selected alternative is identified, along with a summary of the rationale for its selection.<br>• **Performance commitments:** The finalized performance commitments for the selected alternative are presented, along with the final performance measure risk tolerances and performance measure ordering used to derive them.<br>• **Risk list:** The risk list for the selected alternative is presented, indicating the risk-significant conditions extant at the time of the analysis, and the assessed impact on the ability to meet the performance commitments.<br>• **Decision robustness:** An assessment of the robustness of the decision is presented. |

***Table 2: Example of Content in NASA Decision Report [25]***

## Conclusion

Pharmaceutical regulations currently require a degree of evidence to support decision-making e.g., who made the decision, the date, the supporting evidence, etc. Significant decisions are made within the PQS elements and these require accountability and traceability. These are the 'diamonds' which assure product quality. These 'diamonds' are not in the QRM process flow chart from ICH Q9, they are within the PQS elements that QRM and KM support.

Diamonds are one of the strongest materials on earth, due to the strength of the supporting bonds. Significant PQS decisions should be equally strong, supported by the twin enablers of QRM and KM.

Diamonds are also valuable and (to stretch an analogy, even further) there is also value in improved formality around critical decisions within the PQS. For these types of decisions, having a structure to organise and understand the reliability of the supporting information, to clarify and detail the range of options available, to demonstrate why and how an option was taken, can only contribute positively to the accuracy, transparency, and traceability of these decisions. With complex decisions, this will also add clarity to the uncertainties or risks that should be subsequently monitored to assure an accurate outcome, or, inversely, it will inform the signals that should be applied for early indications of concerns.

Pharmceutical operations should seek to identify the type of decisions that would benefit from formality and may find the criteria used by NASA useful – high stakes, complex, a degree of uncertainty, multiple objectives and stakeholders. This work – looking to the stars to resolve diamonds - will be continued by this author.

**Bibliography**

[1] Expert Working Group, ICH, "ICH.ORG," 13 Nov 2020. [Online]. Available: https://database.ich.org/sites/default/files/Q9-R1_Concept%20Paper_2020_1113.pdf. [Accessed 28 Dec 2020].

[2] ICH, "ICH Q9: Quality Risk Management," International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), 2005.

[3] F. B. Gilbreth and L. M. Gilbreth, Industrial Efficiency, American Society of Mechanical Engineers, 1921.

[4] P. C. Nutt, Why Decisions Fail: Avoiding the Blunders and Traps That Lead to Decision Debacles, Berrett-Koehler Publishers, 2002.

[5] R. Howard, "Decision Analysis, Applied Decision Theory," in *Proceedings of the Forth International Conference on Operational Research*, 1966.

[6] ICH, "Q10: Pharmacutical Quality System," International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), 2008.



https://arrow.tudublin.ie/level3/vol15/iss2/18
DOI: https://doi.org/10.21427/yfw0-hy89

[7] M. J. Lipa, K. O'Donnell and G. A, "Managing Knowledge and Risk – A Literature Review on the Interdependency of QRM and KM as ICH Q10 Enablers," *Journal of Validation Technology,* vol. Aug, 2020.

[8] M. J. Lipa, K. O'Donnell and A. and Greene, "Introducing a Model and a Framework to Unify the Pharmaceutical Quality System Enablers Quality Risk Management & Knowledge Management".

[9] F. H. Knight, Risk, Uncertainty and Profit, 1921.

[10] P. Zhu, Decision Master: The Art and Science of Decision Makin, BookBaby, 2017.

[11] C. Vick, W. Edwards, I. Kiss, G. Majon and M. Toda, "What Constitutes a Good Decision?," *Acta Psychologica,* vol. 56, pp. 5-27, 1984.

[12] K. O'Donnell, "QRM in the GMP Environment: Ten Years On—Are Medicines Any Safer Now? A Regulators Perspective," *Journal of IVT,* no. Dec, 2015.

[13] K. O'Donnell, "QRM in the GMP Environment beyond 2020: What Should we strive for?," in *An Audience with the International Regulators in the Manufacture of Medicine: QRM and KM*, TU Dublin, 2018.

[14] M. Bujar, N. McAuslane, P. Connelly and S. Walker, "Quality Decision-Making Practices in Pharmaceutical Companies and Regulatory Authorities: Current and Proposed Approaches to Its," *Therapeutic Innovation & Regulatory Science,* no. May, 2002.

[15] R. A. Howard, "The Foundations of Decision Analysis Revisited," in *Advances in Decision Analysis*, Cambridge University Press, 2007, pp. 32-56.

[16] H. A. Simon, Administrative Behaviour 3rd Ed, MacMillan, 1986.

[17] J. Birkinshaw and J. Cohen, "Make Time for Work that Matters," *Harvard Business Review,* vol. Sept, 2013.

[18] R. T. Clemen and T. Reilly, Making Hard Decisions 3rd Ed, South Western CENGAGE Learning, 2014.

[19] Project Management Institute, "Capturing the Value of Project Management through Decision Making," PMI, 2015.

[20] Project Management Institute (PMI), PMBOK® Guide – Sixth Edition, PMI, 2017.

[21] R. Y. Wang and D. M. Strong, "Beyond Accuracy: what Data Quality Means to Data Consumers," *Journal of Management Information Systems,* vol. 12, no. 4, p. 5–33, 1996.

[22] H. Garland and D. Conlon, "Too Close to Quit: The Role of Project Completion in Maintaining Commitment," *Journal of Applied Social Psychology,* vol. 28, no. 22, pp. 2025-2048, 1998.

[23] E. Ramnarine, A. Vinther, K. Bruhin, C. Tovar and M. Colao, "Industry One-Voice-of-Quality (1VQ) Solutions: Effective Management of Post-Approval Changes in the Pharmaceutical Quality System (PQS)—through Enhanced Science and Risk-Based Approaches," *PDA Journal of Pharmaceutical Science and Technology,* vol. 74, no. 4, pp. 456-467, 2020.

[24] G. Claycamp, "Controlling Subjectivity in Risk Decision Making: the benefits of Multi-Criteria Decision Analysis," in *An audience with international regulators in the manufacture of medicines: quality risk management (QRM) and knowledge management (KM*, Dublin, 2018.

[25] NASA, "Decision Analysis," in *Systems Engineering Handbook*, 2007.

[26] S. Mattsson, P. H. U. Gullander, G. Backstrand, A. Fasth and A. Davidson, "Testing Complexity Index – a Method for Measuring Perceived Production Complexity," in *45th CIRP conference on Manufacturing Systems*, 2012.

[27] G. W. E. Frizelle, "Measuring complexity as an aid to developing operational strategy," *International Journal of Operations & Production Management,* vol. 15, no. 5, pp. 26-39, 1995.

[28] H. A. Simon, Adminstrative Behaviour, Free Press, 1947.

[29] H. A. Simon, The New Science Of Management Decision, Prentice Hall, 1997.

[30] Harvard Business Review, "Good Data Won't Guarantee Good Decisions.," April 2012. [Online]. Available: https://hbr.org/2012/04/good-data-wont-guarantee-good-decisions. [Accessed 21 Aug 2020].

[31] K. O'Donnell, "Demonstrating the Effectiveness of the PQS from a QRM Perspective," in *PDA Workshop -The Practical Implementation of QRM*, Cork, Ireland, 2019.



https://arrow.tudublin.ie/level3/vol15/iss2/18
DOI: https://doi.org/10.21427/yfw0-hy89