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An Audience with International Regulators in the Manufacture of Medicines 2018: Quality Risk Management (QRM) and Knowledge Management (KM)

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DIT Academic Press



An Audience with International Regulators in the Manufacture of Medicines

*Quality Risk Management (QRM)
and Knowledge Management (KM)*



Anne Greene, Kevin O'Donnell and Nuala Calnan *(Editors)*



DIT Academic Press

An Audience with International Regulators in the Manufacture of Medicines

*Quality Risk Management (QRM)
and Knowledge Management (KM)*

A monograph

based on a seminar organised by The School of Chemistry & Pharmaceutical Sciences, Dublin Institute of Technology, with Regulatory Science Ireland, and with The Health Products Regulatory Authority

3 October 2018



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Message from Professor Brian O’Neill, Director of Research & Enterprise and Dean of the DIT Graduate School

The DIT has a long tradition of scholarly research and publishing from among its various Schools and Colleges. It is inevitable now, as the pace and intensity of research, scholarship and innovation increases, that we need to take advantage of new modes of dissemination to a global user. An Academic Press which combines the best of traditional publishing modes in the sciences and humanities, and which makes good use of online publishing tools and repositories, is a very welcome development as the DIT moves with its two partner Institutes to form the Technological University Dublin in 2019. We look forward to forging a unique TUDublin Academic Press in the future which emphasises access to scholarship excellence for the public good.

Message from Professor Michael Devereux, Director of the College of Science & Health, DIT

The DIT, together with the Health Products Regulatory Authority and Regulatory Science Ireland, was delighted to host ‘An Audience with International Regulators’ in our Aungier Street Campus on 3 October 2018. The event brought together some of the world’s thought-leaders to discuss the real value that can be delivered by practicing effective Quality Risk Management in the manufacture of medicines, not just as a compliance requirement, but also as a means to reduce risk to patients and to the industry. In addition, some exciting research outputs in the fields of Quality Risk Management and Knowledge Management generated through DIT’s industry-based research postgraduate programme were also presented. The industry-based postgraduate programme enables interested qualified individuals from the Biopharmaceutical sector to remain in full-time employment whilst pursuing a research postgraduate award up to PhD level based on a topic that adds value to their organisations.

This Monograph, the first to be published by our Academic Press, heralds DIT’s major development as we merge with our partner Institutes in Tallaght and Blanchardstown to form Ireland’s first Technological University.

Message from Professor Declan McCormack, Head of School, Chemistry and Pharmaceutical Science, DIT

The School of Chemical and Pharmaceutical Sciences is delighted to support this worthy initiative to document the debate and outcomes from the recent audience with the regulators. Since its establishment, the Pharmaceutical Regulatory Science Team (PRST) under the stewardship and direction of Professor Anne Greene, has grown from an initial tenet of the importance of risk management in good manufacturing practice to a high performing international network which draws together realworld expertise and leadership in the life sciences, national pharma regulators and thought leaders within the spirit and rigour of academic enquiry.

The expertise and experience within PRST are truly remarkable with regulators (Dr Kevin O’Donnell), experts (Dr Nuala Calnan) and industry practitioners (Dr Paige Kane, Dr Ian Jones and Dr Kelly Waldron) who complement so well the academic expertise within the DIT. As the discipline of Regulatory Science emerges as an essential element to the development and production of new medicines and new medical technologies and therapies it is essential that there is a forum and a conduit for scientific debate to ensure that every policy

developed and every decision taken is in the best interest of the patient. As a founding member of Regulatory Science Ireland, DIT understands the importance of this body as a mechanism to ensure that rigour and excellence are integral to a patient-focussed approach to new research and developments. This monograph provides a firm foundation for future debates and we look forward to contributing further to the discipline, most particularly through our current cohort of work-based PhD students. The School is always seeking bright and inquisitive minds and if regulatory science is an area which instils passion then please come forward to us and together we can look to ways to communicate and collaborate as we seek to add to the knowledge base of the discipline.

Foreword

On the ten-year anniversary of ICH Q10 ‘Pharmaceutical Quality System’ the Dublin Institute of Technology (DIT) and the Health Products Regulatory Authority (HPRA) are delighted to jointly present this monograph based on the presentations delivered at our joint seminar ‘An Audience with International Regulators’ chaired by Dr Mike Morris, HPRA (retired) held on 3rd October 2018 in the DIT.

ICH Q10 describes a model for an effective quality management system for the pharmaceutical industry which advocates the use of Knowledge Management (KM) and Quality Risk Management (QRM) as enablers to achieve its 3 key objectives of: Achieving Product Realisation; Establishing and Maintaining a State of Control; Facilitating Continual Improvement. It proposes that QRM and KM would provide the means for science-based and risk-based decisions related to product quality.

In the last 10 years it has been our privilege to work with regulatory and industry thought-leaders within the fields of QRM and KM. While many publications on both topics have been produced in the decade, they are usually treated as separate enablers. Our vision for the seminar and this resulting monograph was to explore how QRM and KM work together to enhance our decision-making with respect to pharmaceutical product quality.

The monograph begins with regulators’ perspectives, opening with Dr Gregg Claycamp from the FDA exploring how to control subjectivity in risk decision-making and the benefits of multi-criteria decision analysis. This is followed by an article by Dr Kevin O’Donnell from HPRA which examines the state of QRM in the GMP environment and what might be achieved beyond 2020. Among many other suggestions Kevin puts forward the idea of developing a certification programme for QRM practitioners, and this is the very topic of the third paper where Ghada Haddad presents her research on developing a framework for building QRM Competencies. The focus then shifts to KM as Dr Paige Kane presents a blueprint for managing knowledge as an asset across the product lifecycle. Then, bringing QRM and KM together, Dr Magda Bujar explores frameworks for improving quality decision-making practices for building institutional knowledge management (KM). The role of the two enablers acting together is further advanced in a thought-provoking article by Prof. Frank Hallinan who imagines what a Pharmaceutical Quality System for Advanced Therapies might look like.

The monograph then concludes with an overview of current developments in Japan and a newly proposed guideline from ICH titled ICH Q14 – Analytical Procedure Development - based on a presentation given by Dr Yukio Hiyma, a well known retired Japanese regulator. It is appropriate that we should conclude with a paper by Dr Hiyma, who is leading the work on ICH Q14 as well as the development and revision of Q2(R1) guideline on Analytical Validation, because back in 2008, when ICH Q10 was being written, Yukio played a key role in ensuring QRM and KM were identified as enablers to a PQS, as envisaged by ICH Q10. While QRM may have advanced significantly since then, we have to thank him and the Q10 team for their insightfulness in ensuring KM was also identified as an enabler.

On behalf of all the authors and the editorial team, we hope you enjoy this monograph and that it will encourage further dialogue and exploration of the interaction between both enablers going forward.

Anne Greene and Kevin O’Donnell

December 2018

Acknowledgements

This first Monograph from DIT Academic Press is a response to the growing need for an accessible forum for scholar-researchers and their associates to disseminate their field-specific knowledge on-line to a wider readership. It is a natural progression from the first DIT open access journal *Level3* in 2003 and the development of the Arrow Repository in 2008. DIT Academic Press is a complementary and supportive publication mode for the many DIT staff who publish journals, books and conference proceedings both through Arrow and through other fora. The initial Scientific Board – Dr Anne Murphy, Higher Education Policy Research Unit, Directorate of Research and Enterprise; Dr Brendan Devlin, College Librarian, Kevin Street Campus; Ms Yvonne Desmond, Library Systems Development Unit, and Dr K.C. O’Rourke, Digital Campus Architect - acknowledge the support of DIT colleagues Professor Anne Greene and Dr Nuala Calnan in the College of Science and Health particularly, the Health Products Regulatory Authority (HPRA), Regulatory Science Ireland (RSI) and the contributor-authors, in generously providing the proceedings of their industry-related seminar *An Audience with International Regulators in the Manufacture of Medicines - Quality Risk Management (QRM) and Knowledge Management (KM)* held on 3 October 2018 as the content of this first DIT Academic Press publication.

Author Profiles

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Dr H. Gregg Claycamp, M.S., PhD., is currently a **Senior Biomedical Research Scientist, Risk Analysis and Decision Analysis in the FDA Center for Veterinary Medicine**. He provides R&D leadership in risk management, particularly risk analysis and decision analysis for human health risks from food, animals and drugs, and risk-based decision-making for drug reviews. Dr Claycamp's history in risk analysis and quality risk management including serving as the regulatory rapporteur for the Final International Conference for Harmonisation Guideline "ICH Q9: Quality Risk Management."

Kevin O'Donnell, PhD - HPRA

Dr O'Donnell is the **Market Compliance Manager at The Health Products Regulatory Authority** in Ireland. He is responsible for a number of compliance-related and market-surveillance programmes at HPRA such as the quality defect and recall programme and its sampling and analysis activities. Kevin is also a senior GMP Inspector at the HPRA.

Ghada Haddad - PRST, DIT PhD Candidate - MSD

Ghada Haddad is the **Executive Director, Global cGMP Compliance and Auditing Organisation at MSD**. She holds a chemistry degree and an MBA. She has over 18 years of experience working in the Biotech and Pharmaceutical industries in the areas of Quality Risk Management (QRM), Quality Systems and Regulatory, including research, management (people and projects), process development, auditing, regulatory agency inspection, change control and validation. Her experience in Quality Risk Management (QRM) includes deploying global QRM programmes, training others in the concepts and tools, and on integration of QRM into Quality Systems. She is also a faculty member for PDA's Training and Research Institute and a Science Advisory Board member.

Paige Kane, PhD, - MSD

Dr Paige Kane graduated with a PhD from the DIT in October 2018 on the topic of the ICH Q10 Enabler of Knowledge Management. Paige is employed full-time with MSD as a Director in the MMD Knowledge Management Center of Excellence, joining in 2016 from Pfizer (Wyeth/Genetics Institute). She is a regular industry speaker with over 25 years' experience in biopharmaceuticals, spending the past 11 years leading KM programmes and approaches for the Pharmaceutical Industry. Prior to KM, she led Quality Systems Groups (Change Control, Document Management, Computer/Equipment Validation and Data Integrity) and new facility start-ups in the US and Ireland, with prior compliance experience across GLP/GCP/GMP areas. Dr Kane is a co-editor of, and contributor to, '*A Lifecycle Approach to Knowledge Excellence in the Biopharmaceutical Industry*' (2017).

Magda Bujar, BSc, MSc, PhD - CIRS

Dr Magda Bujar is a Project Manager at CIRS. She received her undergraduate degree in Biochemistry from the University of Bristol, a Master of Science in Biochemical Engineering from University College London, and a Doctor in Philosophy from the University of Hertfordshire.

At CIRS, Magda's scope of responsibilities covers supporting the Global Development and the Health Technology Assessment Research programmes, as well as coordination of *ad hoc* special projects with regulatory authorities, pharmaceutical companies and other research organisations. She has authored and co-authored a number of CIRS Research and Development briefings, books and journal articles, focusing on various aspects of regulatory and reimbursement science, including benchmarking of processes, alignment and quality of decision-making.

Frank Hallinan, PhD - UCC

Professor Frank Hallinan is a biopharmaceutical operations expert with many years industry and Regulatory Agency experience. He is the founder-owner of Quality System Support, a consultancy focused on providing support to pharmaceutical companies in the Quality Systems area. Frank graduated in Biochemistry from UCC, Ireland and received his PhD from the University of Southampton, UK.

After some years in biomedical research Frank worked with Schering-Plough in development, quality and regulatory functions for over eleven years. He was CEO of the Irish Medicines Board from 1998-2002 during which period he was responsible for a number of new developments within the Agency including overseeing the Agency taking responsibility as national competent authority for medical devices. He joined Wyeth Biopharma in 2002 to head-up the Quality Unit at their Grange Castle facility subsequently worked in Pfizer Corporate Quality in Collegeville, PA, and as SVP, Global Head of Quality with Jazz Pharmaceuticals. He founded Quality System Support in 2012.

Nuala Calnan, PhD, DIT PRST - BioPharm Excel

Dr Calnan has over twenty years experience in the biopharmaceutical industry across operations, new product introduction, facility start-up and manufacturing. Nuala's current focus is on the integration of Knowledge Excellence, Operational Excellence, and Cultural Excellence in delivering enhanced quality outcomes for the patient. Nuala works across the BioPharma and Medtech industries, as well as with service providers to these industries, delivering research, consultancy and training that drives innovation. She works closely with industry in assisting organisations to deliver quality excellence, designing metrics that matter to the patient and the business, good data governance programmes and implementing behaviour-based quality through cultural excellence programmes. She is currently a member of the team conducting research on behalf of the FDA examining the role of Quality Metrics in driving enhanced quality performance. Nuala co-leads the ISPE Quality Culture Team that published the recent ISPE Cultural Excellence Report and the ISPE/ PQLI Task Team on Knowledge Management. She is also currently an Adjunct Research Fellow with the Pharmaceutical Regulatory Science Team (PRST) at the DIT, Ireland, where she teaches and leads a number of patient-focused regulatory science research projects at Masters and PhD levels.

Yukio Hiyama, PhD - MHLW

Dr Hiyama is a visiting (retired) Scientist at the National Institute of Health Sciences (NIHS), Ministry of Health, Labour and Welfare, Japan. He leads MHLW's study groups to draft GMP-related guidance and to propose their regulatory frameworks. He led an industry-government human science project on evaluation methods for pharmaceutical development and manufacturing control. He has been involved in the ICH discussion for Q8, Q9 and Q10. He is still active in reviewing new drug applications and in participating in JP committees as PMDA's external expert.

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1 — Controlling subjectivity in risk-based decision-making: the benefits of multi-criteria decision analysis.¹

H. Gregg Claycamp, US Food and Drug Administration

1. Introduction

Risk managers are ultimately charged with making risk-informed decisions to accept, mitigate or control risks to the patient. In quality risk management (QRM), risk-informed decisions rely partly on risk assessments using quality endpoints to stand-in for risks to the patient. It is assumed that, if a drug is not manufactured according to its quality profile, then the safety and efficacy found in the original approval cannot be assured.

In recent years, quality and risk professionals have raised concerns for possible problems caused by uncontrolled subjectivity in risk assessment and in risk management. QRM thought leaders are hearing concerns that decisions can be too subjective even though there are numeric systems of scoring on defined, thus, apparently coherent scales [1-5].

Other authors in this monograph, [6, 7], and others [1] have individually discussed the topic in either papers or platform presentations, especially where subjectivity can impact the use of quality risk management (QRM) tools [4]. We hear in the risk assessment and risk-management literature both advocacy and concern about the popular risk management tools, such as risk matrices, FMEA, and other qualitative or semi-quantitative methods. The question often arises as to whether these practices are a divergence from the historically quantitative nature of risk-management and risk-analysis.

This paper begins with a discussion of subjectivity in risk assessment and risk management and how that is partly a reflection of subjectivity more generally in the sciences. It finishes the first part suggesting that we are taught a simplistic control of subjectivity and that we have in too many instances thought that statistical tests, etc., are automatic controls for subjectivity. In Part 2, I discuss how subjectivity is a necessary part of decision-making under uncertainty and quality risk management. Experts are consulted to provide estimates of probabilities for parameters, scenarios and the likely consequences. I end with an introduction to multi-criteria decision analysis as an approach for structuring complex decisions under uncertainty, both for our daily lives and for team decision making in our organisations.

2. Subjectivity in risk assessment and risk management

Ever since the development of the modern concept of risk assessment [8]¹ it has been understood that risk assessments frequently include assumptions about the nature of the hazard, possible exposure pathways, and judgments for the likelihood that alternative risk scenarios might occur [9]. Gaps in the data and information about hazards, uncertainty about the most likely projection of risk, and incomplete understanding of possible scenarios contribute to uncertainties in risk assessment and risk management. In 1994, concerns about uncertainty and subjective judgments in environmental risk assessments led to a detailed analysis and recommendations from the US National Academy of Sciences, *Science and Judgment in Risk Assessment*, [10].

Indeed, concerns for subjectivity in risk assessment and risk management are not new. If we look over the history of the risk sciences, there is a rich primary literature and growing library of applied methods. Some risk scholars have reviewed the seeming unsolvable divide between objectivist and subjectivist schools of thought about risk (e.g., [11-14]). The mixture of objective and subjective status was well known even as a discipline of risk analysis was emerging. For example, Kaplan and Garrick set out to provide a quantitative definition of risk because “[r]ational decision-making requires, therefore, a clear and quantitative way of expressing risk so that it can be properly weighed, along with all other costs and benefits, in the decision process.” [8].² Risk analysis in its formative years evolved around highly technical safety risk assessments, such as those for nuclear reactor power, and health risk assessments for cancer and non-cancer health effects from exposures to small amounts of chemicals or radiation. Risk management decisions and policy making were commonly driven by quantitative and probabilistic risk assessment that can appear to completely objectify risk. On the other hand, there is a whole side to risk and risk evaluation that is based on cognitive and emotional responses to hazards and even feelings [16]. Moreover, some risk scholars argue that risk is always socially constructed [17]. Thus, risk is at once both objectively verifiable and what we perceive or feel it to be. Thus, risk assessment and risk management are inherently infused with a measure of subjectivity.

But rather than surrender to an *ad hoc* analyses and arbitrary subjectivity, risk managers and decision makers can rely on scientifically-based processes of risk assessment and risk management as the processes intended to explicitly confront uncertainties in decision making. Of course, some of this confrontation of uncertainty relies on subjective judgments of probabilities [18, 19].

There are volumes to review on the nature and history of subjectivity in risk assessment and risk management that might take us well beyond the purpose of this discussion. We might ask instead whether the scientific method—as the foundational process for risk analysis—also struggles with too much uncontrolled subjectivity.

¹ Kaplan and Garrick [6] are the originators of the triplet of simple questions, “What can happen? (i.e., What can go wrong?)”; “How likely is that it will happen?”; and “If it does happen, what are the consequences?” These questions were included in *ICH Q9 Quality Risk Management* [FDA2006].

² Here I refer to the broader academic meaning of risk analysis as “the application of *analysis* to matters of risk.” 15. NRC. *Understanding Risk: Informing Decisions in a Democratic Society*. Washington, DC: 1996., rather than only the quantitative estimation of risk as used by ISO standards and the ICH Q9 guideline.

3. Subjectivity in risk as a reflection of subjectivity in science?

Risk assessment and risk management are often touted by managers and executives as evidence of “science-based” – presumptively objective -- processes and decision-making in their organisations. In fact, the scientific method itself is not, nor can it be, completely objective. Witness the centuries-long philosophical debates about the meaning and consequences of subjectivity in both theoretical and applied science. The works of great science philosophers, Hume [20], Kuhn [21] and Popper [22] among others [23], convey their deep thought and reasoning on the differences between observations of what must exist in the natural world and the human imposition of reality through observations—a subjectively constructed world.

Although future scientists from secondary school through postdoctoral training may be presented with these science philosophies, the training can be simplistic—objectivity taught as though it can be controlled with a personal on-off switch for our human subjective tendencies. Few natural sciences curricula offer deeper training in recognising and controlling subjectivity in scientific experiment and decision making, whether it occurs during the design of experiments or even later when writing and reviewing scientific papers. The history of decision making under risk and uncertainty tell us differently: we are not often in control of our subjectivity when facing decisions under risk or uncertainty [19, 24, 25].

The evidence suggests that subjectivity, i.e., as *subjective expert judgments*, is a consistent part of the scientific method generally and risk processes specifically. From here, it is useful to ask what benefits do subjective judgments provide, and are subjective judgments even necessary for risk assessment and risk management?

4. Uncertainty in risk decisions and the subjective judgments of experts

Risk is a *future* chance of loss given exposure to a hazard. Some risk definitions used in risk management and QRM focus on the risk consequences by subsuming “exposure to a hazard” into “harms” -- adverse consequences or outcomes of the exposure to the hazard [26]. Either way, risk estimates, or qualitative ratings of risk, are necessarily projections of *future* consequences. Thus, the true probability of the risk event and its consequences cannot be known in advance. This creates a need for subjective judgements to fill-in information about an uncertain future.

The theories of risk analysis and decision making are interrelated and inseparable [24, 27, 28]. Knight [29] is credited with defining decisions in which the chances of possible consequences are known, given a chosen alternative, as “decisions under risk”. Decisions in which the chances of each possible consequence are unknown are “decisions under uncertainty.” So called risk-based and risk-informed decisions are mostly decisions under uncertainty; again, because risk as used here is an uncertain *probability* of selected harms, conditioned by the system, product or process under risk assessment [26]. In essence, subjective judgments are a necessary part of dealing with our uncertainties in decision making for QRM.

When it is said that “risk assessment *informs* risk management decisions,” it is meant principally that the risk

assessment process provides probabilities of the possible risk scenarios, parameters, models and outcomes (risks), given the set of risk management alternatives (options). These probabilities might be inferred statistically from existing data or supplied by the judgments of experts [30-33].

5. How do we measure uncertainty in risk decisions?

It has been said that risk is both intuitive and arcane: everyone has a mental picture of risk, but the formal mathematics of risk analysis are inaccessible to most. The analogous conclusion suits probability—the informal and formal tool we use to measure our uncertainty. Probability is intuitive and ubiquitous in our lives. Meanwhile, probability theory continues to baffle most of the population. Here, I continue with the notion that subjectivity enters risk assessment and management in a probability context and framework. It is often a necessary subjectivity that provides probability measures of the uncertainties in risk assessment. With measures of uncertainties in hand, risk managers are better informed for decision making.

There are two major schools of thought: the frequency school and the subjective probability school. The frequency school says probability is based on a count of the number of successes divided by total number of trials. Uncertainty that is readily characterised using frequentist probability methods is “aleatory” – due to randomness (or random sampling in practice). Frequentist methods give an estimate of “measured” uncertainty, pure and simple [34]; however, it is arguably trapped in the past because it does not lend itself to easily to predicting future successes. In contrast, the subjectivity school of thought favours probability as stemming from the degree of belief about the uncertainty distribution and its parameters. In this purely subjective, epistemic mindset, probability itself does not exist: it only matters at that moment in time and to the individual making the judgment. Moreover, Bayesians look at probabilities as available for updating using information that is new to the (subjective) expert. The two forms of uncertainty and measures of uncertainty are shown in **Figure 1.1**.

The reality of contemporary risk assessment and risk management is that uncertainty is measured with a combination of frequentist and subjectivist probability distributions. For example, a manufacturing process risk assessment might begin with classical statistical control data and analyses. But projecting the risks from a process change might call for expert judgments of e.g. possible failure modes and the probability that particular failures might occur during a defined period. The risk assessor(s) bring prior expert knowledge and, if we are lucky, some prior data, and start to focus the target of the risk decision using subjective judgments of probabilities.

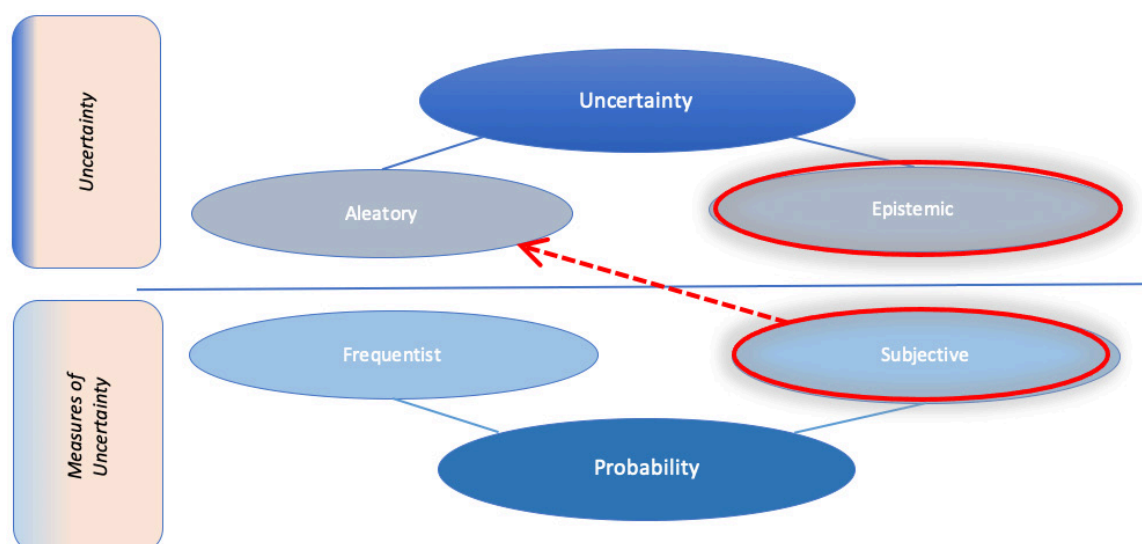


Figure 1.1 — Probability is the measure of uncertainty. Uncertainty in risk assessment and risk management decisions can be thought of as a combination of aleatory (random) variation and the epistemic (degrees of belief) having to do with the knowledge about the uncertainty. Sometimes, subjective probability are used to give a starting point for aleatory or statistically verifiable distributions.

6. Subjectivity *per se* is not the problem

Given that subjectivity is ubiquitous in science and is likely a necessary part of many risk-based or risk-informed decisions, perhaps, it is an obvious conclusion that subjectivity cannot be eliminated from either the theory or application of QRM. Moreover, it is not even an inherent limitation in most situations. Rather, the “problem with subjectivity” more precisely concerns two elements:

- A failure to recognise where and when subjectivity enters and might create problems in risk assessment and risk-based decision making; and
- A failure to implement controls on subjectivity where it is known to occur.

Some have argued that a failure to formally control subjectivity — in relation to probability judgments - is *the failure* of risk management [35]. But, given that risk is about the chance of adverse outcomes of events that are yet to occur, subjective judgments of one form or another will always be required in both risk assessment and risk management decision-making.

7. Approaches to controlling for subjectivity in Quality Risk Management

In this part of the paper, I turn to describing the ways that subjectivity can be controlled and remain useful for QRM decision making. Risk analysis, and generally speaking risk management, is currently undergoing a paradigm shift marked by a greater reliance on decision theory from the psychology and behavioural economics disciplines, in addition to its own development using more quantitative decision analysis. It is at the nexus of these disciplines that significant improvements in risk-based decision making for complex,

uncertain, and multi-objective risk problems are being reported.

There are numerous approaches for controlling subjectivity in QRM. The general approaches include the following:

- Raising awareness of where/when subjective judgments of probability occur in risk assessment and risk management;
- Identifying heuristics and biases where they occur;
- Improving the understanding of probability among the team and individual experts;
- Calibrating experts individually;
- Applying knowledge from formal expert elicitation; and
- Use expert group facilitation when group probability judgments are sought.

Decisions that matter in QRM often rely partly on the judgments of one or more experts. In reality, these “judgments” are *subjective estimates* of the probability that a parameter takes on a particular value. More likely than not, your subject matter experts are not queried about probability distribution. Your experts, rather, are asked a direct question such as: “what is the risk/likelihood or severity score?”. In contrast to informal opinion gathering, expert elicitation is a formal way to extract knowledge about the quality or probability distributions of uncertain parameters. Expert elicitation is a structured process to elicit useful information to inform uncertainty in risk decision making from subject matter experts.[30, 31, 33, 36]. Expert elicitation seeks subjective judgements of probabilities for risk assessment and the relative probabilities where there is inadequate information. That is inherently a subjective process!

The theory is that we think there is a true value of a parameter that has its uncertainty. We begin the exercise not knowing either the most likely value of the parameter or its uncertainty. Experts are quizzed to determine either of these. Shown in **Figure 1.2** is the theoretical distribution and a stylised view of an expert’s judgements. The figure is purposefully drawn with more narrow uncertainty than the reality. Expert judgments of the distribution of a parameter is often “over-confident” expressed as too narrow of an uncertainty projection. When including multiple expert judgments, both complexity and concerns often emerge about how mathematically the individual judgments should be aggregated.

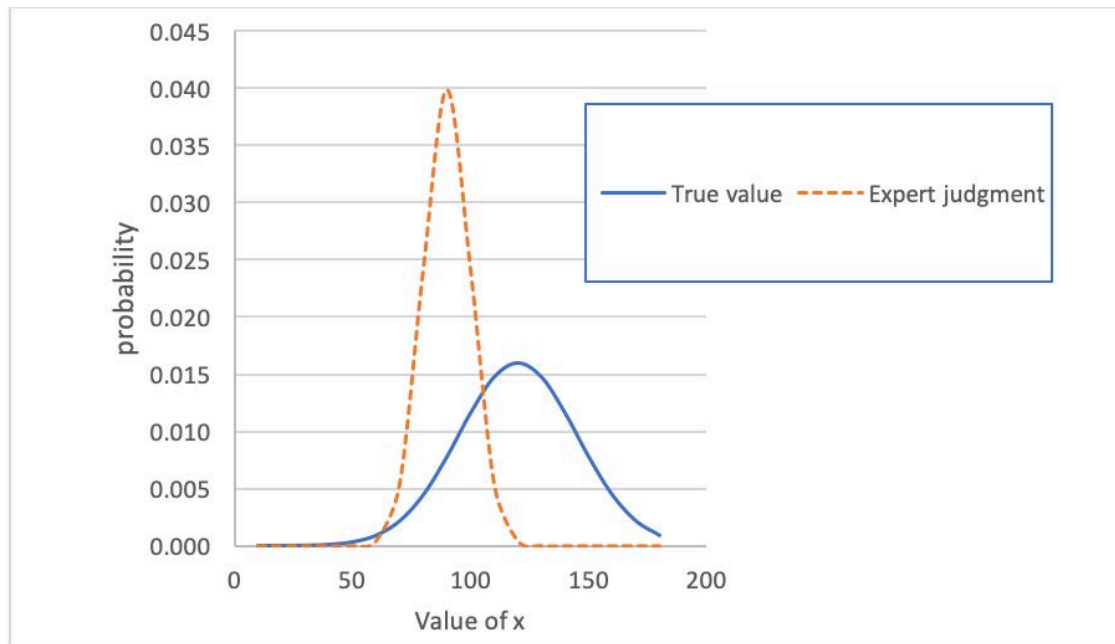


Figure 1.2 — *Idealised distributions from theory of expert judgment. A notional expert elicitation result is shown. Assume that a true distribution of the parameter and its uncertainty exists, but cannot be obtained. Instead, a calibrated expert is quizzed for an estimate of the parameter and its uncertainty. In general, experts are “over-confident,” judging the uncertainty to be narrower than the true value.*

Hubbard and others have raised concerns for the quality of expert judgements if obtained from uncalibrated experts [33, 35, 37, 38]. Calibration of experts is often skipped in risk-informed decision making and is surprisingly a basic method. It is unlikely that any pharmaceutical manufacturer today would not calibrate analytical laboratory equipment. Experts are the instruments for measuring uncertainty in conditions of scarce objective information, so why not calibrate these instruments?

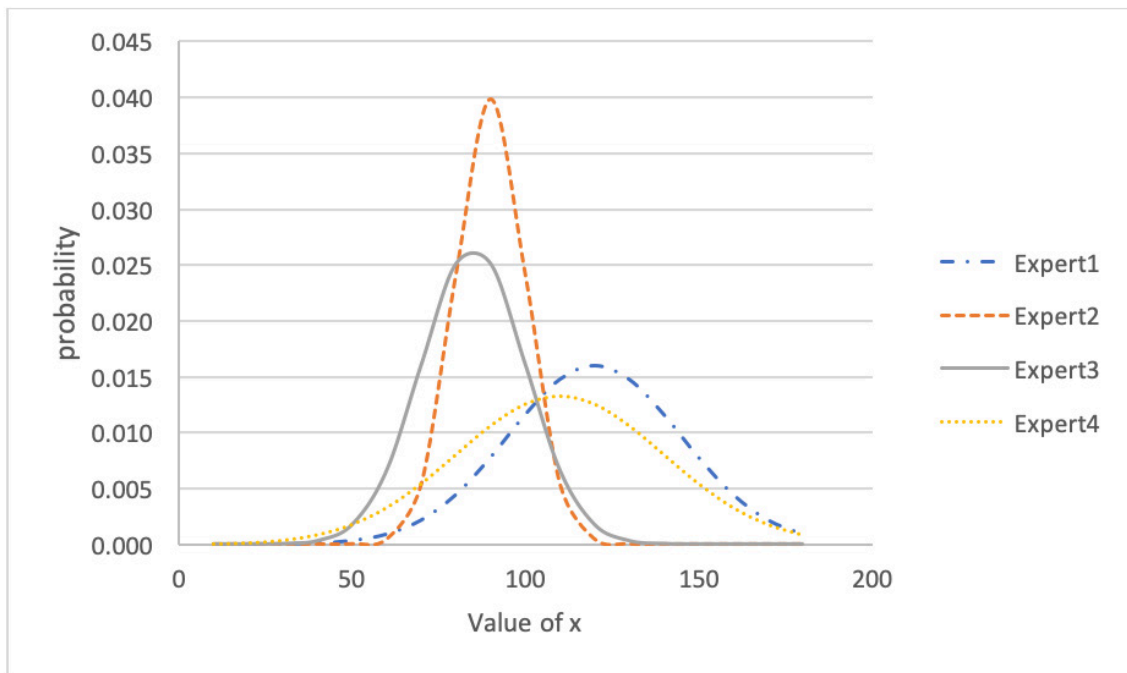


Figure 1.3 — Multiple expert judgments of uncertainty. When multiple experts are quizzed on the value of a parameters and its uncertainty, a diversity of uncertainty distributions may result. There are difficult questions about the appropriate way to combine the results into a team aggregate for group decisions.

8. The Collective Judgments of Teams

It is safe to say that modern organisations run on the work and advice of teams. Sometimes the teams are truly interdisciplinary and other times consisting of a more focused expertise within a discipline. The question is: how do you take multiple experts and pool their expert judgements for the best estimate of probability and subsequently the best decision with the data and information available?

The aggregation of individual judgments into a team judgment is an active part of decision-analysis research because there is no fundamental theory from which to build upon [31, 38-41]. Although there is several hundred years of decision theory for individuals, it is not clear what parts of the theory transfer to group decision making.

There are a couple of general ways to deal with this and with related concerns about uncertainty in such activity. One is the mathematical school which is based on the idea that we elicit opinions from experts individually: we do some mathematical magic algorithmically combined individual judgments into a grouped value (**Figures 1.3 and 1.4**). The other general means of aggregating expert judgments is behavioural. For example, a common approach is to gather experts around a table and use either a Delphi or other structured brainstorming process [42, 43]. Here, the judgments of the individual experts are exposed to well-known group dynamic influences on their judgments. Both approaches have their merits in different situations. Both methods have their critics.

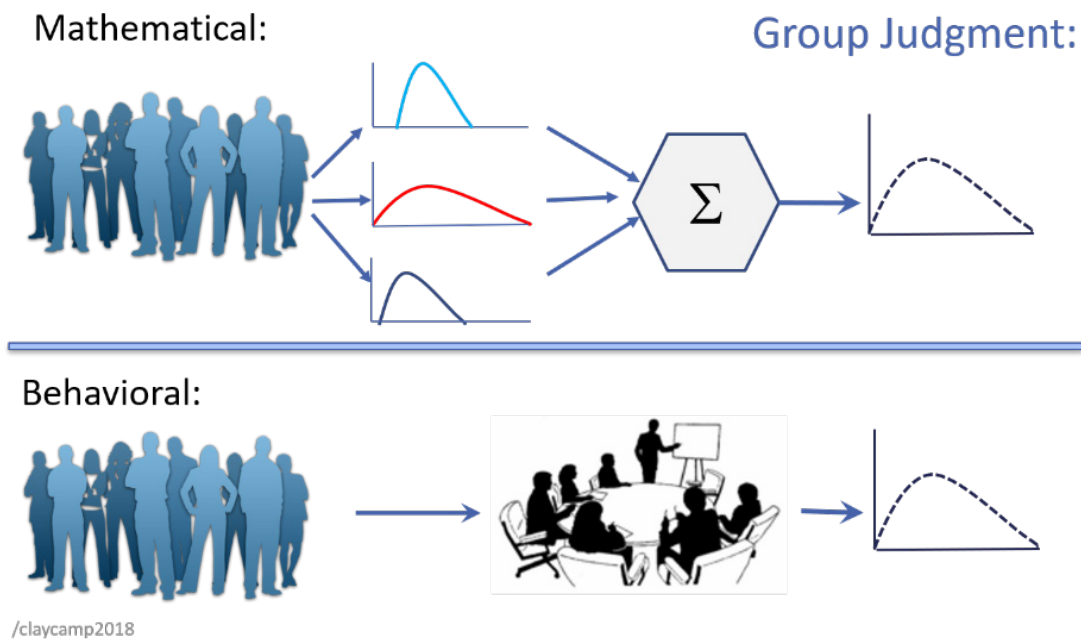


Figure 1.4 — Two general approaches to aggregating expert judgments. Top: individuals are elicited for the uncertainty distribution of a parameter or variable. The results are mathematically combined to a single distribution representing the group’s expert judgment. Bottom: Using a social group process, such as Delphi, a facilitator helps the group formulate a single expert uncertainty distribution.

Subjective probability judgements obtained through behavioural approaches typically use a group exercise such as the Delphi process. In Delphi, each expert submits their judgments anonymously as before the group collects the judgments for review and ranking. Delphi and similar structured group elicitation processes attempt to limit known group behaviours that might derail the expert elicitation process. Some of these well-known problems include follow-the-leader, group think, and dictator-based decisions, etc. One or two strongly extrovert-types can have an exponential impact on the group’s decision-making.

9. Multi-Criteria Decision Analysis

So, how do we wrap all these thoughts into a method for controlling subjectivity in risk-based decision making? How do we raise awareness about solutions and best practices among QRM practitioners who may be discouraged by “too much subjectivity” in QRM methods?

There are many approaches to managing individual and group decision making under uncertainty. Collectively, the methods fall within risk-based decision making (RBDM)—the very functions of risk assessment and risk management! More recently, the methods of RBDM might be said to fall within multi-criteria decision analysis (MCDA). The early work in MCDA derives principally from Keeney and colleagues [43-47]; however, many others have contributed useful approaches [38, 48-50]. For useful help, QRM practitioner might look across disciplinary boundaries and find practical approaches to MCDA in (e.g.) *Multi-Criteria Analysis: A Manual* [51].

My personal experience with taking many groups through an MCDA process is that there is no unique “cookbook” of MCDA that fits every risk decision situation. I believe this is a result of the rich, multidisciplinary environment of our organisations and teams. Some teams may favour more quantitative group decision making methods, while others favour behavioural methods. A risk and decision coach versed in a variety of methods can guide the group to an *engaging* method. If the group finds the process too tedious or inaccessible, the decision can easily derail.

Although there are many variants on MCDA, there are principle-driven similarities among the various methods. These include: clearly defining the decision objective; identify and thorough exploring the alternatives and possible outcomes; defining the decision criteria; defining attributes from which to measure performance of the criteria on the alternatives. The general approach in my risk-focused prioritisation (RFP) process is given in **Figure 1.3**. Missing in the detail of a top-level process flow is the abundant opportunity a structured process creates for identifying and correcting for subjectivity in risk decisions. (The details are too long for this brief paper.) The structured group MCDA applications of subjective probability assessments can produce a markedly different performance for difficult, multi-criteria decisions than when a team relies only on *ad hoc* discussions of subjectivity—hoping to apply their on-off switches!

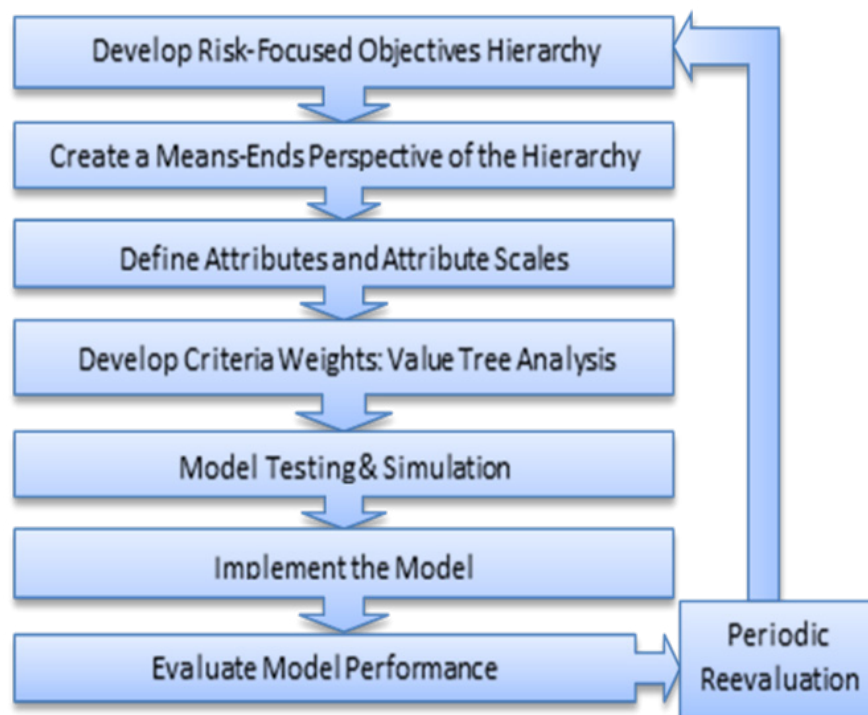


Figure 1.5 — *Risk-Focused Prioritisation*. This multi-criteria decision process draws much from Keeney (1992) and others. Prioritisation refers to the use of the multicriteria methods to risk prioritise portfolios of risk “objects,” such as manufacturing sites, products, vendors, contracts, etc.

Decision-making is making an informed choice among alternatives to achieve the possibility of a preferred outcome. Like risk, probability, and subjectivity, decision analysis is both intuitive and arcane. In fact, most people make multi-criteria decisions every day [44, 52]. Examples include major purchases (automobile, house), both selecting a job and selecting a job candidate, choosing a supplier for manufacturing, and many others. In team MCDA we make a more formally structured approach, seeking transparency, consistency and coherence among the multiple objectives.

When learning a new risk management approach or tool from another discipline, an oft-cited concern by management and teams is whether such a detailed and formal process is necessary for every risk-based decision. In fact, the answer is emphatically no! This process is usually limited to a small number of major decisions that might justify the attention and the detail. These decisions or risk-based prioritisations are usually stuck in discussions, strongly different beliefs and bureaucratic process. Fortunately, most of what we decide in our work places is more routine, of minor consequence, or a “no-brainer” decision [47].

10. Risk-based decisions put risk-preventative and mitigation controls in place!

The bow-tie visualisation of risk events is helpful for depicting possible risk-management interventions for preventing or controlling risk. The so-called **bow-tie model of risk** (Figure 1.6) where there is a risk event that occurs on a timeline drawn from causes through consequences. For example, risk controls can be designed to either prevent the risk event from occurring by eliminating the causes of the event or by lessening the chances of the event. But once that defined risk event has occurred, only mitigating controls can lessen the severity of the consequences. The key idea is that it is purposeful risk-based decision-making that puts risk controls in place.

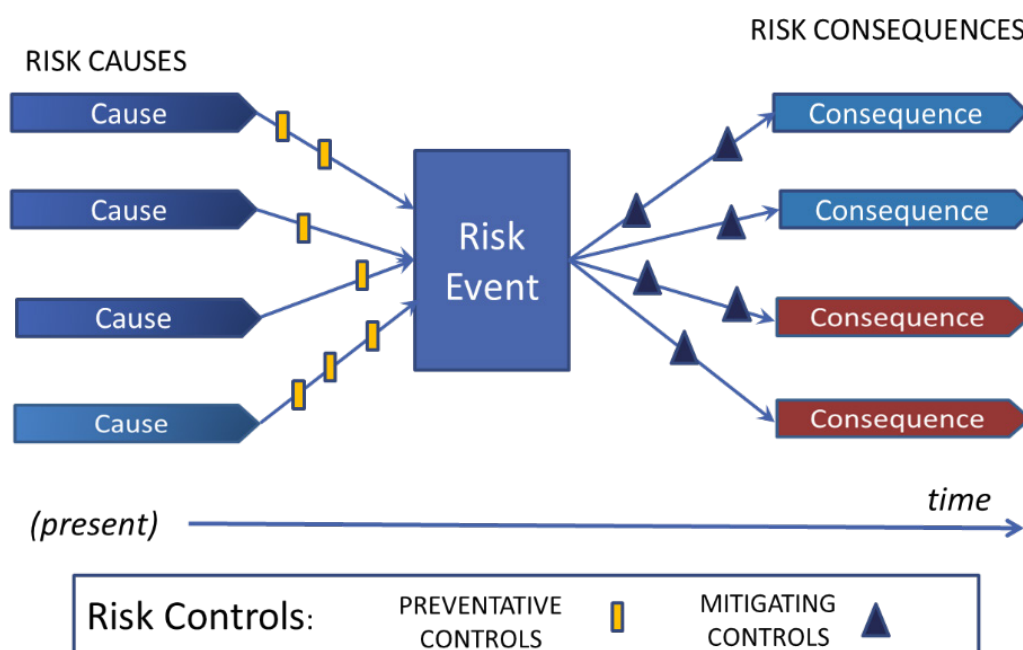


Figure 1.6 — A bow-tie model of risk events. In this visualisation of a risk event, the event occurs on a timeline from causes to consequences. Risk managers can put in place preventive or mitigating controls intended to manage the overall risk. Often missed in discussion is the fact that it is risk-based decisions that lead to putting the controls in place.

Risk assessments provide the decision maker with objective and subjective probabilities for the likelihood of harm under each decision alternative. Although the “probability of occurrence” assessments in a failure mode effects analysis (FMEA) seems far removed from a fully probabilistic risk assessment, nonetheless, human judgments of probabilities are generally necessary.

11. Summary and Conclusion

It is not surprising that subjectivity occurs in quality-risk management. Subjective probabilities are often necessary to address gaps in data, information about scenarios and the choice of risk models. The problem with subjectivity in QRM is in identifying where subjectivity occurs and, perhaps, is even necessary; and, it is also about controlling for the undesirable effects of improper subjective judgments. Learning from disciplines with a longer history in risk analysis, and which regularly use expert-judged probabilities with controls for known heuristics and biases, is likely to be productive for controlling subjectivity in QRM. QRM can follow the lead other disciplines to embrace uncertainty and to analyse risk [53].

References

1. Waldron K. Risk Analysis and Ordinal Risk Rating Scales—A Closer Look 2015. Available from: <http://www.ivtnetwork.com/article/risk-analysis-and-ordinal-risk-rating-scales---closer-look>.
2. Claycamp HG. Probability concepts in quality risk management. *PDA J Pharm Sci and Tech.* 2012; 66:78-89.
3. Claycamp HG. Risk, uncertainty, and process analytical technology. *J Process Analytical Technology.* 2006;3(2):8-12.
4. Strong JC, McDermott TS, Heinzerling O, Claycamp HG. The risk of trusting priority numbers. *AAPS Newsmagazine.* 2017 February 2017:14-8.
5. O'Donnell K. Practical Strategies for Improving Quality Risk Management Activities in GMP Environments. 2009.
6. O'Donnell K. Strategies for addressing the problems of subjectivity and uncertainty in quality risk management exercises: Part 1: the role of human heuristics. *J Validation Technol.* 2010;16(4):3.
7. Vesper J, O'Donnell K. Current challenges in implementing quality risk management. *Pharmaceutical Eng.* 2016:73-9.
8. Kaplan S, Garrick B. On the quantitative definition of risk. *Risk Anal.* 1981;1(1):11-27.
9. Kaplan S, Haimes YY, Garrick BJ. Fitting hierarchical holographic modeling into the theory of scenario structuring and a resulting refinement to the quantitative definition of risk. *Risk Anal.* 2001;21(5):807-19.
10. Council NR. *Science and Judgment in Risk Assessment.* Washington, DC: 1994.
11. Hansson S. Risk: objective or subjective, facts or values. *J Risk Res.* 2010;13(2):231-8.
12. Otway H, von Winterfeldt D. Expert judgment in risk analysis and management: process, context, and pitfalls. *Risk Anal.* 1992;12(1):83-93.
13. Hermansson H. Defending the conception of "Objective Risk". *Risk Anal.* 2012;32(1):16-24.
14. Solberg O, Nja O. Reflections on the ontological status of risk. *Journal of Risk Research.* 2012;15(9):1201-15.
15. NRC. *Understanding Risk: Informing Decisions in a Democratic Society.* Washington, DC: 1996.
16. Slovic P, Finucane ML, Peters E, MacGregor DG. Risk analysis and risk as feelings: Some thoughts about affect, reason, risk, and rationality. *Risk Anal.* 2004;24(2):311-22.
17. Kasperson RE, Renn O, Slovic P, Brown HS, Emel J, Goble R, et al. The Social Amplification of Risk: A Conceptual Framework. *Risk Analysis.* 1988;8:177-87.
18. Kahneman D, Slovic P, Tversky A. *Judgments Under Uncertainty: Heuristics and Biases.* Cambridge, England: Cambridge University Press; 1982.

19. Tversky A, Kahneman D. Judgment under uncertainty: Heuristics and biases. *Science*. 1974;185:1124-31.
20. Hume D. *A Treatise of Human Nature: Being An Attempt to Introduce the Experimental Method of Reasoning Into Moral Subjects*. London 1739.
21. Kuhn TS. *The Structure of Scientific Revolutions*. Chicago: Univ. of Chicago Press; 1962.
22. Popper K. *The Logic of Scientific Discovery*. Germany: Mohr Siebeck; 1934
23. Rosa EA. Metatheoretical foundations for post-normal risk. *J Risk Res*. 1998;1(1):15-44.
24. Kahneman D. *Thinking, Fast and Slow* 2011.
25. Sunstein CR, Thaler R. *Nudge: Improving Decisions About Health, Wealth, and Happiness*. New Haven, CT: Yale University Press (Caravan); 2008.
26. FDA. *ICH Q9 Quality Risk Management*. Rockville, MD: U.S. Food and Drug Administration, 2006.
27. Fischhoff B, Kadavy J. *Risk: A Very Short Introduction*. New York: Oxford University Press Inc.; 2011 .
28. Rakow T. Risk, uncertainty and prophet: The psychological insights of Frank H. Knight. *Judgment and Decision Making*. 2010; 5(6):458-66.
29. Knight FH. *Risk, Uncertainty, and Profit*. Boston: Hart, Schaffner & Marx; Houghton Mifflin Co.; 1921 1921.
30. Ayyub BM. *Elicitation of Expert Opinions for Uncertainty and Risks*. Boca Raton, FL: CRC Press; 2002 2002.
31. Bolger F, Rowe G. The aggregation of expert judgment: do good things come to those who weight? *Risk Anal*. 2015;35(1):5-11.
32. Winkler RL. The consensus of subjective probability distributions. *Management Sci*. 1968;15(2).
33. Cooke R. *Experts in Uncertainty: Opinion and Subjective Probability in Science*. Oxford, UK: Oxford University Press; 1991 1991.
34. Trimmer PC, Houston AI, Marshall JAR, Mendl MT, Paul ES, McNamara JM. Decision-making under uncertainty: biases and Bayesians. *Anim Cogn*. 2011;14:465-76.
35. Hubbard D. *The Failure of Risk Management*. New York: Wiley; 2009 2009.
36. Cooke R, Goossens L. Expert judgement elicitation for risk assessments of critical infrastructures. *J Risk Res*. 2004;7:643-56.
37. Hubbard D. *How to measure anything: Finding the value of intangibles in business*. Third ed. Hoboken, NJ: John Wiley & Sons; 2007.
38. Saaty T, Peniwati K. *Group Decision Making: Drawing Out and Reconciling Differences*. 2013; 2008 ed. Pittsburgh, PA: RWS Publications; 2013.
39. Saaty TL, Shih H-S. Structures in decision making: on the subjective geometry of hierarchies and networks. *European Journal of Operations Research*. 2009;199:867-72. Epub April 1, 2009.
40. Baker E, Olaleye O. Combining Experts: Decomposition and Aggregation Order. *Risk Analysis*. 2013;33(6):1116-27.
41. Mosleh A, Bier V. On Decomposition and Aggregation Error in Estimation: Some Basic Principles and Examples. *Risk Analysis*. 1992;12(2):203-14. doi: 10.1111/j.1539-6924.1992.tb00668.x.
42. Keeney R. Value-focused brainstorming. *Decision Analysis*. 2012;9(4):303-13.
43. Keeney R. Foundations for group decision analysis. *Decision Analysis*. 2013;10:103-20.
44. Hammond J, Keeney RL, Raiffa H. Even swaps: a rational method for making trade-offs. *Harvard Business Review*. 1998;March-April(Reprint 98206):1-11.
45. Keeney R, Raiffa H. *Decisions with Multiple Objectives. Preferences and Value Tradeoffs*. 1993 ed. New York: John Wiley, Reprinted Cambridge Univ. Press, 1993; 1976.

46. Keeney RL. *Value-Focused Thinking*: Cambridge University Press; 1992.
47. Keeney R. Making better decision makers. *Decision Analysis*. 2004;1(4):193-204.
48. Linkov I, Satterstrom FK, Kiker G, Seager TP, Bridges T, Gardner KH, et al. Multicriteria decision analysis: a comprehensive decision approach for management of contaminated sediments. *Risk Anal*. 2006;26(1):61-78.
49. Saaty TL. Decision making--the analytic hierarchy and network process. *J Sys Sci and Sys Eng*. 2004;13(1):1-35.
50. Haimes Y, Kaplan S, Lambert J. Risk filtering, ranking, and management framework using hierarchical holographic modeling. *Risk Analysis*. 2002;22(2):383-97.
51. (UK) DfCaLG. *Multi-Criteria Analysis: A Manual*. West Yorkshire, UK: 2009. Report No.
52. Hammond J, Keeney R, Raiffa H. *Smart Choices. A Practical Guide to Making Better Decisions*. Paperback; Original--1999 hardcover ed. New York: Broadway Books; 2002 2002.
53. Spiegelhalter D, Riesch H. Don't know, can't know: embracing deeper uncertainties when analysing risks. *Phil Trans R Soc*. 2011;369:4730-50.

2 — Quality Risk Management in the Good Manufacturing Practices (GMP) environment beyond 2020 – what should we strive for?

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1. Introduction

One of the challenges in including a reference to looking beyond 2020 in the title of a Quality Risk Management (QRM) paper like this is that one cannot usually foretell the future with very much accuracy. The wise approach is not to try to predict the future, but to instead consider the main QRM challenges that face us as we move towards that time, and how we might best respond to those challenges. This paper is an attempt to do that. It discusses challenges in the areas of risk reduction measurement and QRM competency development, and it explores the benefits in demonstrating the effectiveness of the QRM activities that are undertaken. The paper refers to some of the concepts introduced by Dr Claycamp in his paper within this monograph, and indeed there is much cross-learning among all of the papers presented here.

2. Where is the industry right now in its approach to QRM?

To reflect on this, let me introduce as an illustrative example a recent Quality Defect case with a medicinal product which affected Ireland. (*Note:* The author obtained permission from the Marketing Authorisation Holder of the product to share this information.) The medicine in question is an oromucosal midazolam solution in syringes. It is indicated for prolonged, acute, convulsive epileptic seizures in infants, toddlers, children and adolescents (from 3 months to 18 years).

The quality defect related to the plastic syringe component of the medicine: the syringe was used to deliver the medicine into the oromucosal cavity within the patient's mouth, during an epileptic seizure. A plastic cap on the tip of the syringe was comprised of two different components which in some cases became separated when the carer went to administer the medicine to the patient. The issue was that one of the two components of the tip-cap sometimes inadvertently remained on the syringe tip when the cap was pulled off. This had the potential for that plastic component to be injected into the patient's mouth when the medicine was administered into the oromucosal cavity. There had been four cases of this within the EEA (two in Germany and two in Ireland), and a global recall of the defective batches of the product was ultimately required in order to mitigate the risks presented by the defect. This recall followed the issuance of cautionary letters to healthcare professionals and patient caregivers about the defect and the choking risks that it presented.

Viewing this case through the lens of QRM, it was evident that that manufacturer had not adequately applied QRM principles to the control strategy relating to the plastic components making up the syringe tip cap, and that the risks presented by the design of the tip cap had not been adequately managed.

For example, the relative dimensions of the plastic components making up the tip cap were not considered important enough to apply the necessary level of monitoring and control to them. Over time, changes in the dimensions of one of the components led to the quality defect in question arising – the separation of the two components from each other when the cap was removed from the syringe tip. There was a failure to proactively identify at the drug product manufacture location the risks of not adequately controlling the dimensions of the transparent component at goods-in or in Quality Control, and there was a lack of QRM principles applied when determining the critical attributes of the packaging components.

Other examples of serious Quality Defects and Recalls in 2018 are given below in **Table 2.1**.

March 2018	Product Mix-up issue at a compounding site	Nitrofurantoin (an antibiotic for bladder infections) was mistakenly used when manufacturing a Nadolol (beta-blocker) oral solution for a patient. The batch in question was discarded prior to use.
April 2018	Various Packaging and Labelling Issues	Wrong expiry dates assigned to 9 batches of a product. Recall required in Ireland. Wrong package leaflet supplied with a bisphosphonate product. Recall required in Ireland.
June 2018	Probable Carcinogenic Impurity in batches of Valsartan API	Global recall. (22 different products across 6 companies recalled in Ireland.)
August 2018	Use of the wrong excipient resulting in benzyl alcohol contamination of the product	Company’s risk assessment for the issue not accepted by the HPRA. Several batches recalled in Ireland.
September 2018	Risk of silicone particles in a steroid eye implant product	Global recall, over 80 batches recalled to user level in various countries.

Table 2.1: Examples of Quality Defect and Recalls in 2018

As regulators, we analyse each quality defect and recall cases to look for learning opportunities. In all of the above cases, and indeed in most of the quality defect investigations performed by the Health Products Regulatory Authority (HPRA) each year, 3 common factors were in place:

- i. The defective batches in question were manufactured using *qualified* equipment;
- ii. They were manufactured by *trained and qualified* staff;
- iii. They were manufactured using processes that had earlier been *validated*.

It is worth considering the implications of this and what it might tell us about the state of QRM within the GMP environment at this time.

3. Common GMP inspection findings relating to QRM

In addition to studying quality defect and recall issues, it is also worth reflecting on good manufacturing practices (GMP) inspectional findings and observations that relate to QRM. In my own inspectional experience the following general issues have often been present:

- **The absence of clear links between risk assessments, proposed control strategies and the design of validation protocols** – this can limit how much true risk-based validation is achieved. Few of the currently available QRM tools were designed to link these 3 elements.
- **Risk Ratings and Risk Assessment outcomes which are often not supported by good science or data.** This can result in highly subjective and heavily biased QRM outputs and decisions, resulting in a significant level of guesswork in risk ratings.
- **Risk Assessments for change controls which fail to consider the question: “What can go wrong if we implement this change?”** This can result in problems for the process later on, but rarely is this simple question posed in change-control procedures. Instead, companies design their change-control processes that focus on assessing the impact of the proposed change on various things such as on current documentation, equipment cleaning processes, equipment qualification, process validation, training, etc. While these things are very important to assess, asking the question about what might go wrong is also important as it is an opportunity for companies to try to prevent problems that might be associated with the proposed change after its implementation.
- **Designating changes as like-for-like in the absence of supporting data.** Changes that are assigned a like-for-like classification are often not risk-assessed, and are awarded limited oversight from a GMP perspective. These can sometimes result in major problems for companies, as was experienced by one company a few years ago. In that case, one of its contract manufacturers changed a door seal in an item of equipment which was used in an aseptic process. The change in question was deemed like-for-like, and little attention was given to it until a failed process simulation exercise on the manufacturing process some months later revealed that the seal in question was not suited to the equipment - it was not actually like-for-like. But by then it was too late – product had to be rejected due to an inadequate level of sterility assurance, and the medicine in question went out of stock in many different countries while the issue was being resolved. The medicine was also a critical one for patients in several countries, including Ireland.
- **Risk Assessments that are used to support already made batch release decisions following serious deviations.** This represents an inappropriate application of QRM principles and it should not occur.
- **Superficial risk assessments applied to contract manufacturing organisations (CMOs)** – these can lead to a false sense of security in the supply chain of a medicinal product or material.
- **Mis-classifying relatively serious deviations as minor.** This is an example of the poor application of QRM principles - it can lead to potential risks to product quality not being identified or acted upon. It often results in a lack of meaningful root cause analysis being applied to the deviation at hand, to ineffective corrective action, preventative action (CAPAs) (if indeed any CAPAs are implemented) to recurring manufacturing problems, and ultimately, it can lead to increased risk for patients.
- **Not using risk indicator systems (e.g. deviations, complaints, Product Quality Reviews (PQRs) to generate knowledge** – the issue here is that, while these systems can directly indicate the level of

residual risk that is present in a manufacturing process or product, they are often not used as a source of residual risk information, and so the learnings that can be extracted from the information and data those systems hold are often not realised. This can lead to required control strategy improvements not being identified or implemented in a holistic manner.

To illustrate some of the above concepts, the following are examples of recent QRM-related deficiencies that were identified during GMP inspections.

1. High Levels of Uncontrolled Subjectivity in Risk Assessments

The Product X Risk Assessment that focussed on cracked vials was not considered sufficiently science-based or robust...

- The GMP controls in place to prevent vial cracking were not documented in the risk assessment, yet a low probability of occurrence score of 2 had been assigned;
- The controls to detect cracked vials had also not been documented and their effectiveness had not been determined - yet the highest detectability rating (a score of 1) had been assigned to those failure modes;
- Marketplace complaint data regarding cracked vials had not been considered in the risk assessment exercise;
- There was a significant degree of bias in many of the occurrence and detectability scores, and there were generally no data or rationale documented to support those scores.

2. Risk Assessments that do not reflect the process being risk assessed

In the Risk Assessment of aseptic process X, the following were not taken into account and they had the potential to lead to increased levels of risk:

- The worst-case number of aseptic manipulations (at 216);
- The compounding tank remained open for over 2.5 hours during additions;
- Not all items loaded into the isolator were sanitised, e.g. Environmental Monitoring (EM) plates;
- The VHP loading pattern – the positions of items in the load were variable for each cycle and were not in line with the validated loading pattern;
- The extent of occluded surfaces on the isolator gloves and the fact that the isolator door had to be opened a number of times to fix the gloves into position;
- Gloves were not subject to further sanitisation after exposure to Grade C conditions;
- The risk assessment stated that both sterility testing and environmental monitoring were design controls: this was not considered scientifically sound.

3. *The misapplication of QRM in Deviation Investigations and in Decision-making*

QRM exercise X, which was the basis for the use of starting material lot Y (grossly contaminated with hard solid round particles) to produce API Z was not acceptable, given the following factors:

- The starting material was contaminated, and it was known that using it would result in an out-of-specification (OOS) batch of crude active pharmaceutical ingredient (API);
- No information had been documented on whether reworking this material could remove the contaminant prior to use;
- Several of the probability and severity ratings were not supported, e.g. the low probability of occurrence for the failure mode concerning producing contaminated final API material;
- No tests were performed to determine if the contaminant material had actually been removed from the process prior to release of the API batch;
- The ‘minor’ classification assigned to the deviation was not justified, given the significance of the issue and the risks it presented.

It is important to note that there is always some subjectivity associated with risk analysis and risk-based decision-making. This subjectivity also applies to the judgements made by GMP inspectors when reviewing company risk assessments. But experience has shown that the kinds of deficiency issues cited above can and do lead to the following:

- *inefficient manufacturing processes*
- *ineffective control systems*
- *adverse GMP inspection outcomes*
- *batch rejects*
- *serious quality defects*
- *product recalls*
- *product shortages*
- *and patient impact.*

A case in point is the change control example mentioned earlier, where the company made a change to a door seal and managed it as a like-for-like change control. This change inadvertently led to a shortage in the related medicinal product for patients in 15 countries for approximately two years. A robust application of QRM principles to that change may have helped prevent that.

4. *What is all this telling us about the current state of QRM with the GMP environment?*

My own view is that true risk-based validation is probably not being achieved fully or consistently yet. While it is clear that the industry has done a lot of work in the area of QRM, it may have reached a plateau in that

work, where advances in the area have stagnated to some extent. There appears to be a lack of innovation with respect to the development of QRM tools, with little emphasis on learning from the experiences of other industries.

The benefits of QRM are probably not being realised for patients - at least not to the extent envisaged by ICH Q9. Despite some improvements in doing Risk Assessments, there is still a long way to go in the overall area of QRM, including Risk Control and Risk Review. The emphasis has probably been more on the *mechanics* of risk assessment tools/scores rather than on the *quality of decisions made* based on the outcomes of risk assessments.

The benefits of QRM are probably not being realised for companies either: qualification and validation costs are probably still very high, and few are being given any meaningful regulatory relief on the basis of their QRM activities.

5. Looking beyond 2020 – what should we strive for in QRM?

Three strategic recommendations are presented for consideration as we strive to improve how QRM principles are applied within the GMP environment.

Strategy 1: Focus on Evidence-Based Risk Reduction

It would be useful to develop ways to estimate risk reduction in more scientifically sound ways where subjectivity is better controlled. This would bring many advantages, and while it is hard to do, one can learn from other industries that have devoted time and effort to this area, especially US Aeronautics, US nuclear power generation, and semi-conductor manufacturing.

One could review the peer-reviewed research findings from other fields on the factors that influence probability and risk estimation (e.g. experimental psychology, mathematics, accident theory).

Determining what evidence will be needed to support robust risk reduction estimates is an area in need of focus at this time. Should this evidence be sought in process variability measurements or more formalised process capability data, or could it be based on using customised QRM tools that force one to link all Probability, Severity and Detection risk ratings with GMP controls of known effectiveness?

If one could better *measure* risk reduction in a less subjective manner, that could help determine which GMP controls (or combination of controls) are truly important in risk control (See Annex 15 to the EU GMP Guide for the requirements in this area). That could in turn help companies more easily achieve true risk-based control strategies. The ability to better measure risk reduction should also enable companies to demonstrate increased levels of process understanding and process knowledge, and it should help decision-makers make more informed decisions on the outputs of their sites QRM activities, which might include Risk Control

Strategies and Risk Registers.

Advances in *measuring* Risk Reduction could also lead to more innovative and science-based validation strategies. In this area, it is useful to consider Annex 15 to the EU GMP Guide, which states:

“Process validation should establish whether all quality attributes and process parameters, which are considered important for ensuring the validated state and acceptable product quality, can be consistently met by the process.”

Being able to better measure the extent of risk reduction delivered by GMP controls could allow the controls to be positioned on what might be termed a *Spectrum of Importance (or Criticality)*. Their position on the spectrum could help inform the extent of validation testing and on-going process verification that is applied, and it could help one move away from the current overly simplistic binary approach to process parameter classification – Critical / Non-critical. The 2016 paper by O’Keeffe *et al.* provides further discussion on this spectrum concept.

Strategy 2: Develop a Certification Programme for QRM

The GMPs now place so much emphasis on risk-based approaches they anticipate high competencies in QRM as a pre-requisite. In this regard, highly competent **QRM facilitators** are needed at manufacturing sites, and a certification programme for such facilitators has the potential to be of benefit.

This leads to the question: What might a **certification programme** for QRM facilitators look like? Perhaps the industry could get together to discuss this, and it is useful to note that work has already begun in this area at the Dublin Institute of Technology where Professor Anne Greene and her colleagues are working on developing a competency model for QRM practitioners within the industry. Regulators will also have an interest in this work as QRM competencies are always needed within regulatory agencies as they apply risk-based thinking and decision-making in their day-to-day work.

Focussing on developing increased competencies in the area of QRM will likely result in people with high levels of knowledge of QRM tools – and this should ensure that risk tools are selected that deliver objective results and effective risk controls. New in-house tools could be designed that would deliver more scientific and less subjective risk assessment outputs, and which focus more on preventative controls rather than on detection-related controls. Such competencies could also ensure that risk assessments are informed by a) the controls that may (or may not be) in place, and b) the true effectiveness of those controls. In this regard, the advantages would be as follows:

- All Probability of Occurrence (P) ratings assigned in risk assessment exercises would be based on a formal assessment of the preventative controls that are in place, and/or on the data that support a particular rating.
- All Severity (S) ratings would be based on a formal assessment of the controls that may reduce the severity of a negative event or failure mode, should it occur.
- All Detection (D) ratings would be based on a formal assessment of detection controls.
- All GMP controls important in risk control would be formally assessed for their Qualification or Validation requirements, and the 'Defense in Depth' concepts of other industries would be designed-in from the start.

Competencies in QRM also extend into the other areas. One important area relates to the factors that introduce subjectivity and uncertainty into the outputs of QRM activities. Competency in this area could help assure that the adverse effects of biases and human heuristics (e.g. Anchoring and Adjustment, Representativeness, Availability) are minimised during risk assessments and decision-making. Having sufficient competencies in this area could help ensure that the factors that can influence probability of occurrence estimates – made by Subject Matter Experts (SMEs) and non-SMEs alike - are understood and accounted for when designing QRM tools and their associated procedures. They could also help with the design of robust brainstorming methods for assessing risks, and they could help deal with the factors that can adversely influence risk perception and risk tolerance. Finally, having staff with sufficient QRM competencies could lead to effective risk communications that counteract risk perception problems.

Strategy 3: Demonstrating QRM Effectiveness

The third strategy I am going to mention here concerns demonstrating the effectiveness of a site's QRM activities. The ICH Q10 Guideline outlines the benefits that may be realised by demonstrating the effectiveness of the pharmaceutical quality system. Demonstrating how effective one's QRM activities are is an important aspect of this, given the central role that QRM now plays within the pharmaceutical quality system and within GMP more generally. However, in my own experience, and from discussions with many other GMP inspectors, companies struggle to present evidence that their QRM activities are actually effective. How much risk reduction have the various risk assessment and risk control measures achieved in reality? By how much have they improved the quality of the medicines that are manufactured? How much patient protection have they delivered? These questions usually go unanswered.

While it is difficult to measure, one simple way to better understand QRM effectiveness is to measure the level of **proactive prevention** versus **reactive detection** within a process that had been subject to QRM activities. During risk assessments, one could determine what percentage of total GMP controls in the process are preventative versus detective in nature, as shown in **Figure 2.2**. This ratio could be calculated for each

unit operation and it could be used as a simple but illustrative metric for QRM effectiveness. The ratio of prevention versus detection controls could also be weighted, according to the relative importance of the individual controls, or in terms of how far downstream the unit operation is.

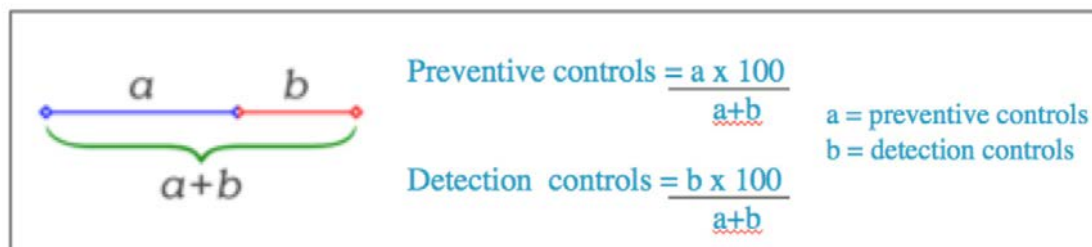


Figure 2.2 — *The ratio of prevention versus detection in relation to GMP controls*

Risk Review is another means by which to demonstrate QRM effectiveness. ICH Q9 cites Risk Review as one of the four elements of the QRM process, but in the experience of many GMP inspectors it is largely ignored and its benefits are often not realised. Many companies seem to struggle with how to perform risk reviews on their manufacturing processes, but they already have the essential components of a formal risk review tool in place through their PQR (Product Quality Review) process. PQRs could be redesigned to serve as a risk review tool and they could also be used to assess QRM effectiveness.

- PQRs could be redesigned to capture and evaluate the outcome of QRM activities on the process / product during the review period;
- They could enable companies to identify weaknesses and strengths in their risk acceptance decision making;
- They could serve as a repository for continuous improvement activities on the process, as well as increases in process understanding.

These data, together with the other standard data in Product Quality Reviews (PQRs), could help companies understand the level of residual risk present in relation to generating sub-standard batches.

6. Final thoughts on the future of QRM

As we work to improve the QRM activities that are undertaken in the GMP environment, it is useful to also consider ICH Q12. This is an ICH guideline entitled “Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management”. It is currently in draft and is undergoing a public consultation at this time (October 2018). One aspect of the guideline concerns the level of oversight that regulators will apply to post-approval changes. Lower levels of oversight than are applied currently are foreseen in certain cases, and it is likely that this will be contingent upon companies being able to demonstrate the effectiveness of their pharmaceutical quality systems, especially with regard to change management.

The ability to measure the extent of risk reduction delivered by change control proposals within a process has the potential to greatly help companies in an ICH Q12 context, as it goes some ways towards demonstrating the effectiveness of the change management processes that are in place.

In addition, having certified and trained individuals in QRM should also be beneficial in an ICH Q12 context as it could help ensure that decision-making for post-approval changes is robust, science-based and not affected by high levels of subjectivity and uncertainty.

Selected References

- **Quality Risk Management in the GMP Environment – 10 years Since the Finalisation of ICH Q9: A Critical Review 2005-2010**, Various Authors & Edited by Kelly Waldron & Paul Pluta, *Journal of Validation Technology*, Vol. 21, Issue 4, December 2015
- **Understanding Problems of Subjectivity & Uncertainty in Quality Risk Management**, Ramnarine, E, *Journal of Validation Technology*, Vol. 21, Issue 4, December 2015
- **The Role of Senior Leadership in Quality Risk Management**, Richter & Haddad, *Journal of Validation Technology*, Vol. 21, Issue 4, December 2015
- **Risk Assessment and Risk Management in the Pharmaceutical Industry**, Vesper, Davis Healthcare International Publishing, 2006
- **On the Psychology of Prediction**, Kahneman & Tversky, *Psychological Review*, 80, No 4, 237 – 251, 1973
- **A Spectrum of Importance - Challenging the Concept of 'Critical/Non-critical' in Qualification and Validation Activities**, O'Keefe, Campbell & O'Donnell, *Journal of Validation Technology*, Vol. 22, Issue 1, February 2016
- **Quality Risk Management – Putting GMP Controls First**, O'Donnell, Zwickovits, Greene & Calnan, *PDA J. Pharm. Sci. Technol.*, May/June 2012, Vol. 66, No. 3. pp 243-261
- **Strategies for Addressing the Problems of Subjectivity and Uncertainty in Quality Risk Management Exercises: Part II – Risk Communication and Perception**, O'Donnell, *Journal of Validation Technology*, Vol. 16, No. 4, Autumn 2010
- **Moving towards Risk-informed Decision-making – A possible path for the EU GMP Environment**, O'Léime, O'Donnell & Greene, Poster presented at the ISPE's Risk-based Qualification & Validation Seminar, Cork, Ireland, October 21st, 2010

3 — Pharmaceutical Manufacturing Quality Risk Management

Professional Framework and Role-Based competencies

Ghada Haddad, Global cGMP Compliance and Auditing Organisation at MSD

1. Introduction

Let me begin by stating that Quality Risk Management (QRM) is my passion, and it is that which led me to embark upon a research journey in the topic. I really enjoyed the other papers on the subject in this monograph, and based on those and my years of experience in the area it is clear to me that the intent of ICHQ9 is not fully realised as such: there are still issues with clarity of decision-making, and understanding of ‘what is our individual role’ in Quality Risk Management? In particular what kind of behaviours should be associated with understanding and applying Risk Management?

My research focuses on developing Quality Risk Management Standards as professional standards for QRM practitioners, and this is the term for the roles I will share with you in this monograph. Based on these professional standards, I am developing role-based technical and behavioural competencies for QRM practitioners in the pharmaceutical manufacturing industry to achieve QRM effectiveness.

i.e. As a QRM practitioner you will have a specific role, and I am exploring the specific technical and behavioural competencies that are needed for these individual roles.

2. Background to QRM in the Biopharmaceutical Sector

The International Conference on Harmonisations (ICHs) ‘Q-topics’ provided the pharmaceutical industry with guidance towards a science and risk-based approach to quality management.

ICH Q9 defines the guiding principles of Quality Risk Management (QRM). In it, QRM was identified as a foundational component to a pharmaceutical industry quality system. In addition, the document outlines a framework for QRM and provides examples of what quality and GMP systems may benefit from QRM application. However, it does not provide application information regarding how QRM can be used to fulfil these purposes.

In my opinion ICH Q9 is a good document in that it has the framework for QRM and provides guidance. However, companies struggle to adopt it, and now, thirteen years since ICH Q9 was published, the benefits of it are still not realised. We have to ask ourselves why?

In addition to companies embracing QRM, in my experience there are differences in regulatory requirements of QRM and in regulatory interpretation. Regulators often have different expectations and it would be useful if additional guidance were provided to the industry, as the lack of concrete guidance constitutes a significant challenge associated with QRM implementation.

Without the critical QRM knowledge required to fulfil their role, those involved in applying the principles of QRM will not understand its benefit and will not be able to sustain it once implemented.

While training is critical to QRM, it only teaches basic concepts in order to execute a task. What is needed is the development of a framework to define and advance individual QRM maturity: defining what each role in QRM does and what kind of competencies are needed in order to advance individual QRM maturity. While we may have mature QRM models at a programme level, I am not sure we have reached the stage where we can measure individual QRM maturity level.

3. Impact and Relevance of Prior Work

Given my work in Quality Risk Management, my passion for the topic, the years spent working on this topic, and my determination and desire to make a difference in advancing this topic, I wanted to pursue academic research aimed at creating value-added, concrete best practices and standard guidance to support the needs of industry Quality Risk Management practitioners. As such, I embarked on a PhD, utilising my experience and previous work to design a research framework with these goals in the forefront.

My QRM journey includes substantial experience in QRM, including installing QRM programmes in two global pharmaceutical companies. In addition, I actively engage with pharmaceutical industry and regulatory thought leaders in QRM through the professional body Parenteral Drug Association (PDA) - a leading global facilitator of science, technology and regulatory information organisation - the Institute of Validation Technology (IVT) Journal, and Knowledge Exchange Network (KENX).

Specifically, my experience includes leading roles in developing industry guidance technical reports to identify what QRM excellence might look like in a practical sense, in particular in the following Parenteral Drug Association (PDA) and Journal of Validation Technology documents:

- Technical Report No. 54, Implementation of Quality Risk Management of Pharmaceutical and Biotechnology Manufacturing Operations; Parenteral Drug Association: 2012
- Technical Report No. 54-2: Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations: Case Study Examples for Quality Risk Management in Packaging and Labelling. PDA 2013
- Technical Report No. 54-3: Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations: Annex 2: Case Studies in the Manufacturing of Pharmaceutical Drug Products; Parenteral Drug Association, Inc.

- Technical Report No. 54-5: Quality Risk Management for Design, Qualification and Operation of Manufacturing Systems, PDA 2017
- Points to Consider for Aging Facilities, PDA 2017
- Role of Senior Leadership in Quality Risk Management, Journal of Validation Technology, December 2015.

In addition, I am a QRM Instructor at the PDA Academy and I have presented widely at international meetings on the topic of 'QRM Integration into Pharmaceutical Systems'.

Based on all this experience I still believe that there is a knowledge gap. Those involved in QRM are often unclear of their roles and responsibilities, especially when it comes to risk control and decision-making.

The most important role in QRM in my opinion is the QRM facilitator: you can't just pick someone off the street to facilitate a risk assessment. There are issues with bias, subjectivity, process knowledge issues, etc. and a facilitator must be aware of these, and has to have the ability to make decisions, influence, guide, lead etc.

4. Research Questions and Research Design

I embarked upon a research study to look at individual QRM roles and associated competencies. The questions I am seeking to answer in this study are:

1. What individual responsibilities must there be in pharmaceutical manufacturing to achieve QRM effectiveness?
2. What are the competencies associated with each of the individual responsibilities?

In addition, I am working on developing a QRM Competency Model for practitioners in the Biopharmaceutical sector.

The research methodology I chose commenced with the prior research I carried out. Then based on that research I established a focus group of experienced global QRM practitioners from industry, Regulatory Bodies and Academia, who took part in a day-long pilot workshop in DIT in February of 2018.

The initial workshop goal was to characterise the competencies needed to further advance QRM, beginning with defining the roles needed for a successful and effective QRM programme. Then, based on those defined roles, I will conduct a competency mapping exercise to identify which key competencies are needed for those involved in QRM based on their role in the organisation. The goal was to focus on developing a model that addresses industry needs through experienced QRM practitioners and regulators' input.

Prior to this workshop all participants completed a survey and at the workshop the results of the survey were shared. In addition, there were discussions on where QRM is currently from a maturity perspective, with respect to QRM programmes and individuals.

Following this pilot study, I determined that a modified Delphi study would be the most appropriate research method to advance my work. The Delphi method is commonly used in academic research as an ideal method to reach consensus among experts, with an advantage over traditional group meeting scenarios in that it doesn't allow for the influence of one person to sway group opinion (Thach & Murphy, 1995; Linstone & Turoff, 1975). The Delphi method is a social research technique which seeks to obtain a reliable group opinion from a set of experts. It is a method of structuring communication between groups of individuals who can provide valuable aid in solving a complex problem.

For my study a Hybrid or Modified Delphi will be used to consider my needs as the researcher and the experts' needs in order to improve the effectiveness of preceding techniques in achieving the scientific and social objectives of the study. All the members of the Delphi study expert team are busy executives in their organisations, and this method is suitable for collecting and combining the knowledge of experts who wish to collaborate in an activity that for them is secondary. My expert group has the knowledge in the subject, but don't have much time to participate in the effort of the study. Also they are based in EU, Asia-Pacific and the US, so it is logistically complex for them to all be in the same place at the same time, and this method avoids that being necessary. In addition, typically in a Delphi study the experts find it an interesting activity that binds them to no commitments, through which they learn, mix with others and test out their ideas, while contributing to a topic they are interested in.

To date, I have carried out the pilot study and survey 1. In addition, I plan to have 2 further Delphi surveys. At the end of my research I hope to publish a competency framework for individual role-based competencies in QRM.

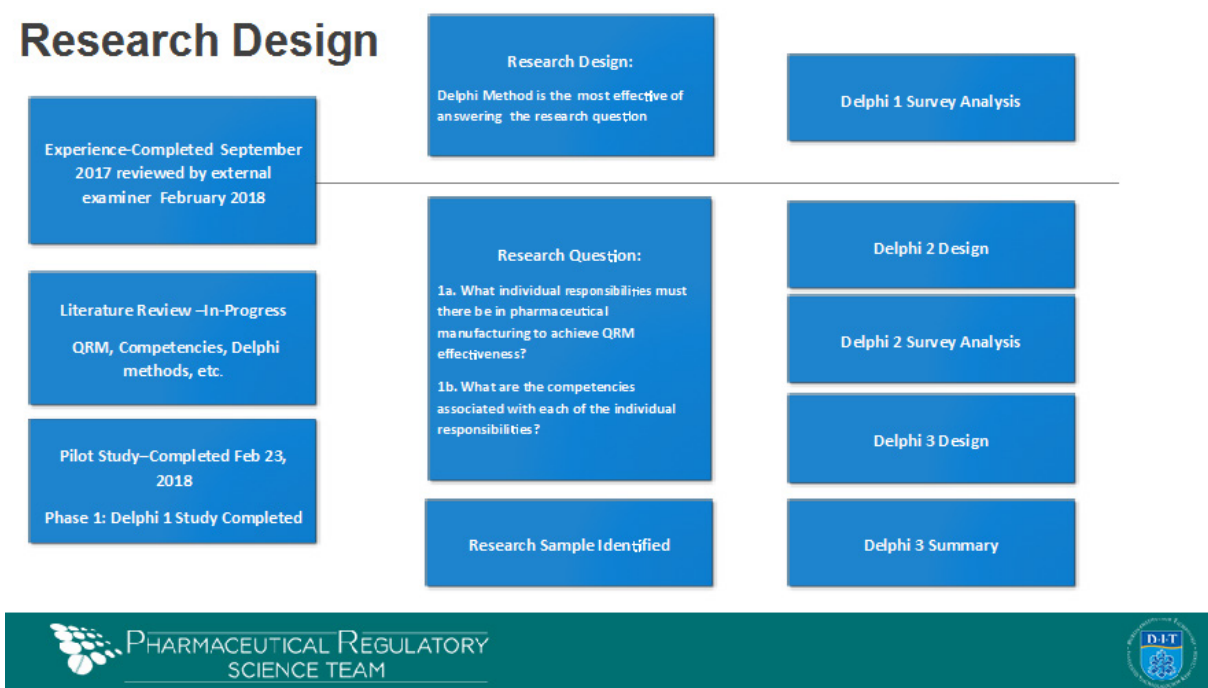


Figure 3.1 — Summary of my research design

5. Research progress to-date

To date, I have identified seven QRM Standard roles based on ICH guidelines, prior research and the Delphi 1 survey and pilot study, as follows:

- i. **Senior Management/Decision Makers:** ICH Q9 emphasises the importance of senior management in decision-making on the status of the risk. They also need to understand the importance of providing resources, not only to carry out risk assessments, but also to support the mitigation of the risks identified. Their role is to understand the external and regulatory environment and to empower people to think proactively, and establish a positive risk culture.
- ii. **QRM Facilitator:** As discussed before in this paper, a QRM Facilitator is essential to not only ensure QRM principles are applied effectively and correctly, but to also adhere to the behavioural competencies during risk management activities. The facilitator must be able to lead the group, understand bias and human heuristics, be able to manage conflict, etc. In my experience not everybody can be a facilitator, not necessarily from a technical perspective, but more from a behavioural perspective.
- iii. **QRM Programme Manager:** Organisations need someone who is responsible to work with management to develop, implement and sustain a QRM programme. In addition, they provide the organisation with continuous learnings while keeping up with latest QRM regulations.
- iv. **Subject Matter Expert (SME):** SMEs are needed for the process and technical knowledge. You need experts from Quality and Manufacturing, including the operators on the floor who are closest to the process.
- v. **Other QRM Users:** This is a new role that I am still searching for a concise word to describe, and I would be happy to take any suggestions! This role is that of for example, the change controllers, or people who handle deviations. They need to be able to understand how QRM is applied in the Quality System. That it is not just a ‘tick the box’ exercise, but a way to determine what the real quality impact of the issue is.
- vi. **Quality Risk-Assessment Lead:** This is a role like that of project manager for a specific risk assessment being done. The role of a QRA lead is to get the right SMEs together with the facilitator to conduct the risk assessment. Then, this person will be responsible for communicating outcomes of QRA to stakeholders and decision-makers, and will be in charge of driving the completion of mitigations.
- vii. **Quality Unit:** A quality unit representative is needed in Quality Risk Assessment to ensure the team is adhering to the company QRM policy and to the regulations. Usually, they get to approve the QRM documents too just like any other GMP documents.

These roles are summarised in **Figure 3.2**.

Roles	Description
QRM Facilitator	Person(s) with the competence and skills to facilitate the QRM process as an independent QRM expert; Facilitate Quality Risk Assessment sessions and provide guidance for completion of QRM documents, risk control and risk review activities.
Subject Matter Experts (SMEs)	Person(s) with the expertise in the area/topic being risk assessed who is able to provide technical expertise to support QRM activities including identification and implementation of risk controls
QRA Lead	Person(s) with the competence and skills to manage the planning, completion, communication, review and approval of QRM deliverables as well as tracking of risk controls measures
Other QRM Users	Person(s) with basic QRM understanding to apply it as an enabler to the Quality Systems. These include staff in all areas of GMP who are expected to apply risk based principles within their work (e.g. change controls, deviations, batch record review, etc.)
Senior Management Staff/Decision Makers	Person(s) with the competence and authority to make timely QRM decisions and who is authorized to accept the risk and direct response strategies for risk mitigation and follow-up. Person(s) with the authority to provide resources to conduct quality risk assessment and management activities, including implementation of risk control measures.
QRM Program Manager	Person(s) with the competence to develop and consistently deploy a QRM program across manufacturing site/operation within the area of responsibility.
Quality Unit	Person(s) with the competence to review, assess, and approve QRM documents within areas of responsibility, while ensuring compliance with internal Quality System requirements and external regulations

Figure 3.2 — Summary of proposed QRM roles

Currently, I am preparing to send my Delphi 2 survey questionnaires to the QRM focus group discussed above.

The purpose of these questionnaires is to identify key areas of consensus and divergence among respondents on the need for QRM role-based technical and behavioural competencies.

This Questionnaire has 4 parts:

- **PART 1** – About you, the expert respondent
- **PART 2** – About Quality Risk Management roles
- **PART 3** – Role-based QRM technical competencies
- **PART 4** – Role-based QRM behavioural competencies.

Based on the results of the questionnaires I will be developing core individual competency standards for QRM Practitioners in the Pharmaceutical Industry. I hope to publish it Spring 2019, and it will be available to download from arrow.dit.ie.

References

- Linstone, H.A. and Turoff, M. (Eds) (1975 and 2002) *Delphi Method: Techniques and Applications*, Addison-Wesley: USA
- Thatch, E. and Murphy, K. (1995) 'Competencies for distance education professionals', *Education Technology Research and Development*, 43(1), 131-150

4 — A Blueprint for Knowledge Management in the Biopharmaceutical Sector

Paige Kane, MSD Knowledge Management Center of Excellence

1. Introduction and Research Context

This paper provides a brief overview of my four-year PhD journey exploring Knowledge Management (KM) across the product lifecycle in the Biopharmaceutical sector. When embarking on my research I was keen to bridge knowledge management theory to practice in, and for, the biopharmaceutical sector. So here I present a brief overview of the context of my research and a summary of my outputs.

Prior experience working across multiple phases of the biopharmaceutical product lifecycle uniquely positioned me to explore the challenges of managing biopharmaceutical lifecycle knowledge. In my 25 years in the sector, I have had the opportunity to provide quality oversight for toxicology studies in good laboratory practices (GLP), good clinical practice trials in animals and humans (GCP), and have held several operational roles in the good manufacturing environment (GMP). As a result, I have had first-hand experience of the challenges arising due to the difficulty, and sometimes inability, to find the knowledge we should know. This results in business and compliance challenges when we cannot effectively use that knowledge. These points are also made by Kevin O'Donnell earlier in this monograph e.g. product defects, drug shortages, inability to deliver medicines to patients in a timely manner because of rework or relearning.

As an industry, we are not learning from how others effectively manage knowledge. My study focuses on how we take those learnings from others, apply them to the sector and enable knowledge to flow to where it is needed.

2. Research Drivers, Methodology and Research Questions

A key research driver for me was the realisation that despite being a highly regulated industry, the Pharmaceutical Industry is not unique. To quote from Cindy Hubert (Trees & Hubert, 2017, p. 48):

'The Pharmaceutical Industry has a very strong belief in its own uniqueness.'

Investigating further we find that aerospace and nuclear industries are also highly regulated and have a keen focus on KM and Risk Management. Reflecting on knowledge management for our sector, it is discussed by six sentences in ICH Q10. Since the publication of Q10 in 2008 we haven't seen a lot of conversation on KM.

I think that is because it is a bit ambiguous: while everyone agrees that we must manage our knowledge, it is very difficult to understand what exactly that means, and what it looks like to implement KM.

At the commencement of my research in 2014 very little guidance existed on how to manage product and process knowledge. My literature review was challenging as I pondered '*Why can I not find relevant literature?*' After countless hours of research, I concluded that it did not exist. Conversely, ICH Q10 twin enabler of Quality Risk Management (QRM) has a dedicated ICH Guidance document (Q9) since 2005 and is the topic of many publications and industry discussions. This realisation further fuelled my desire to pursue this research.

The **aims** of my research were to explore how best to *utilise existing new and emerging pharmaceutical knowledge* to enhance the **quality of medicinal products**, by examining approaches to facilitate *flows of knowledge* in order to **reduce the risk of failures affecting the business or the patient**.

In order to address these aims I developed the following research questions to focus my study:

- **Q1** — What are the current levels of adoption of Knowledge Management in the Biopharmaceutical Sector?
- **Q2** — What is 'Critical Knowledge' and 'Prior Knowledge' in relation to the product realisation and continuous improvement vision of ICH Q10?
- **Q3** — What would a Pharma KM Blueprint look like to help the industry start moving along the curve to implement Knowledge Management?

3. Research Outputs

In the course of my study I contributed to the body of industry knowledge by leading focus groups, chairing conference sessions on the topic, and presenting widely, building the momentum for Knowledge Management within the sector.

In addition, I was part of the editorial team and key author of a book entitled: '*A lifecycle approach to knowledge management in the biopharmaceutical industry*' (Calnan, Kane, Lipa, & Menezes, 2018). This book is unique in that it is a book on Knowledge Management specifically written for the sector. It includes perspectives from Regulators, Patients, Academics and Industry case studies from clinical, manufacturing and commercialisation areas.

As my work matured, I developed a range of tools and assets to support knowledge management, using insights gathered from over 230 focus group participants over three years. These informed the major output of my research - the Pharma KM Blueprint - which is designed as a methodology to start bridging the gap from KM theory to practice, and is shown in **Figure 4.1**:

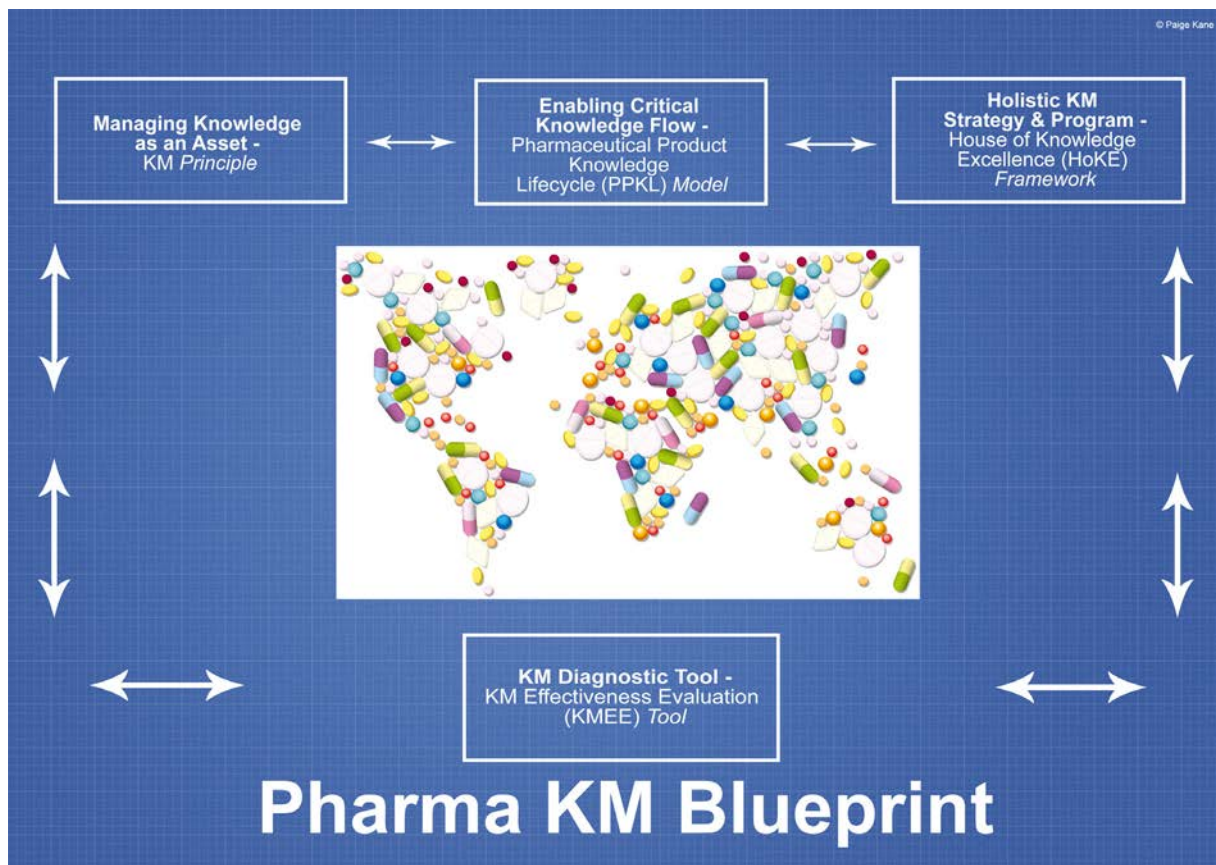


Figure 4.1 — Pharma KM Blueprint (Kane, 2018)

3.1 The Pharma KM Blueprint

The Pharma KM Blue print is composed of four elements:

- i. Managing Knowledge as an Asset
- ii. The Pharmaceutical Product Knowledge Lifecycle (PPKL) Model
- iii. The House of Knowledge Excellence Framework (HoKE)
- iv. Knowledge Management Effectiveness Evaluation (KMEE).

i. Managing Knowledge as an Asset

The first component of the blueprint addresses the need to value and maintain *knowledge assets* in the same way as physical assets within an organisation.

Example – A Bioreactor

If we treated our knowledge like we do a bioreactor, what would that look like?

We would do considerable research on our equipment before spending money to design/purchase or a bioreactor. We give a lot of thought to how we use it, where it fits in the facility - the more we use the bioreactor the more value it brings. Empty equipment that is not making product doesn't bring us value.

So, thinking of Knowledge as an asset: like the bioreactor, the more the asset is used the more value it creates. That can be said for knowledge also: the more we use it the more value it creates.

Assets can appreciate or depreciate. Not all knowledge has the same value over time. There is some knowledge that we just don't need anymore, and that's ok. We have record retention policies to deal with explicit knowledge past its useful life.

Both physical and knowledge assets have a value: they can be traded. When I think back to my time working in the start-up of a manufacturing facility, we had subject-matter experts (SMEs) coming in from all over the world to bring their knowledge to help us start up the facility. You can buy some knowledge. The industry spends a lot of money on consultants for good reason: because they have knowledge we don't.

My founding premise is that there is a market value for knowledge, so it must be treated as an asset, and we must manage it as an asset. Linking back to the bioreactor example, there is a process to manage, maintain and decommission a bioreactor. Do we have such processes and roles to manage our knowledge? Reflecting on this notion may mean we need some new roles in our companies that don't already exist.

ii. The Pharmaceutical Product Knowledge Lifecycle (PPKL) Model

The second component of the Pharma KM Blueprint addresses the challenge of enabling knowledge flow in order to increase visibility, access and use of the product and process knowledge assets across the product lifecycle. To encourage this, I reimagined the pharmaceutical lifecycle as depicted in **Figure 4.2**:

Pharmaceutical Product Knowledge Lifecycle (PPKL) Model

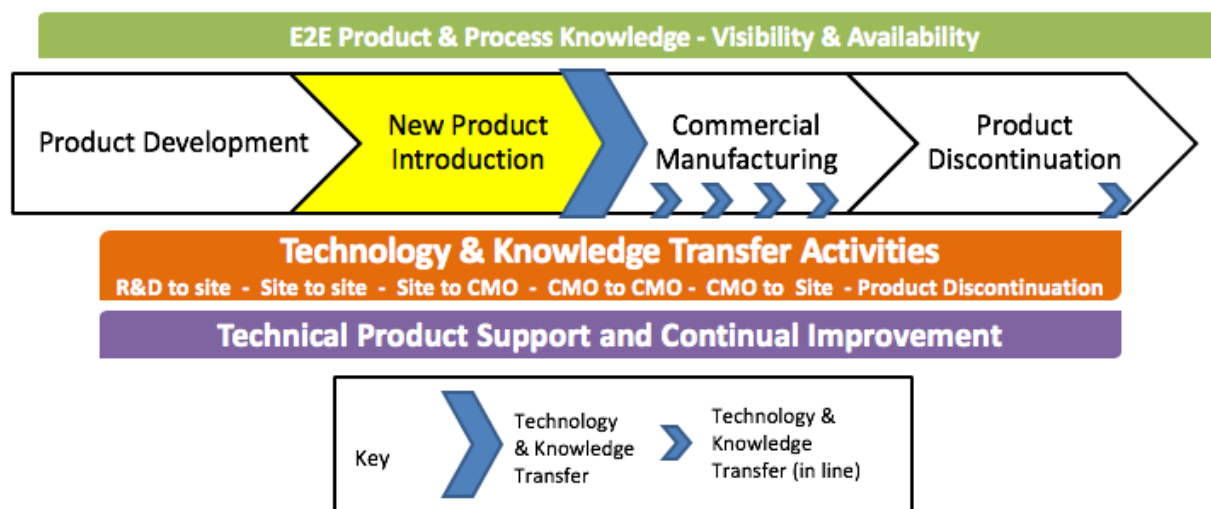


Figure 4.2 — Pharmaceutical Product Lifecycle (PPKL) Model (P. E. Kane, 2018)

In practice, who owns the product knowledge across the lifecycle? In my experience it is fluid and typically changes (if even acknowledged) as the product moves along the lifecycle. Sometimes it is a team of people: we know the saying “when it is everybody’s job, it is nobody’s job!”

We need to think differently about how we manage product and process knowledge. This is reflected in the Product lifecycle model which is adapted from the diagram in ICH Q10 (Figure 4.2). The ICH Q10 diagram is very important as it is one of the few places where the lifecycle model is articulated. It depicts ‘technology transfer’ as one stage in the lifecycle. However, I believe technology transfer is not a once-off activity, nor is it a linear activity. It is an activity that for many products will happen multiple times in its life. Technology Transfer is a knowledge-rich step where a tremendous amount of knowledge is generated. Much of this knowledge is tacit knowledge, which is in somebody’s head: it is *what we know*. Do we have a way to really capture that tacit knowledge? In particular, when we look ahead to ICH Q12 and the promise of regulatory relief, there is a tremendous expectation that we understand our products. In order to demonstrate that we understand our product and process knowledge, I would suggest that it is more than risk assessments that we need.

So, in my research I present a different way to look at the product lifecycle to enable us think differently about how we manage our knowledge. In the PPKL model shown above ‘*Technology Transfer*’ is depicted by blue arrow symbols, and in fact, I prefer to call it ‘*Technology and Knowledge Transfer*’ as it is the knowledge that we are transferring. In the model the Technology Transfer activities occur throughout the entire lifecycle. The emphasis on them may be different at different stages, hence the different sizes of the blue arrows. In addition, we should think about what business processes we need to enable knowledge flow throughout the lifecycle of the product. Whether we are doing a technical transfer or not, there are always technical

support and continuous improvement activities. Thinking about continuous improvement activities, when you capture that knowledge is that available to all? Often it is stored somewhere different than with the rest of the knowledge of that product, making it challenging to get a holistic view of *what we know* about a product.

Another topic we don't reflect much on is product discontinuation, a key lifecycle phase identified by ICH Q10. When we discontinue a product, do we think about what knowledge we need to keep? I suggest we typically focus on record retention, but if we have other products on similar platforms we may be losing valuable knowledge about them if we don't consider this as a knowledge sharing opportunity.

The focus on this reimagined Pharmaceutical Product Lifecycle (PPKL) model is on End-to-End process knowledge. Removing the silos, which can be generated by roles in the lifecycle, and focusing on what we need to do to make the knowledge visible to everyone along the lifecycle. In addition, in the course of my research it became apparent that it is difficult for product development teams to get knowledge and learnings back from commercial manufacturing activities. We need to ensure knowledge is not just flowing from left to right in the diagram.

iii. The House of Knowledge Excellence (HoKE) Framework

The third component of the Pharma KM Blueprint is a framework for a systematic KM programme linked to strategic objectives of an organisation, incorporating KM practices, pillars (people, process, technology, governance), and enablers to support the effective management **and** flow of knowledge assets.

This Framework, entitled 'The House of Knowledge Excellence Framework', is published by Kane and Lipa, 2018, and is depicted in **Figure 4.3** (opposite).

The House of Knowledge Excellence is a high-level overview of what a knowledge management **programme** would look like. To enable the flow of knowledge (not the management of knowledge) this programme suggests looking at the four pillars of people, process, technology and governance. Where there are very specific practices, most not unique to the pharmaceutical industry, which should be adopted to enable flow, the systematic approach to Knowledge Excellence must reflect the direction of the organisation. It has to deliver value and there has to be some catalysis for success.

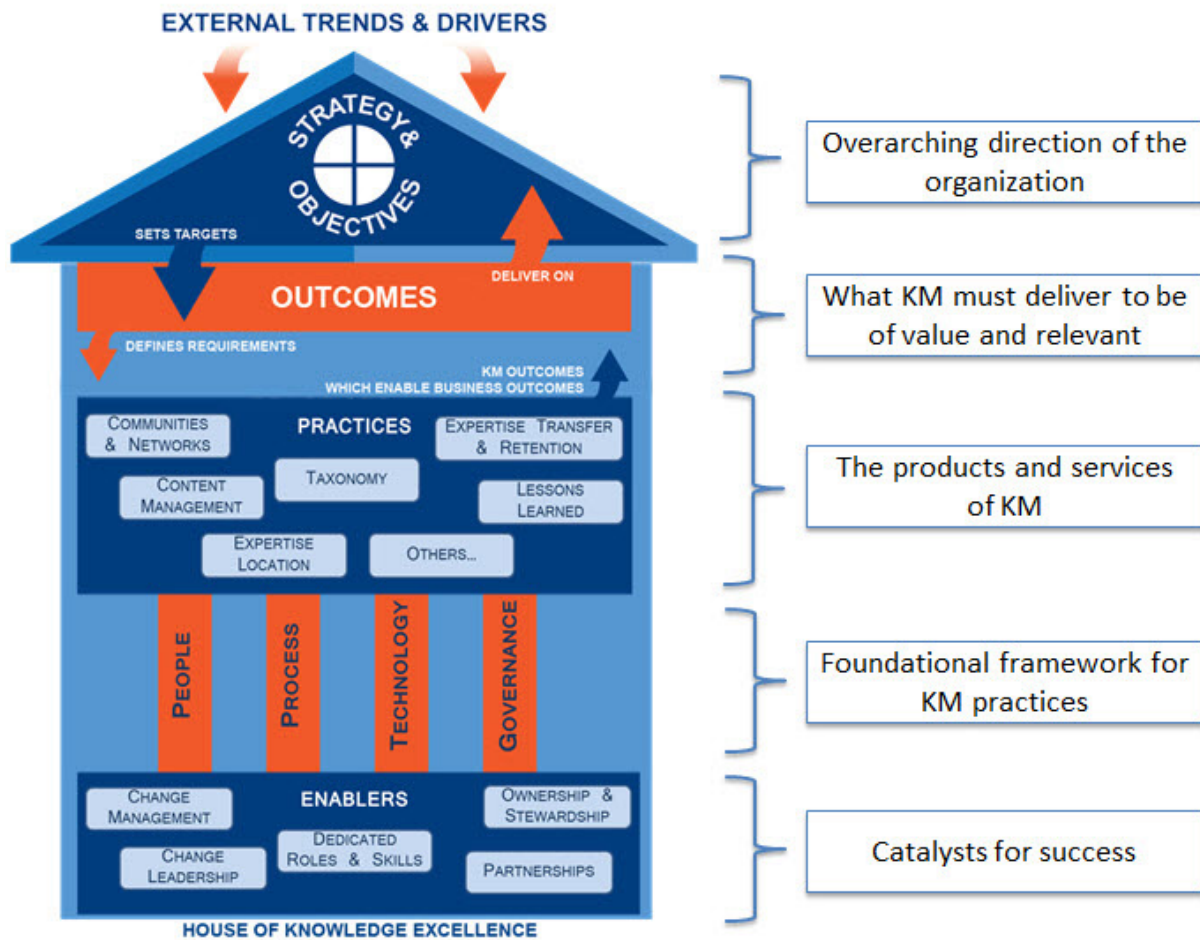


Figure 4.3 — House of Knowledge Excellence Framework (P. Kane & Lipa, 2018, p. 219)

iv. Knowledge Management Effectiveness Evaluation (KMEE)

The final component of the Pharma KM blueprint is a practical KM diagnostic tool that may be used to identify and evaluate areas of opportunity and to track progress on closing knowledge gaps. This is an on-the-ground practitioner diagnostic which can be used by teams to pose two important questions:

- **Q1** — Are teams/organisations availing of knowledge tools and best practices they have?
- **Q2** — Do they understand what knowledge they need and their knowledge flow problems?

This evaluation diagnostic evaluation includes examples of how identified gaps can be closed.

4. Conclusion and further information

In conclusion, the main output of my research is the **Pharma KM Blueprint** which presents the principle of managing knowledge as an asset, the reimagined lifecycle of a pharmaceutical product model depicting how knowledge can flow, the holistic programme for KM, and the diagnostic tool. The items can be used separately or in conjunction to lay the foundation for how you can approach knowledge management in your organisation.

For further information on the Pharma KM blueprint and all the elements presented in the paper, I direct you to my PhD thesis entitled 'A blueprint for Knowledge Management in the Biopharmaceutical Sector' and is available to download from the DIT repository Arrow, at the following link:

<https://arrow.dit.ie/do/search/advanced?q=author:%22Paige%20Kane%22&start=0&context=490738&sort=score&facet=>

References

- Calnan, N., Kane, P., Lipa, M., & Menezes, J. C. (2018). *A Lifecycle Approach to Knowledge Excellence in the Biopharmaceutical Industry*. (N. Calnan, P. E. Kane, M. J. Lipa, & J. C. Menezes, Eds.). Boca Raton, FL: CRC Press.
- Kane, P. E. (2018). A Blueprint for Knowledge Management in the Biopharmaceutical Sector. Dublin Institute of Technology. Retrieved from [https://arrow.dit.ie/do/search/advanced?q=author:%22Paige Kane%22&start=0&context=490738&sort=score&facet=](https://arrow.dit.ie/do/search/advanced?q=author:%22Paige%20Kane%22&start=0&context=490738&sort=score&facet=)
- Kane, P., & Lipa, M. (2018). The House of Knowledge Excellence— A Framework for Success. In *A Lifecycle Approach to Knowledge Excellence in the Biopharmaceutical Industry* (pp. 181–224). Boca Raton, FL: CRC Press.
- Trees, L., & Hubert. (2017). Accelerating the opportunity for the pharmaceutical industry through Knowledge Management. In *A Lifecycle Approach to Knowledge Excellence in the Biopharmaceutical Industry* (p. tbd).

5 — Framework for improving quality decision-making practices and building institutional knowledge management (KM)

Magda Bujar, The Centre for Innovation in Regulatory Science (CIRS)

Note — This presentation describes the work undertaken by the Centre for Regulatory Science (CIRS) in the area of quality decision-making, which has also been the focus of my doctoral research.

1. Introduction to CIRS

The Centre for Innovation in Regulatory Science (CIRS) is a neutral, independently managed UK-based subsidiary company, forming part of Clarivate Analytics (UK) Limited. CIRS's mission is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and health technology assessment (HTA) policies and processes. CIRS provides an international forum for industry, regulators, HTA and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science and to facilitate access to medical products through these activities. CIRS key international stakeholder organisations include many of those who attended the seminar in the Dublin Institute of Technology in October 2018 on which this monograph is based.

The CIRS quality decision-making programme (**Figure 5.1**) represents a natural evolution of CIRS's work which has initially focused on performance metrics to benchmark regulatory agency and company process timeliness, followed by focussed research in the area of good submission and good review practices, and lastly benefit-risk assessment of medicines, where CIRS developed a framework for documenting this process. CIRS initiated work in the area of quality decision-making in 2011 with an aim of developing a framework for improving quality decision-making during the lifecycle of medicines.

Quality Decision Making

4

➤ The Quality Decision Making programme represents a natural evolution of CIRS's work and it has been initiated in 2011

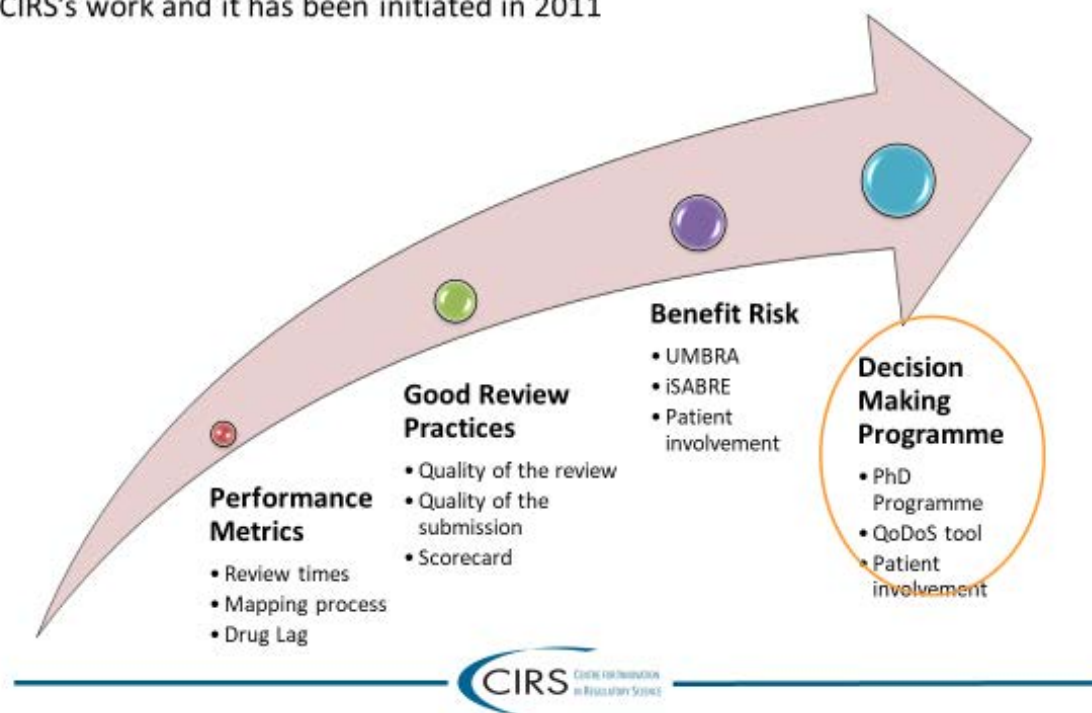


Figure 5.1 — CIRS quality decision-making model

2. The importance of decision-making

Most companies and agencies currently focus on decision-making outcomes as opposed to the process for making the decision. Nevertheless, as noted in Smart Choices (1999), “Decisions under uncertainty should be judged by the quality of the decision making, not by the quality of the consequences.”. Furthermore, as noted by Professor Larry Phillips, Lecturer and Consultant in Decision Analysis (LSE), *“In an uncertain world it is perfectly possible to take a good decision that has poor consequences and equally to make a bad decision and come up with a good outcome. On balance, however, the long-running use of good systems for making decisions will generally give better outcomes”*.

The focus of CIRS's work has been therefore on the process of decision-making to enable quality and ultimately to increase the probability of favourable outcomes. The programme aims to improve awareness of biases and best practices in decision-making in companies and agencies, develop, publish and validate frameworks and tools for use by organisations, and ultimately help organisations to incorporate quality into key strategic decision-making processes.

3. The development of best practices in decision making

In 2010, CIRS and Dr Ronan Donelan, in collaboration with Professor Stuart Walker, Professor Sam Salek and Cardiff University, initiated a study to develop best practices for quality decision-making. In the qualitative stage of the research, in-depth structured interviews were conducted with 29 key opinion leaders from the European Medicines Agency (EMA), the European Union (EU) National Regulatory Agencies, EU and US pharmaceutical companies and US Contract Research Organisations regarding their understanding of the approaches and influences in individual and organisational decision-making during the lifecycle of medicines.

Analysis of the output from these interviews using NVivo 8© software resulted in the identification of 32 major and 97 sub-themes, which were consolidated into 19 overarching themes, as exemplified with quotes from interviews below:

Example Theme 1: Experience in previous decision-making

“What qualifies a person to make decisions? Is it scientific or professional training? It is a subjective matter and worth investigating” Pharmaceutical Company.

Example Theme 2: Individual versus corporate decision-making

“There is a difference between the corporate decision-making process and that of the individual. We have a good understanding of how a committee makes a decision, but we do not necessarily understand how individuals on that committee have made their own decision” Regulatory agency.

Example Theme 3: Education and awareness of evolving decision-making techniques

“It is important that we are trained in decision-making. We also need an understanding and practical application of the tools that can assist our decision-making” Pharmaceutical company.

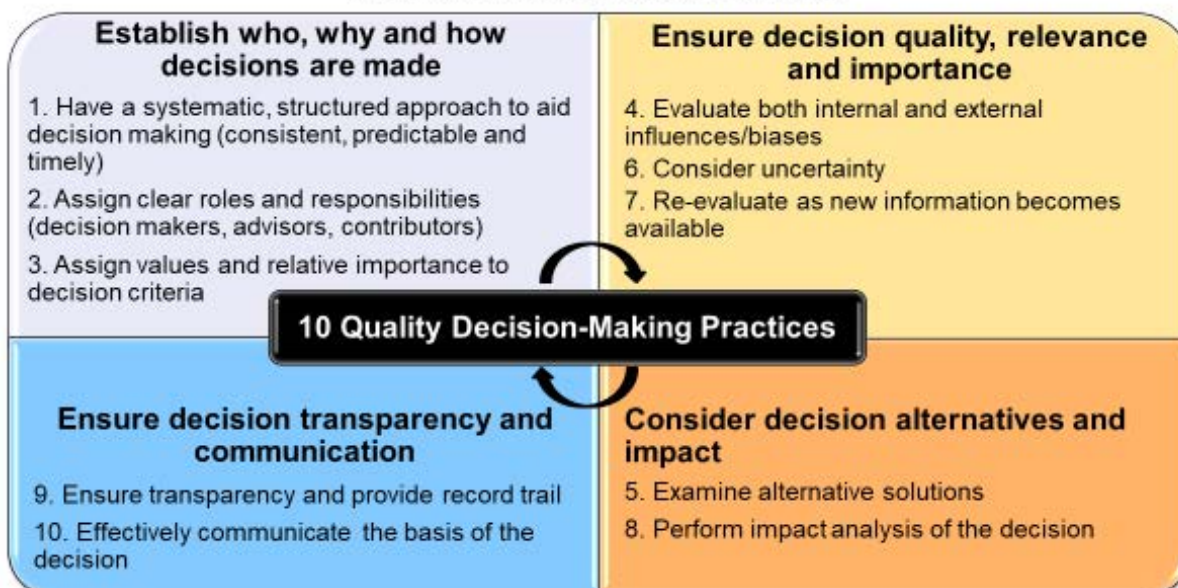
These themes were further distilled into ten Quality Decision-Making Practices (QDMPs) which can be structured into four areas: *Structure and Approach, Evaluation, Impact and Transparency and Communication.*

Although these may seem like common sense to organisations, they are not always common practice, as demonstrated through subsequent studies.

10 Quality decision-making practices

9

Quality is difficult to define, but we can define the practices that make up a quality decision-making process



Donelan, R., Walker, S. and Salek, S. (2015). Factors influencing quality decision-making: regulatory and pharmaceutical industry perspectives. *Pharmacoepidemiology and Drug Safety*, 24(3), pp.319-328.

Figure 5.2 — Ten quality decision-making practices

4. Evaluation of decision-making processes, challenges and solutions

In 2015-2017 CIRS carried out studies with pharmaceutical companies (regulatory and health outcome departments) as well as regulatory and HTA agencies using structured questionnaires to determine the processes, challenges and solutions to quality decision making. As many decisions are made within these organisations on a daily basis the study was anchored to specific high-level decisions made by the organisations, namely the submission and assessment of medicines. Questionnaires on reimbursement decision making were sent to 16 HTA agencies in Australia, Europe, Canada and Latin America and 24 multinational companies. The responses were compared with published results of questionnaires sent to 25 companies and 14 regulatory agencies in Australia, Asia, Europe and North America. An average response rate of approximately 65% was received from the four groups, which suggested interest in this topic.

Some similarities were identified between the decision-making processes of pharmaceutical companies, regulatory authorities and HTA agencies, such as the use of committees, and having a primarily mixed (qualitative/quantitative) internal decision-making system. Nevertheless, the results indicate differences as companies and agencies use diverse processes to arrive at the final decision, either through consensus,

through majority vote, or an individual making the decision. Secondly, the study evaluated the use of frameworks to structure the decision-making processes within companies, regulatory authorities and HTA agencies. Importantly, although the majority of agencies and companies have a framework in place that forms the basis of their respective decision-making process, a formally defined and codified framework was not always used within organisations, particularly within companies, whereas a number of participants used an informal framework which had never been clearly agreed but over time became practice (by “custom and practice”).

The only way organisations can learn how to make better decisions is by first evaluating the quality of their decision-making. Consequently, companies and agencies were asked whether there are evaluations in place to periodically measure the quality of decision-making. The results indicated that companies and agencies did not generally have such formal assessment in place, despite recognising the need to improve how they currently make decisions.

The following key challenges for quality decision-making were identified from the questionnaires:

- Occurrence of biases: optimism, stability and historical biases from previous decisions
- Misalignment and competing interests
 - » Internally, for example, within companies - between HTA and regulatory functions and requirements (focus primarily on registration)
 - » Externally, for example, relating to agency requirements and standards – local versus global; HTA versus regulatory
- Time pressure – need to decide quickly and reluctance to start early.

Furthermore, the respondents proposed the following solutions to address those challenges:

- More formal review of decision-making process, outcomes (both positive and negative) and feedback from stakeholders
- Establish or implement a structured DM framework/method that requires values/preferences/uncertainty to be made explicit
- Education and training regarding decision-making and communication.

5. Development of an instrument for assessing quality decision-making practices

CIRS has been contributing to a number of solutions identified by the questionnaires, particularly regarding having a “more formal review of decision-making process” by developing a diagnostic tool for this purpose, the Quality of Decision-Making Orientations Scheme (QoDoS). This project has been initiated in collaboration with Cardiff University and is now continued through a collaboration with the University of Hertfordshire. The QoDoS items were generated from face-to-face semi-structured interviews that were also used to develop the ten QDMPs, as described earlier. Psychometric evaluations including factor analysis, reliability and construct validation were also performed. This study resulted in a 47-item QoDoS instrument organised into four sections namely:

- i. organisational decision-making approaches
- ii. organisational decision-making culture
- iii. individual decision-making competencies
- iv. individual decision-making style.

The 47 QoDoS items can be assessed on a 5-point Likert scale. The questionnaire can be completed in 10-15 minutes. The QoDoS item responses have also been mapped to the 10 QDMPs.

Finally, the practicality and applicability of QoDoS to evaluate quality decision-making was assessed through a study with 76 participants from the pharmaceutical industry and regulatory agencies. The results of this pilot study revealed that 39% of participants said that their organisation never, or only sometimes, used a structured approach to decision-making and that 70% indicated that they have never or only sometimes received training in decision-making. Furthermore, the findings demonstrated that the QoDoS has the ability to identify differences in decision-making between individuals and their organisation as well as differences between companies and agencies.

CIRS is currently undertaking a number of in-depth case studies with companies, regulatory and HTA agencies, using QoDoS to assess the quality of decision making across various committees and teams within the participating organisations. The objectives are twofold: firstly to raise awareness of biases and practices in decision-making, and secondly to identify strengths and areas for improvement and to assess incorporation of best practices within review teams. High level results from selected case studies are currently being prepared for a publication.

What QoDoS does very well is letting individuals see their short-comings in decision-making. Nevertheless, understanding shortcomings is not enough to fix them as it is hard to correct a bias in our decision-making process just by being aware of it. Consequently, it is important that, following a QoDoS study that may highlight potential weaknesses, an organisation’s select frameworks and tools to improve quality and counter the most relevant biases, as well as embedding practices in formal processes to ensure they are applied consistently.

6. Documentation of practices for better decision-making and enabling knowledge management

Building on the past research, CIRS is now seeking to determine what should be documented at the time of decision to improve knowledge management and future decision-making. Indeed, companies and agencies are continually evaluating how to improve their internal decision-making practices and are evolving systems and processes to ensure that not only is quality built into the process but also that accurate information from past decisions is available to inform current and future decisions. As such, companies and agencies want to correlate their decision-making with outcomes, but this can only be done by documenting what would be the expected outcome of the decision at the time the decision is made. Such documentation would enable a comparison of the expected outcome with the actual result and the impact of the decision without “hindsight bias.” This information can help improve future decision-making, and indeed is a way of ensuring that knowledge gleaned is fed back into a learning system, or what today may be called “institutional knowledge management”.

FDA Commissioner, Scott Gottlieb, has also recently highlighted the importance of documentation of quality decision-making for improving institutional knowledge management:

“Right now, if you asked me how we made a particular review decision in the past, I’d begin by asking our review staff if they’ve confronted a similar clinical circumstance, how it was decided and why. We have limited options to query review decisions to extract how we reached certain conclusions. We can’t store and interrogate the scientific precedent we establish every day. This sort of knowledge management system is essential to how we’re modernising medical product review programmes and establish scientific precedents established every day.”

Over the last three years, CIRS, as part of its research into what practices companies and agencies should consider when building quality into the decision-making process, has reviewed what should be documented at the time of a decision. This was deliberated at a CIRS workshop in 2017 when a Syndicate Group identified internal considerations for measuring the processes and outcomes of decision making, as follows:

- Perform status quo analysis of an organisation’s decision-making process and continue to re-evaluate it in future particularly with process improvement initiatives
- Ensure the availability of documentation at the time of a decision
- Examine and highlight the importance of the rationale for quality decision making not just the methodology
- Document the expected outcome at the time of the decision so that there is a basis for comparison
- Assess the quality of decision-making across multiple decisions.

CIRS is currently undertaking research to develop methods for documenting quality decision making, including a checklist-based approach, to ensure the implementation of quality decision-making practices at the time the decision is made.

7. Conclusion

The methods and approaches developed and validated during this programme of research, namely the questionnaires, the QoDoS and the checklist, led to the development of a roadmap for improving the quality of decision-making processes within companies and agencies for key strategic decisions. This roadmap therefore describes the steps an organisation could undertake to improve the quality of key decision-making processes, namely by first defining the decision, evaluating the ten QDMPs and subsequently better incorporating them into their organisational framework, illustrated in **Figure 5.3** below.

Roadmap for Improving Quality Decision-- -Making Practices and Building Institutional Knowledge Management

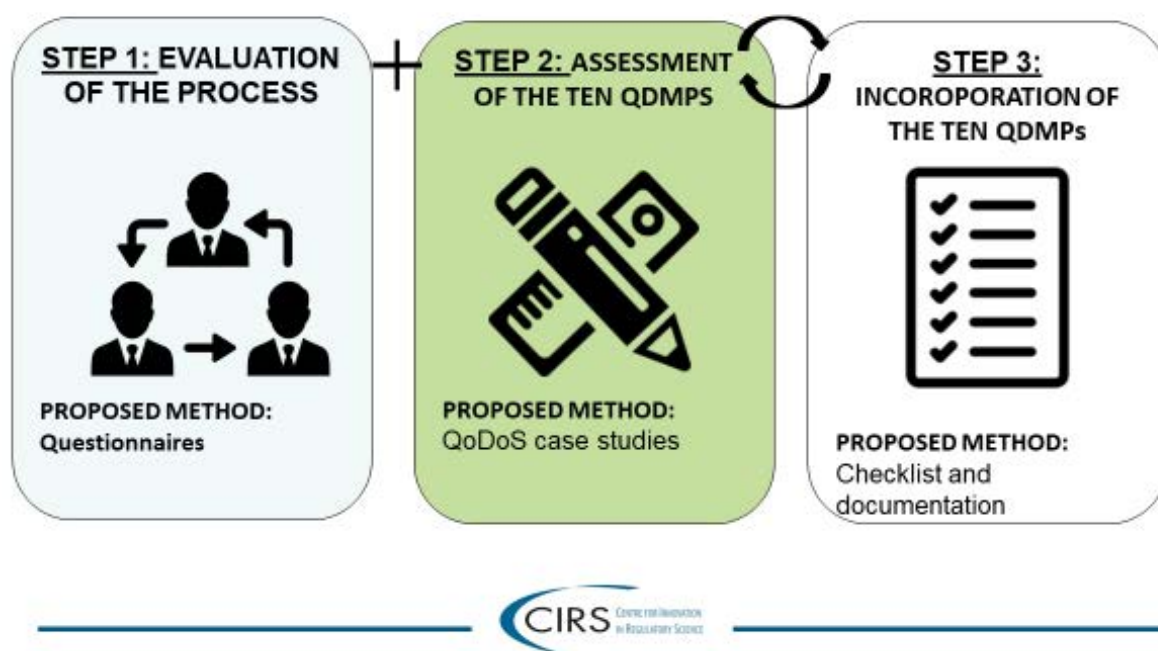


Figure 5.3 — Roadmap for improving quality decision-making

This ongoing CIRS programme of research in the area of quality decision-making marks a milestone in addressing the gap between the well-recognised science of decision-making with that addressed in the area of regulation and reimbursement of medicines. This could revolutionise the way companies and agencies

make and document decisions, which may ultimately increase the probability of good quality outcomes as well as lead to improved organisational knowledge management. Furthermore, as described by one of the CIRS questionnaire participants “the value of quality decision-making is not only just for the decision (and its implications), but to the effectiveness of teams, better productivity between teams and leadership, and to ensure a level of trust across the broader organisation as well as between various stakeholders”.

6 — The PQS for Advanced Therapies – The Role of QRM and KM

Frank Hallinan, University College Cork

1. Introduction

Multi-faceted leadership in sectoral industry research in the pharmaceutical manufacturing sector, such as is evident in this monograph, is really important as we get more breakthrough therapies and as we get more complex technologies. This paper focuses on the Pharmaceutical Quality System (PQS) for Advanced Therapies (ATs) and specifically the role of QRM (quality risk management) and KM (knowledge management) within that system. I will commence by talking about what Advanced Therapies are, the challenges they pose, or, more particularly, the challenges of assuring their quality, and the current pharmaceutical quality paradigm. There will be inevitable overlap with other papers in this monograph, but it is necessary to contribute to discourses about both QRM and KM as they currently are, and as they need to be, to deal with new products into the future.

For me, medicinal products, where the active substances were genetically engineered, with well-characterised biologics, marked the dawn of a new era for medicines. In a way, we are now in a new phase of this new era, and this phase can be considered as the Advanced Therapies era as this new class of more complex biologics are rapidly coming to the forefront. Indeed, some of these ATs are personalised medicines with the various complexities associated with that concept.

In this paper I propose that, in light of the complexities of these new products, we need to look again at the PQS, albeit it is not that old, and how it is configured, particularly with respect to QRM and KM – two really critical elements of the modern PQS. I also want to draw attention to the importance of Regulatory Science Ireland and their support for research and discussion on these matters. In RSI, and particularly with the Dublin Institute of Technology (DIT) and University College Cork (UCC), we have been drawing attention to the need for critical research in regulatory science and the importance of such research for the continuing vitality of this sector in the overall national economy. One practical example where RSI may be able to contribute is in facilitating the move towards a formal certification process for QRM facilitators as mentioned in Magda Bujar's paper.

2. The new era of complexity and Advanced Therapies

In 2017, the USA FDA (Food and Drugs Administration) approved Kymriah, Yescarta and Luxturna, three new AT medicines which illustrated to many that we have entered a new era. Indeed the FDA Commissioner Dr

Scott Gottlieb commented in a news release in December 2017 coinciding with the Luxturna approval that: “... more than 600 active investigational new drug applications related to gene therapy products. Researchers at the Massachusetts Institute of Technology estimate that about 40 gene therapies might win approval by 2022, from a current pipeline of 932 development candidates. They estimate that 45 percent relate to treatments for cancer.”

Dr Gottlieb further stated at the Alliance for Regenerative Medicine Congress in May 2018: “We’re at a key point when it comes to cell and gene therapy. These therapies have the potential to address hundreds, if not thousands, of different rare and common diseases.” So, we can forecast a dramatic change in high-technology medicines with possibly 45% of those related to treatments for cancer. Essentially, this is just the tip of the iceberg. There are a lot of other new products dealing with other medicinal problems on the horizon also. In parallel with this regulatory activity the last year or two has seen a phenomenal growth in business interest in the area at this time, with pioneering companies in this field being acquired by more established BigPharma for eye-watering sums and new governmental initiatives, such as, the Cell and Gene Therapies Catapult in the UK.

2.1 Advanced Therapies

The term Advanced Therapies originated in the European medicines regulatory system and is incorporated into an EU Regulation issued in 2007 (Regulation (EC) No 1394/2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004). Essentially the definition of *Advanced Therapies* includes medicinal products based on three different types of technology, namely: gene therapy, somatic cell therapy and tissue engineering. The FDA traditionally refers to these as *cell* and *gene* therapies. The term Advanced Therapies is gradually gaining broad global acceptance and is becoming more commonly used.

In this context Kymriah and Yescarta are two cell therapies, i.e. the active component of the medicine consists of living cells. They are both CAR T cell therapies, which I will explain further later. Luxturna, on the other hand, is a gene therapy whose active component is a virus that has been genetically engineered to carry a gene into the cells infected by this virus and the expression of this gene has a beneficial therapeutic effect.

Kymriah and Yescarta are both personalised CAR T cell therapies in that they are based on blood-derived T lymphocytic cells from an individual that are modified in the laboratory and then reinfused back into that same individual to achieve their therapeutic effect. This type of product has been described as an arm-to-arm therapy with the patient at its centre. A sample of the patient’s blood is taken and the T lymphocyte fraction purified from the blood plasma. These cells are then cultured *in vitro* in a cell culture laboratory environment during which they are activated and genetically modified using a retroviral vector to express a so-called chimeric antigen receptor (CAR): The CAR T term being the acronym of Chimeric Antigen Receptor T cell. The genetically modified T cells express this receptor on their cell surface as an integral membrane

protein. In Kymriah the receptor is directed against a particular antigen called CD 19. Different CAR Ts could (and indeed are being) generated against various other antigens as well as CD 19. However, CD 19 was selected in the first instance as it is an antigen that is expressed on the surface of B lymphocytes during their development and commonly on cancers that arise from this type of cell - notably B cell lymphomas, acute lymphoblastic leukaemia (ALL), and chronic lymphocytic leukaemia (CLL). The majority of B cell malignancies express normal to high levels of CD19 and it appears that the CD 19 protein plays an active role in driving the growth of these cancers, making it a very desirable target for therapy. The engineered cells are cultured for a period of time to expand, or increase, the number of cells. As that process is on-going, the patient receives a preparative chemotherapy therapeutic regime that will deplete their circulating lymphocytes. Then the engineered CAR T cells are infused back into the patient. Within the patient they grow and divide, and bind to circulating cells expressing the CD19 antigen. Through this binding an immune response is initiated by the CAR T cells leading to killing of the CD 19 antigen carrying cancer cells. Clearly this is very different from the conventional therapies we are used to in the world of pharma or biopharma. The medicine is a living cell rather than a relatively simple (in the case of the classical chemical drugs) or, complex (in the case of the newer protein based biological drugs) molecular substance. Because these Advanced Therapies are so different they present certain new and different challenges in terms of how they must be dealt with to ensure that there is a consistent quality from batch to batch. Indeed, Dr Gottlieb spoke about these challenges in a 2018 presentation to the Alliance for Regenerative Medicine's Annual Board Meeting when he stated that compared to traditional drugs the agency review is focused on the clinical part of the product, with less focus on the product-related issues. But he continued that *"I'd say that this general principle is almost completely inverted when it comes to cell and gene therapy. The initial clinical efficacy is often established early, and sometimes in small series of patients. The more challenging questions relate to product manufacturing and quality, or questions like how much you can change, or enlarge, the gene cassette that you load into a vector before the gene insert will change the conformation of the vector in ways that also fundamentally alter the entire product's safety or performance."* So, the new challenging questions for the Regulator are around quality manufacturing and product consistency issues. As framed by Dr Peter Marks – Director of FDA's CBER Division – who will be the primary point for review of such products, these questions would include issues like:

- Product consistency: e.g. How can the sponsor ensure the extent of lot-to-lot variation in transduction efficiency is acceptable?
- Product tracking and labelling: e.g. For a personalised medicine it is critical to ensure that the correct product is administered to the correct patient, so how does the sponsor guarantee their system is error proofed?
- Testing for potency: Assurance of consistent potency between batches is a foundational element of assuring product quality and one of the key issues for cell and gene therapeutics that may have a number of biological effects is deciding which assays are most appropriate?
- Testing for replication-competent vector: Assurance of product safety requires understanding and

control of the generation of variants of the vector that develop a capacity to replicate. There are different assays in this area but generally all are extremely complex and possess different sensitivities and consequently limits of detection. So, there is an onus on the sponsor to justify the adequacy of their chosen method.

- Personalised products: For most, if not all ATs, the time window for release testing may be limited and there may be insufficient time to execute lengthy assays (e.g. the conventional sterility test). So, the sponsor may need to justify progressing the product to the patient before certain tests have been completed. Indeed, for personalised products (such as CAR Ts) made from biological materials from individuals with serious life-threatening illnesses there can also be difficult decisions to be made if some specifications fail to be met, but the product represents a 'last chance' for the patient.

Many other questions could be asked particularly in regards to the management of changes. Every time the product sponsor needs to deal with different vendors, particularly of critical reagents. How can the sponsor determine the criteria for the acceptance of specific changes that potentially could have ramifications, particularly further along in the process? So, that is just one aspect of the challenges before us.

3. Is the process the product?

At the recent inaugural CASSS meeting on Cell and Gene Therapies in Washington, DC, the keynote speaker CBER's Dr Peter Marks commented that for ATs 'the process is the product'. Interestingly, this is what was always said in the past and was always the key differentiator between small molecule pharmaceuticals and the biological pharmaceuticals. The concept was that small molecule pharmaceuticals can be characterised analytically in the laboratory, whereas biological pharmaceuticals were thought of as akin to a black box. In the context of a situation where 'the process is the product' the implication is that you need to control every element of the process so that you get the same product every time. Otherwise a clinical trial would need to be done with every batch. When rDNA derived protein biologicals became commonly available, along with increasingly powerful analytical methods for their characterisation and routine control, there was a push-back against the simple notion that 'the process is the product'. As a result, over time the notion of the **well characterised** protein biopharmaceutical became established leading ultimately to the acceptance of biosimilars that are similar to, although not necessarily identical to, the originator product. When dealing with a well-characterised molecule change was acceptable once it was done under a comparability protocol type system which was gradually accepted by the major worldwide regulatory agencies. Consequently, Marks's comment seemed potentially controversial but was accepted by the audience without any significant disagreement.

So, for advanced therapies we must start from the position that once again 'the process is the product' and manage in that light the challenges of introducing changes to them, such as scaling up, changing different vendors, and so forth, that seem highly likely to be required through the products lifecycle. In this situation

a key question is how can quality be assured without going back into clinical trials again every time a change like those mentioned above is necessary?

It is clear that Dr Marks had not made an off-the-cuff remark as he has made similar comments in 2015 when specifically speaking about CAR-T therapies. At that time, he said that the quality challenges of CAR Ts included product consistency: fundamentally – how can the sponsor be assured that every lot is the same when there are so many variables that potentially effect it?

Testing for potency was another big topic at the CASSS meeting. It is a very complicated area in a context where protection and the product are the most important things. In summary, with Cell and Gene Therapies we are entering a new era and we must expect to face new challenges around the systems we use to ensure that at all times the patient is protected in the context of a fit-for-purpose quality system.

4. An ideal quality system?

Can we imagine what this pharmaceutical quality system might look like? To do so we need to start with the nature of the entities we want to control and how they differ from what the classical PQS was designed for. Essentially the current PQS as described in ICH Q10, and as shown diagrammatically in **Figure 6.1**, was described when most quality experience had been with small molecules largely (although not exclusively) formulated in relatively simple ways and with the avalanche of protein-based biologicals looming. In transitioning from the small molecule to the biological we went from a relatively small and manageable number of quality impacting variables requiring control to an order of magnitude larger number. In moving to advanced therapies we add further orders of magnitude of impactful variables.

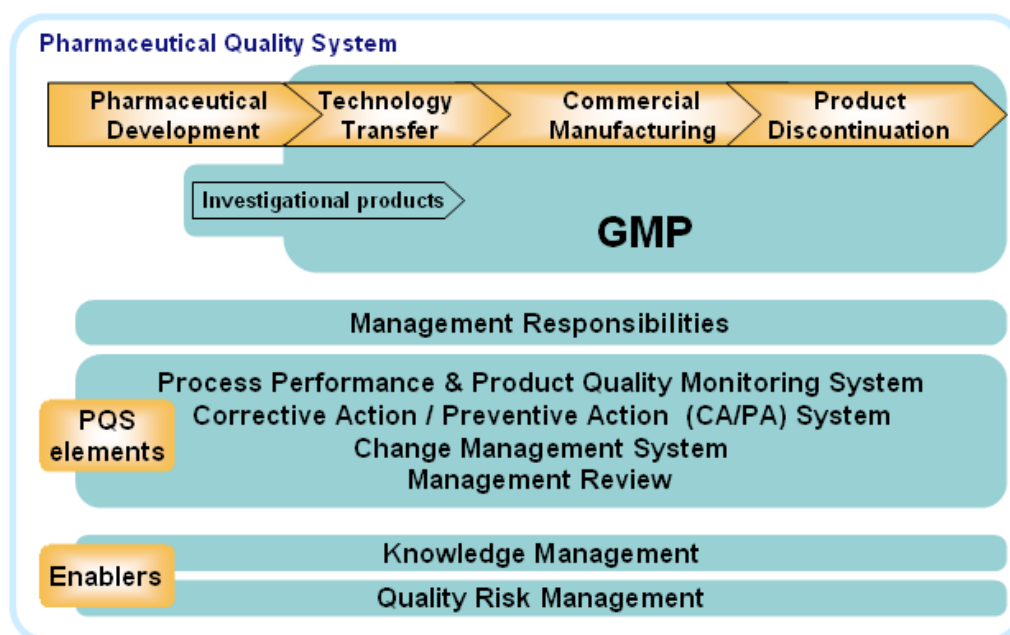


Figure 6.1 — The Pharmaceutical Quality System

Being imaginative, one could envisage that we have gone from something like the horse and carriage via the racing car to the space shuttle as we go through these different entities.

Whatever analogy one uses the reality is that advanced therapies are both highly complex and highly diverse and it seems intuitively obvious that the level of control required, the level of education and training required to assure their control is more demanding and sophisticated than when dealing with the simpler categories of medicines.

It is also sadly the case that, if you look at the history of great technological endeavours like the space shuttle, you can have relatively simple quality and cultural defects leading to human disasters as in the case of the Space Shuttle Challenger where a defective O-ring seal led to the failure. Indeed, it is reported that some of the engineers in NASA at the time suspected the O-ring might not be adequate. Sadly, their concerns never navigated up the management levels in the organisation, which goes to the very heart of the culture in the organisation.

5. The main challenge facing us now

Ultimately, the core issue for Advanced Therapies is the challenge of the number of variables in their manufacture relative to their predecessors. How then can their quality be adequately controlled within the current, conventional paradigm which is the ICH Q10 pharmaceutical quality system and its associated documentation?

The essential thing that must be done is to ensure that the number of impactful variables is manageable and this can only effectively be achieved by continuously, iteratively ranking the variables that impact on the quality of the product. Therefore, the variables with greatest potential quality impact must be identified. These then need to be rank ordered and this order continuously adjusted as more pertinent information is acquired and translated into knowledge. This involves systematic utilisation of all the knowledge that is generated through the life-cycle.

Translating this into the workings of the current PQS approach, quality risk management (QRM) and knowledge management (KM) systems, need to be systematically used from the outset of development i.e. from the inception of the product through its discontinuation. So QRM and KM need to be placed at the centre of the PQS and applied systematically from the very earliest phase.

Arguably there is nothing particularly new about this. Indeed, in the 2003 conception of the ICH Q10 PQS it was stated that the objective of the PQS was to develop a harmonised quality system that covers the lifecycle of the product, that emphasised an integrated system of QA and science, involving both QRM and KM as enablers. So, our PQS becomes all about systematic valid data rather than a more *ad hoc* approach to quality that arguably preceded this. So, in a way, that was conceived at a particular point in time. The diagram in **Figure 6.1** has been around for quite some time and is useful in thinking about the essentials of

the PQS, illustrating the lifecycle from origination, through product development, to transfer and commercial manufacturing, to quality discontinuation.

The role of management is critical. You can see the various elements of the PQS in **Figure 6.1**. You can also see that QRM and KM are considered as ‘enablers’ in the achievement of quality. How then is an enabler to be defined and more importantly how are QRM and KM currently used? An enabler is something that makes it possible for something else to be achieved. So QRM and KM then enable quality or make it possible to achieve quality within the PQS. In reality however, while QRM is very widely used in the industry, its use is primarily as another tool in the quality toolset rather than as a central element or an enabler. It is generally not used, with some exceptions, in a fully-operationalised manner i.e. as a lifecycle-oriented foundational element of the PQS. KM is generally used as a concept more than as a systematic operation. This point is elaborated in Paige Kane’s paper in this monograph.

6. Operationalising QRM

In considering the operationalisation of QRM an organisation needs to recognise that risk **assessment** is not risk **management**. Indeed, QRM is just one component in the total enterprise’s management of risk, and this should also include at least safety risk management, regulatory risk management and business risk management. A fully-operationalised QRM system should have the following three elements:

- **Infrastructural element:** including quality standards, various QRM-related processes, a library of risk assessments etc.
- **Communicative element:** a process of risk reporting, and a process for decision-making tied into the reporting process
- **Training element:** training from the introductory level up to the certification of facilitators for example, is essential with supporting tools and processes.

This need for certified training is also dealt with in other papers in this monograph. So that is what I mean by operationalising risk control.

Finally, it is also essential to have a risk control strategy associated with the product or facility concerned, and an associated risk register, all of which are subjected to systematic risk review rather than periodic review.

7. The future

So, the future ATM PQS will need to have QRM and KM fully operationalised within the pharmaceutical quality system. That means that there is an on-going review of the variables that are most impactful in the context of the known risks to quality and to scientific understanding of the knowledge and processes generated up to that point in time.

QRM and KM need to be co-enablers at the centre of the pharmaceutical quality system, so that they are continuously referenced in quality decision-making with all the other tools. Thus, change control processes need to systematically refer back to the risk register and so on. This approach must commence at the outset of product development and not just be added on at some later point in time.

In conclusion, ATMs are beginning to emerge as effective, highly personalised therapeutic options. This complexity requires a rethink of how they can be effectively controlled to ensure their on-going consistency and adequate quality and safety. The PQS of ICH Q10 provides a good starting-point for this, but we need to ensure that QRM and KM take their place as originally envisaged as ‘enablers’ of quality rather than merely as occasionally utilised tools within the PQS. QRM and KM need to be fully operationalised and integrated into all quality systems. Disposition decisions need to consider, not only the specific data related to that lot of product, but also the overall quality risk profile and the product knowledge profile, updated as of today.

Endnote

This contribution is merely a start and ideally will lead to more dialogue between regulators and the end-users to help define in greater detail what are the required characteristics of this type of use as an ‘enabler’. Hopefully the excellent work of the DIT group will catalyse this dialogue. Such a dialogue is merely the beginning because an effective PQS for Advanced Therapies may also need other changes. So, for example, in terms of culture, we need a culture that firstly motivates the least motivated, and secondly, ensures that knowledge and information are appropriately communicated through the organisation in a manner that is in the best interest of the patient. For regulatory science it is the essential key, and I applaud the academic work that lead to the publication of this monograph. I also applaud the colleagues who continue to give enthusiastic leadership in this regard to continue making Ireland a locus of quality manufacturing for the pharmaceutical industry.

References

1. US FDA DRAFT Guidance for Industry (2016) Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls.
2. ICH (2004) Harmonised Tripartite Guideline Q5E - Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process.

7 — Overview of the proposed ICH Q14 and current developments in Japan

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Summarised by Nuala Calnan, PhD, Dublin Institute of Technology

It is a great pleasure that this seminar afforded the Pharmaceutical Regulatory Science Team in the Dublin Institute of Technology an opportunity to extend a warm welcome to our esteemed and learned colleague Dr Yukio Hiyama on his return to Dublin to share his insights and knowledge with us.

In his closing address to the seminar delegates Dr Hiyama shared an overview of current developments in Japan with respect to medicinal product regulation. He began by addressing what is happening with the Submission/Approval process in Japan, confirming that the Japanese Medicines Regulator, PMDA, had commenced a trial in early 2018 of a new *Comparability Protocol* which was prompted by the international work of the ICH Q12 Post Approval Change Management Plan. In addition, the Ministry of Health Labour and Welfare (MHLW) has published a rational (simplified) *Description Rule for Test Methods* which will now be considered as approval matter within any submission.

Dr Hiyama then shared that within the regulatory process in Japan they have convened a QbD study group which actively contributes to new regulatory developments across a number of subgroups, including Active Pharmaceutical Ingredients (API), ICH Q12 and Post Approval Change Management, Continuous Manufacturing, Control Strategy and Analytical QbD. Both of the new work products included in the submission / approval process outlined above were based on outputs from this study group.

On the subject of what is happening in Japan with regards to the GMP Process, in 2014 the MHLW published a study based on an industry survey which showed that 30% of Japanese GMP Managers were not aware of the 2008 ICH Q10 *Pharmaceutical Quality System (PQS)* guideline. Arising from that, in 2016, the QbD study group developed a PQS-based model for continual improvement as well as producing an example of a typical *PQS Quality Manual*. This has now been adopted by the PMDA inspection division and earlier in 2018 they presented how they will evaluate each organisation's PQS using this new *PQS Model*. To further strengthen the importance placed on the PQS, Dr Hiyama confirmed that it will be incorporated into the overall GMP Ordinance in 2019 or 2020. A final development shared was that a new revision of the Good Distribution Practice (GDP) guideline has recently been published by the MHLW study group.

Moving to his continued work with the *International Conference on Harmonisation* (ICH) Dr Hiyama has been appointed as rapporteur for an exciting new ICH topic which will involve two work streams: a revision of ICH Q2(R1) *Analytical Validation* and the development of a new ICH guidance entitled Q14 *Analytical Procedure Development*. The General Assembly of ICH approved Q2/Q14 (and Q13 Continuous Manufacturing) as new topics in their June 2018 meeting based on a proposal round which had started in early 2017. At that time the US FDA proposed the need for a Q2 revision while the MHLW proposed the need for a new guideline for Analytical Development. Consequently ICH Q2/Q14 will align both topics going forward. The final concept paper for Q2(R1)/ Q14 has been prepared and the first face-to-face meeting of all parties is scheduled for the USA in November 2018.

His friends at colleagues within the PRST commend Dr Hiyama for his tireless dedication to the development of new knowledge which continues to drive improvement in the regulation and manufacture of high quality medicines to the benefit of patients around the world.

End of Monograph



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