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 the 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.

<table>
<thead>
<tr>
<th>Month</th>
<th>Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 2018</td>
<td>Product Mix-up issue at a compounding site</td>
<td>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.</td>
</tr>
<tr>
<td>April 2018</td>
<td>Various Packaging and Labelling Issues</td>
<td>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.</td>
</tr>
<tr>
<td>June 2018</td>
<td>Probable Carcinogenic Impurity in batches of Valsartan API</td>
<td>Global recall. (22 different products across 6 companies recalled in Ireland.)</td>
</tr>
<tr>
<td>August 2018</td>
<td>Use of the wrong excipient resulting in benzyl alcohol contamination of the product</td>
<td>Company’s risk assessment for the issue not accepted by the HPRA. Several batches recalled in Ireland.</td>
</tr>
<tr>
<td>September 2018</td>
<td>Risk of silicone particles in a steroid eye implant product</td>
<td>Global recall, over 80 batches recalled to user level in various countries.</td>
</tr>
</tbody>
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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.

\[
\text{Preventive controls} = \frac{a \times 100}{a+b} \\
\text{Detection controls} = \frac{b \times 100}{a+b}
\]

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


- **On the Psychology of Prediction**, Kahneman & Tversky, Psychological Review, 80, No 4, 237 – 251, 1973


- **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
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.

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

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 year 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:

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 a 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.

**Research Design**

- **Research Design:** Delphi Method is the most effective at answering the research questions.
- **Research Question:**
  1a. What individual responsibilities must there be in pharmaceutical manufacturing to achieve QRM effectiveness?
  1b. What are the competencies associated with each of the individual responsibilities?
- **Research Sample Identified**
- **Delphi 1 Survey Analysis**
- **Delphi 2 Design**
- **Delphi 2 Survey Analysis**
- **Delphi 3 Design**
- **Delphi 3 Summary**

**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.
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**