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Understanding the Concept of Formality in Quality Risk Management

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Abstract

Formality in Quality Risk Management (QRM) is an interesting concept. What makes a QRM activity 'formal' and what makes one 'informal'? A simplistic viewpoint might be that formal is when a QRM tool is used to manage risks, and informal is when no such tool is used. But is it that simple? And are there different degrees of formality in QRM - is it a spectrum, or is it a binary concept? These questions are explored in this paper. Since the introduction of ICH Q9 in 2005, there have been discussions in the pharmaceutical industry and between regulators regarding the concept of formality in QRM. ICH Q9 presents two principles of Quality Risk Management, and one of those refers to formality – it states that “the level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk”. What formality in QRM means at a practical level is currently not clear. A lack of understanding of this concept has probably led to certain negative consequences – ranging from a lack of scientific rigour being applied during certain complex risk assessments, to the overuse of quite resource intensive and highly formalized QRM activities to address relatively straight forward GMP problems and risk questions. In response to this lack of clarity, regulators and industry representatives initiated work to explore the concept of formality in QRM, with a view to achieving a shared understanding as to what it means at a practical level. It was of interest that there was strong support expressed among industry and GMP inspectors for the use of less formal approaches to QRM. The primary outcome of that work is a set of suggested definitions for formal and less formal approaches to QRM. There are several anticipated benefits to this work – including that a better understanding of formality may lead to resources for QRM being used more efficiently – where lower risk issues are dealt with via less formal means, freeing up resources for managing higher risk issues and more complex problems, which usually require increased levels of rigour and effort.

1. Introduction - Why discuss formality in Quality Risk Management?

Understanding formality in QRM is not just of academic interest - it is of practical relevance to the day-to-day application of QRM in pharmaceutical manufacturing and control. This is because the guideline that has served as the basis for most risk-based approaches in the pharmaceutical industry for the past 15 years, ICH Q9 (1), places formality (alongside other concepts) firmly at the centre of QRM. ICH Q9 indicates that, although 'a systematic approach to quality risk management is generally preferred, it is neither always appropriate nor necessary to use a formal risk management process'. It indicates that the use of 'informal risk management processes may also be acceptable'.

ICH Q9 presents two principles of quality risk management:

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

With regard to the reference to formality in the second principle, it is useful to consider what this means at a practical level, as, while it may seem intuitively easy to grasp, our experience is that the concept of formality in QRM is not so straight forward. Our research has found that it remains unclear to many practitioners in the pharmaceutical industry, and to many GMP Inspectors too, just what formality in QRM actually means, and what differing levels of formality might look like in practical terms. The purpose of this paper is to present our work in this area and to put forward suggested definitions for formal and less formal approaches to QRM, in an effort to bring clarity to this concept. A greater understanding of formality in QRM has the potential to lead to more fit-for-purpose applications of QRM, the better use of resources for such work, more effective, scientific and data-driven risk assessment outputs, and an improved level of GMP compliance overall.

2. Exploring the Concept of Formality in Official Guidance and Standards

The use of formalised Quality Risk Management (QRM) approaches in the pharmaceutical manufacturing sector was catalysed by the publication of ICH Q9 in late 2005. Since then, and with the publication of the ICH Q8(R1) (2), Q10 (3), Q11 (4) and more recently the Q12 (5) guidelines, there has been a steady move towards *risk-based* approaches in the industry generally.

As noted above, the concept of formality is embedded in one of the two core ICH Q9 principles of QRM. Apart from that, the guideline makes several other references to formality in QRM too. In its introductory section, for example, it states: "It is neither always appropriate nor always necessary to use a *formal* risk assessment process (using recognised tools and/or internal procedures, e.g. SOPs). The use of *informal* risk management processes (using empirical tools and/or internal procedures) can also be considered acceptable." (1) This statement indicates that the use of empirical tools constitutes *informal* approaches to QRM, whilst the use of recognized tools constitutes *formal* approaches. It also indicates that internal procedures can constitute both formal and informal approaches.

The section in ICH Q9 on Risk Control also refers to formality; it states that risk acceptance "can be a *formal* decision to accept the residual risk or it can be a passive decision in which residual risks are not specified." (1)

The section titled 'Risk Management Methodology' states that, traditionally, "risks to quality have been assessed in a variety of *informal* ways (empirical and/or internal procedures) based on, e.g., compilation of observations, trends and other information" and that such approaches "continue to provide useful information that might support topics such as handling of complaints, quality defects, deviations and allocation of resources." (1) It goes on to state that, additionally, "the pharmaceutical industry and regulators can assess and manage risk using recognised risk management tools and/or internal procedures (e.g. SOPs)" and a list is provided in the guideline of some of those tools. (1)

Based on the above, it is evident that ICH Q9 places the use of recognised tools at the heart of formal approaches to QRM. There are many tools available that may be used to support and/or perform Quality Risk Management-related activities. These include Preliminary Hazard Analysis (PHA), Hazard and Operability Studies (HAZOP), Fault Tree Analysis (FTA), Failure Modes and Effects Analysis (FMEA), Failure Modes, Effects and Criticality Analysis (FMECA), Hazard Analysis and Critical Control Points (HACCP), among others. The available tools differ widely in design - some lead to qualitative assessments of risks (e.g. Preliminary Hazard Analysis), whilst others are quite complex, highly structured and rule based, such as the Probabilistic Risk Assessment techniques that are often used by nuclear power plants and which involve the use of complicated mathematical concepts such as Monte Carlo simulations when arriving at probabilistic expressions of risk (6, 7).

Other tools lie somewhere in the middle, such as FMEA (Failure Modes and Effects Analysis) and HACCP (Hazard Analysis and Critical Control Points), which, at best, provide for semi-quantitative risk ratings, although one could argue that those particular tools are perhaps more qualitative than quantitative, even when they generate numerical expressions of relative risk in the form of *Risk Priority Numbers* (RPNs), (8) The reason for this is that RPN numbers are usually arrived at via the multiplication of what are called *ordinal scale numbers*. These are numbers that indicate relative positions on a scale (e.g. on a probability scale of 1 to 5, 4 is higher than 2, but it may not represent double the probability of an event occurring). With ordinal scale numbers, their magnitude (and thus their multiplication) is not meaningful in a mathematical sense (9, 10, 11).

In addition to considering the use of QRM tools, might formality in QRM be related to how risks are assessed? When risks are based on estimates of the probability of occurrence of hazards or failure modes, the severity of their potential effects, and the detectability of those hazards or failure modes, does that make it a formal approach to QRM? And when risk estimates are not based on those factors, does that make the approach informal? This is useful to think about.

Are there different degrees of formality in QRM? Is it a spectrum, or is it a binary concept? The section in ICH Q9 titled 'Risk Management Methodology' states that the "degree of

rigor and *formality* of QRM should reflect available knowledge and be commensurate with the complexity and/or criticality of the issue to be addressed” (1). This links formality with knowledge, complexity and criticality, which are useful considerations, and the reference to the ‘degree’ of formality suggests that there may be a spectrum of formality, rather than it being a binary thing.

Several Risk Management standards and other official guidelines also refer to formality. The 2010 WHO guideline on QRM (12), for example, makes several references to formality, and is perhaps the publication that deals most comprehensively with this concept. For example, in relation to inspecting the QRM system at pharmaceutical manufacturers, the guideline indicates that inspectors should be “pragmatic regarding the level of scrutiny and degree of formality required for any given situation”, and it states that “the procedures for risk-based decisions and formality of approach should be commensurate with the level of patient risk”.

The WHO guideline also requires critical issues to be addressed “with appropriate high urgency and formality”. In the section on Risk Communication and Documentation, the guideline indicates that it is not necessary to issue “a full report for every risk assessment”, and that “the level of effort, formality and documentation of the QRM process can be commensurate with the level of risk”. It goes on to state that an organization “can be pragmatic regarding the degree of formality that is required; however, appropriate evidence of mitigating activities should be available, and a written output must be retained.” The guideline also indicates that “increased formality and detail” is expected for more significant risks. (12)

It is interesting that, despite its highly structured approach to risk management, the ISO standard on the use of risk management in relation to medical devices, ISO 14971:2019 (13), makes only two brief references to formality – one is in a note about records, which indicates that records serve as a means to formalize traceability. The second relates to risk management plans, which are required by the standard to describe the “activities related to collection and review of relevant production and post-production information”. The standard indicates that the reason for this is the need for “a formal and appropriate way to feedback” such information “into the risk management process” (13).

The International Standard ISO 31000:2009, titled Risk Management – Principles and Guidelines (14), also refers to formality. Its *Introduction* section indicates that “when a formal process is in place within an organization for particular types of risk or circumstances, the organization can decide to carry out a critical review of its existing practices and processes”. And in the *Terms and Definitions* section of the Standard, reference is made to both “formal and informal decision-making processes” as they relate to the internal context in which an organisation performs its risk management activities (Ref 14).

Taken together, the above references indicate that formality is generally considered an important concept in risk management and in quality risk management activities, and that there can be different degrees (or levels) of formality.

3.The benefits of having clear definitions for what Formal & Less Formal QRM mean

The references to formality in ICH Q9 and other official publications indicate the important role that formality plays when assessing and managing risks, but it is also useful to consider the benefits that increased clarity for this concept may bring. There are several benefits that can reasonably be anticipated:

- Clarity around formality in QRM can help ensure that the extent of scientific and methodological rigour that is applied during QRM activities is commensurate with the level of risk.
- Business resources for QRM can be more efficiently allocated in accordance with the level of potential risk that needs to be managed – lower risk issues can be dealt with more efficiently via less formal means, and this can free up resources for managing higher risk issues which usually require increased levels of rigour and effort.
- A better understanding of formality in QRM may lead to a more pluralist approach when selecting the most appropriate tool for a given QRM activity –where an increased

understanding will allow selection of the most appropriate tool for the situation at hand, instead of defaulting to a standard tool (e.g. FMEA) regardless of the complexity of the risk question at hand or the complexity of the process or activity being risk assessed. It is important to note also that different QRM tools and approaches can involve differing levels of rigour, and increased clarity around formality may help users select the most appropriate tool or approach in a given situation.

4.Characterising Formality in QRM activities – Initial Industry / Regulator work, 2016-2017

Following discussions in 2016 between the Health Products Regulatory Authority (HPRA) in Dublin, Ireland, the Pharmaceutical Regulatory Science Team (PSRT) at the Technological University, Dublin, McGee Pharma International and the Irish Chapter of the Parenteral Drug Association (PDA), two workshops were run with representatives from pharmaceutical manufacturing companies in Ireland to explore the meaning and practical application of formality in QRM activities.

A total of 80 staff from 50 pharmaceutical companies attended the workshops; these included staff from several large biotech manufacturing sites, as well as staff from small molecule API sites, non-sterile and sterile finished non-biological product sites, amongst others.

The first workshop (November 2016) focused on a number of key questions and issues, including:

- How can different degrees of formality in QRM be applied whilst still effectively managing risks to product quality?
- Will regulators accept informal approaches to QRM?
- When is it appropriate to apply informal QRM in a GMP setting?
- What QRM tools, if any, would be considered to be informal approaches?
- What are the benefits of using informal approaches over formal ones?
- Can informal QRM be used to support qualification and validation activities?
- Can a company use informal risk assessments to comply with EU GMP Annex 15 requirement that, the way in which “risk assessments are used to support validation

activities should be clearly documented”? Or, are companies required to use more formal approaches in this area?

- How would a company document its informal QRM activities?

Work was undertaken to develop a set of keywords that could be used to describe what was meant by formal and informal QRM, and the flowchart shown in Figure 1, which had been included in an ICH Q9 briefing pack (15) on Quality Risk Management and which referred to both formal and informal risk management, was reviewed and discussed. (For a review of this flowchart, please see Appendix 1.)

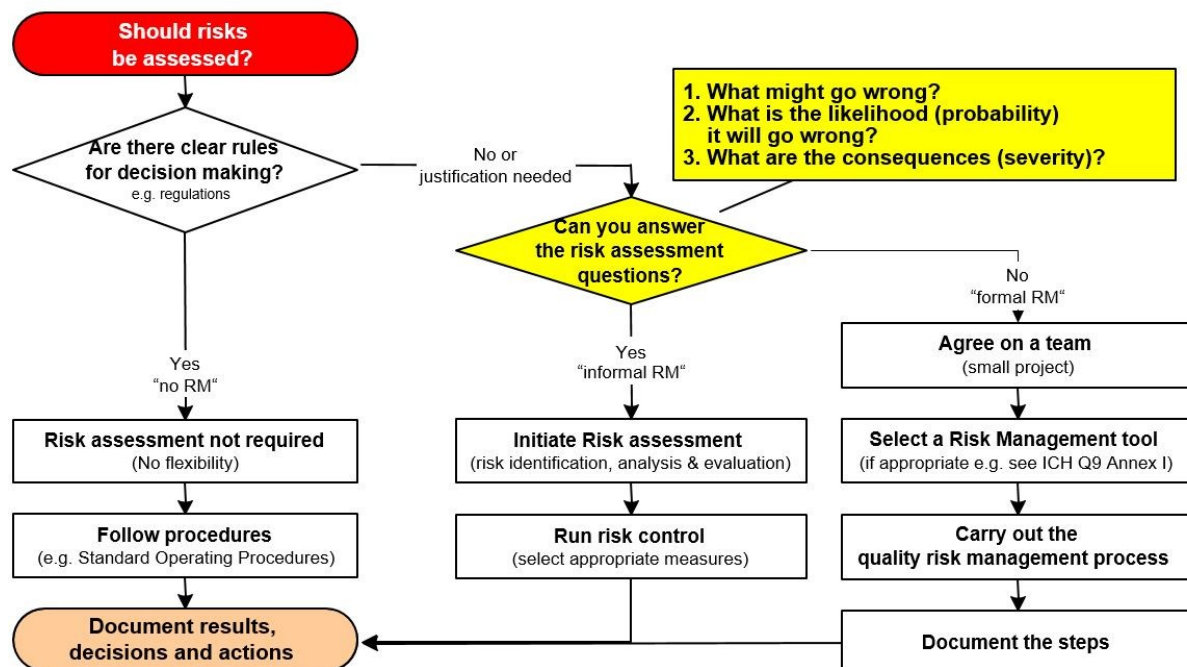


Figure 1: Slide from ICH Q9 Briefing Pack that refers to Formal and Informal Risk Management

The second workshop (March 2017) further explored the issues raised at the first workshop, and it then focussed on characterising what may be meant by formal and informal QRM.

Overall, it was evident from the workshops that there was significant uncertainty about what constituted formality in the context of QRM. There was a lack of clarity on what tools, if any, should be considered less formal compared to other tools and approaches, and in what situations they might be applied. While a set of keywords was developed which illustrated to some extent what might be meant by formal QRM and informal QRM, it was

far from cohesive, it was sometimes contradictory, and it was generally difficult to interpret. It was agreed that the topic of formality in QRM was of direct relevance and interest to medicines manufacturers, and that clearer regulatory guidance in this area was needed.

For a more complete description of the two workshops and their outputs, please see Appendix 1.

5. Industry / Regulator Working Group on Formality in QRM, 2017-2020

Towards the end of 2017, after the two aforementioned-workshops had been held, a small group of QRM practitioners formed a working group to further explore the concept of formality in QRM. This group was comprised of representatives from two pharmaceutical companies (Jazz Pharmaceuticals and MSD), as well as representatives from the HPRA, the medicines regulatory authority in Ireland, Over the course of 24 months, the working group met several times and, as its discussions evolved, it worked on the following goals:

- *To generate insights into the concept of formality in QRM which might support the development of future guidance on this topic.*
- *To encourage more effective QRM applications by the industry and regulators alike, by showing how a better understanding of formality in QRM might help to deliver more value-added and evidence based QRM outputs and a better use of resources, where effort is more commensurate with the level of risk.*
- *To demonstrate the benefits of collaboration between industry and regulators in order to drive continuous improvement in GMP/Regulatory Guidance at a global level.*

Upfront, the working group reviewed the discussions and the outputs from the PDA Ireland Chapter workshops in November 2016 (Cork, Ireland) and March 2017 (Dublin, Ireland), and key learnings from those were extracted and documented. The available guidance and literature was reviewed again, and the experiences of the two companies and the regulators in relation to formality in QRM were shared.

6. Survey with GMP Inspectors on the Concept of Formality in QRM, September 2018

After the working group had distilled and documented its thinking on what constituted formality in QRM, a survey was carried out with GMP inspectors during a PIC/S QRM meeting held in Taiwan in September 2018. This explored their understanding and views about the concept of formality in QRM.

A total of 27 GMP Inspectors from 14 different countries completed the survey. The countries in question were: Austria, Indonesia, Iran, Ireland, Italy, Malaysia, Saudi Arabia, Singapore, Slovenia, Sri Lanka, Switzerland, Taiwan, the United Kingdom and the United States, and the following is a summary of the survey's main findings:

- 85% of the respondents stated that, if ICH Q9 were to be revised, they would like the revision to clarify what is meant by formal QRM and informal QRM.
- Only 22% indicated that they had a good understanding of the concepts of formal QRM and informal QRM; a higher number (30%) indicated either little understanding or a very poor level of understanding in this area. 41% rated their level of understanding as *moderate*, and 7% did not give a rating.
- 81% of the respondents indicated agreement and support for the use of informal risk management processes. 11% did not, and 8% said they didn't know.
- In relation to how formal and less formal QRM might be characterised, as presented earlier in this paper, 74% expressed agreement with all, of most parts, of those definitions. 11% of the respondents disagreed fully or partially with them, and 15% remained neutral.
- The inspectors were asked if there was a need for additional guidance for GMP inspectors (and for the industry) on what is meant by formal QRM and informal QRM. Of the 25 respondents who answered this question, 76% stated that additional guidance was required. 12% stated that additional guidance was not required and 12% said they didn't know.

Overall, the survey results indicated that, while there was clear support among the GMP inspectors for the use of different levels of formality in quality risk management activities, there was also a need for clarity and guidance on what is meant by formal QRM and less formal applications of QRM. There was strong support for the suggested way in which formal QRM might be characterised and for what might constitute lower levels of formality.

7. Suggested Definitions for Formality in QRM

The informal working group on formality in QRM completed its work by a) developing a set of simple definitions on the concept of formality in QRM (see Table 1), and b) writing this paper as a means to communicate those definitions and encourage wider discussion on this topic. The definitions for Formal QRM and Lower Levels of Formal QRM were arrived at following a review of the work completed and the learnings made up to that point, as well as the use of a structured approach involving a *What, When and How* methodology. When developing the definitions, various elements were considered, including QRM procedures, risk assessment and QRM tool selection, training considerations, documentation requirements, issues associated with level of effort, and of course the guidance available in the current version of ICH Q9. At the outset, it was agreed that the definitions had to be brief, concise and easy to understand.

Suggested Definitions for Formality in QRM
<p><i>Formal QRM may be characterised by the following...</i></p> <ul style="list-style-type: none"> • The QRM process is proceduralised, systematic and includes all the elements of QRM as per ICH Q9 (Risk Assessment, Risk Control, Risk Review and Risk Communication). • A stand-alone QRM report is generated, which documents all aspects of the QRM process and which meets current GMP documentation expectations. • A cross functional team is in place for the QRM activity. (Note that having an independent facilitator on the team may represent best practice.) • Recognised or customised quality risk management tools are used in some or all parts of the QRM process – e.g. FMEA, Risk Ranking, HACCP, FTA, Fishbone Analysis, PHA, etc. Note that the tools can differ in terms of their complexity and degree of rigour. • All risk scores / ratings are supported by data or by a written justification or rationale. The ratings and outcomes are based on sound evidence, science and data.
<p><i>Lower levels of formality in QRM may be characterised by the following...</i></p> <ul style="list-style-type: none"> • Elements of the QRM process (e.g. Risk Assessment) are embedded / integrated into other parts of the Pharmaceutical Quality System (PQS), such as in the Change Control process, in the Deviation and CAPA processes, in Validation activities, etc. • Stand-alone QRM reports may not be generated, but the outcomes of the QRM process are documented in the relevant part of the Pharmaceutical Quality System. • A cross functional team may not be required, and risk-based decisions may be made by one or more people. • Recognised or customised quality risk management tools are not required to be used in the QRM process. This means that such tools do not have to be used in order to arrive at estimates of risk (e.g. high, moderate or low) or when deciding which risks may require mitigation. However, in informal QRM, such tools may be used in part or in full.

These definitions are fully in line with the general guidance for QRM as per ICH Q9, and they also reflect key elements of the ICH Q9 briefing pack slide (See Figure 1 above), in that formal QRM is team based, tool-based, and includes all four elements of the QRM process as per ICH Q9 – Risk Assessment, Risk control, Risk Review and Risk Communication. The definitions are also concise and to the point.

The definitions presented here are also supported by the contents of the 2010 WHO guideline on QRM (12), as well as the ISO standard on the use of risk management in relation to medical devices, ISO 14971:2019 (13), and the more generic standard on Risk Management, ISO 31000:2009 (14). For example:

- *In the WHO guideline on QRM, it is stated that an organization can be pragmatic regarding the degree of formality that is required; however, appropriate evidence of mitigating activities should be available, and a written output must be retained. This is reflected in the definitions that are presented here.*
- *The ISO standard on risk management for medical devices requires a formal and appropriate way to feedback information into the risk management process. This is reflected in the definition for formal QRM presented above – which indicates that the QRM process is proceduralised and systematic, where all aspects of the QRM process are documented.*
- *In the ISO 31000:2009 Risk Management standard, reference is made to both formal and informal decision-making processes, and the definitions for formal and less formal QRM as presented here are reflective of such processes.*

Table 2 below provides a high level summary of the above suggested definitions.

QRM characteristics	Formal QRM	Lower Levels of Formality
All four elements of QRM as per ICH Q9 are applied	Yes	One or more of the four elements may be present
Stand-alone QRM reports are generated	Yes	Not required, but outcomes of QRM process are documented in the PQS
Cross functional team is used	Yes	Not required, optional
Use of recognised or customised QRM tools	Yes	Not required, optional
Risk ratings/scores are supported by data/written justification/rationale	Yes	Not required, optional

Table 2: Summary of Suggested Definitions for Formality in QRM

As the above work was underway, an important development within EU regulatory circles pertaining to formality in QRM (and other issues) had been initiated. The EMA and the European Commission had initiated work with ICH to trigger a revision of ICH Q9, in order to provide additional guidance and training materials in certain areas relating to the application of QRM – and the concept of formality in QRM was one of those areas. In November 2019, following a number of presentations to various ICH groups, the ICH Management Committee decided that a revision of ICH Q9 was indeed warranted, and that this would include work to address the concept of formality in QRM.

8. Conclusions and Recommendations

One of the key principles of QRM as presented in ICH Q9 is that the level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk. What formality in QRM means at a practical level is currently not well understood, and this has probably led to certain negative consequences – a lack of scientific rigour being applied during some complex risk assessments, to the overuse of very resource intensive and highly formalized risk assessment activities to address relatively straightforward GMP problems.

While ICH Q9 does not provide examples of what formal versus informal QRM mean, the work presented in this paper shows that there is considerable interest in the industry and among regulators as to what formality actually means in practical terms, and how the concept of formality can be applied in everyday GMP situations.

Within this work, we analysed the concept of formality as presented in ICH Q9, in terms of its practical applications. This work started with two Parenteral Drug Association (PDA) Ireland workshops, in 2016 and 2017, during which key learning were made in terms of the difficulties in understanding this concept, in conceptual terms and also in practical ways. It was of interest that there was strong support expressed among the industry groups for the use of less formal approaches to QRM – and there was a consensus reached that informal QRM can be just as effective as formal QRM, if documented appropriately. A small Industry-Regulator working group was then established in late 2017, to continue to explore this issue

and to develop meaningful definitions for what formal QRM and informal QRM might look like. That working group continued its work intermittently until 2020, and its primary output is this publication. In a survey performed with GMP inspectors, there was strong support expressed among the inspectors for the use of less formal approaches to QRM. This was an interesting finding.

Overall, we found that the concept of formality in QRM is best not viewed as a binary thing – Formal versus Informal; rather, it is probably best considered along a spectrum, ranging from high levels of formality to lower levels of formality. The suggested definitions for formality in QRM presented in this paper reflect this thinking, and in a follow-up paper, they will be further explored via a number of industry/regulator case studies. These will demonstrate the practical application of the suggested definitions presented here, in real life GMP situations.

There are several anticipated benefits to this work. Additional clarity on the concept of formality in QRM may help not only ensure that the extent of scientific and methodological rigour applied during QRM is commensurate with the level of risk, it may also lead to resources for QRM being used more efficiently – where lower risk issues are dealt with more efficiently via less formal means, freeing up resources for managing higher risk issues and more complex problems, which usually require increased levels of rigour and effort. It is considered that a greater understanding of formality in QRM has the potential to lead to more appropriate and beneficial uses of QRM, leading to improved outcomes in terms of pharmaceutical quality, drug availability and patient health protection.

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Appendix 1 – Summary of two Industry-Regulator Workshops (Nov 2016 and March 2017)

As noted earlier in this paper, two workshops were run with representatives from pharmaceutical manufacturing companies in Ireland to explore the meaning and practical application of formality in QRM activities.

- **Workshop No. 1 - November 2016**

After reviewing the guidance in ICH Q9 which refers to formality in QRM, a series of questions was put to the attendees to stimulate discussion and to explore key issues. These questions are shown on pages 5 and 6. It was evident from the discussions that there was a significant amount of uncertainty about what constituted formality in the context of QRM. There was also a lack of clarity on what tools, if any, should be considered to be less formal when compared to other tools and approaches, and in what situations they might be applied. Some participants stated that it was simply not known whether regulators would accept informal approaches to QRM, and that this was an important consideration.

In order to focus the discussions on real-life GMP issues, there was a discussion about the kind of QRM approach (informal, formal or none at all) that might be applied to two quite different GMP situations - a change control proposal to install a PAT-based moisture analyser in a granulate drying process, and a deviation involving a broken metal mesh screen in an API manufacturing process.

The participants were asked to outline the QRM approach they would recommend for the above two situations, in terms of the risks that might need to be managed and the key questions that would likely need to be answered, before a decision on the required level of QRM formality could be made.

The discussions were wide-ranging, and a variety of opinions was expressed in relation to how much QRM formality should be applied to the above two situations. Overall, the outcome was inconclusive - there was just too little understanding of what constituted formality in QRM in the first place. This was an interesting finding, and it served to validate our view that additional clarity and guidance on the concept of formality were required.

During the workshop, an attempt was made to develop a set of keywords that could be used to describe what was meant by formal and informal QRM. This involved a structured brainstorming session during which the following questions were put to the attendees:

- *What is the difference between Risk Assessment and Quality Risk Management?*
- *What five words or phrases would apply to formal QRM?*
- *What five words or phrases would apply to Informal QRM?*

The attendees were also asked to complete the following sentences:

- *Risk Assessment is highly formalised when....*
- *Informal Risk Assessment is when....*
- *QRM is highly formalised when....*
- *Informal QRM is when....*

The above tasks proved challenging - no consensus in terms of keywords was reached and clear and common interpretations were generally not arrived at either, although a number of associative keywords were noted. Formal approaches were described using the words and terms such as *team, proactive, predetermined scoring system, documented, quantitative, tools, FMEA, SOPs, and use of a*

facilitator. Informal QRM, on the other hand, was described by the following words and terms: *empirical, no tools, and less formal communication*. In some cases, the same words or terms were used for both formal and informal, for example, 'SOPs', 'documented' and 'tools'.

Interestingly, the group did indicate, and with a strong consensus, that informal QRM can be just as effective as formal QRM, if documented appropriately.

It was also noted that, during the workshop, the attendees generally agreed that each of the elements of the QRM process as per ICH Q9 (Risk Assessment, Risk control, Risk Review and Risk Communication) should be regarded as representing *formal QRM*. The attendees indicated that formal QRM required a "full loop" approach to those elements - meaning that each of those four elements should be present and applied if a QRM activity can be regarded as being formal in nature. When discussing informal approaches, the general view was that the same four QRM process elements could also apply, *but with less formality*. Again, this indicated the need for a better understanding of the concept of formality in QRM, especially what it might mean in practical terms.

The discussion seemed to suggest that, just like with formal QRM, each of the above four QRM elements should be present before an activity can be considered an *informal approach* to QRM. This indicated that there was difficulty in understanding how formal and less formal approaches differed from each other.

The workshop then focussed on reviewing a flowchart that had been included in an ICH Q9 briefing pack (15) which referred to both formal and informal risk management – see Figure 1 above.

This flowchart is essentially a decision tree for assessing risks and making decisions on those risks. It indicates that, when there are clear rules in place for decision making, no risk management is required and the relevant rules should be applied, without any flexibility. A GMP example here might be when a Qualified Person (QP) in a manufacturing plant in the EU is deciding whether to certify a batch for release or not. If the batch was out-of-specification for one attribute when QC tested, the EU legal requirement, or rule, that batches which are not in line with the relevant marketing authorisation may not be released should be followed. Risk Management in this situation should not be applied during the batch disposition decision-making process. But when a clear rule is lacking, the flowchart indicates that one may apply risk management in the decision-making process, and it indicates that this may be formal or informal in nature. Here, the flowchart requires one to answer three questions in order to decide whether formal or informal risk management should be applied. These questions are:

- *What might go wrong?*
- *What is the likelihood (probability) it will go wrong?*
- *What are the consequences (severity)?*

In cases where these three questions can be answered, the flowchart indicates that informal risk management can be applied. And according to the flowchart, this involves initiating a risk assessment, running risk control measures and documenting the results, decisions and actions. When the above three questions cannot be answered, formal risk management should be applied. This involves agreeing on a team, selecting a risk management tool, applying the QRM process, documenting the steps that were carried out, and documenting the results, decisions and actions.

During the workshop discussions, the general view was that the flow-chart was not sufficiently clear and none of the companies in attendance indicated that they had been applying it as an aide to their decision making. The flowchart was regarded as providing little meaningful differentiation between

what constitutes formal versus informal risk management. It implied that risk assessment and risk control were to be performed when informal risk management was required. However, a team and a risk management tool were required during formal risk management, where the QRM process was to be followed. In relation to the risk assessment and risk control steps in an informal risk management approach, the flowchart was regarded as being unclear. It seemed to imply that a risk management tool was only to be used when performing *formal* risk management, even though the majority of the tools specified in ICH Q9 actually relate to risk assessment and risk control activities, which are positioned in the flowchart as *informal* risk management activities.

It was also considered that the flowchart was unclear as to where risk review and risk communication might be applied. It made no direct reference to those two elements of QRM as per ICH Q9, unless the wording “Carry out the risk management process” in the formal risk management approach implied that all four elements (Risk Assessment, Risk control, Risk Review and Risk Communication) of the QRM process were to be applied there.

Overall, the first workshop indicated a general lack of understanding of what constituted formality in QRM, and that additional guidance in this area was clearly required. While a set of keywords had been developed which illustrated to some extent what might be meant by formal QRM and informal QRM, that was far from cohesive, it was sometimes contradictory, and it was generally difficult to interpret.

- **Workshop No. 2 – March 2017**

During the second workshop, the outputs and findings from the first workshop were reviewed, and the discussion then centred on whether formality in QRM might better be understood by expressing it in terms of *rigour*. The idea was that in less formal approaches to QRM, less rigour is generally applied to the elements that make up the QRM process as per ICH Q9 (Risk Assessment, Risk control, Risk Review and Risk Communication). There was general agreement that rigour could be a more appropriate term to represent the difference between formal and informal QRM.

Work then moved to characterising what was meant by formal and informal QRM. It was suggested that formal QRM can be characterised by the following statements:

- Formal QRM is systems-focused rather than being focussed on evaluating the risks presented by individual events.
- Formal QRM is an end-to-end process, incorporating the four elements of QRM as per ICH Q9 - Risk Assessment, Risk control, Risk Review and Risk Communication.
- Risk Communication is embedded into each element of the QRM process when formal QRM is being undertaken.
- Formal QRM is structured, in terms of its use of SOPs and tools.
- Formal QRM is an integral part of the Pharmaceutical Quality System (PQS), where the following expectations apply:

QRM activities should be subjected to structured governance controls within the quality system;

QRM outputs should be documented in a site Risk Register;

An escalation process to senior management should be in place for certain risk issues. (Note that exactly which risk issues were of concern here were not determined);

Management Reviews and Product Quality Reviews (PQRs) should be regarded as QRM tools in their own right.

With regard to the use of tools, it was discussed how risk assessment tools are different from root cause analysis tools and, while they are not the same, a strong approach to root cause analysis supports risk assessment activities and should be encouraged.

In relation to *informal* QRM, it was observed during the workshop that this was more difficult to characterise. It was suggested that informal QRM was more event-focused than systems-focused, and that it involved more stand-alone risk assessments than complete QRM reports. It was also suggested that expressing formality in terms of the degree of rigour that is applied when assessing and managing risks may be a useful way of differentiating between formal and informal QRM. It was generally agreed that the level of rigour that is applied can also differ based on the degree of risk that is considered to be present.

The discussions at the workshop suggested that both formal and informal QRM can have certain elements in common:

- *Each can make use of facilitators and multi-functional teams, as required;*
- *Each can make use of shop-floor evaluations of risks, where risk assessments need not always be performed in meeting room settings;*
- *Each needs to be supported by a documented process, but with different levels of formality, as appropriate;*
- *Each should be subject to training activities, including training on any QRM tools that are used.*

The question of whether formal QRM could be considered superior to informal QRM was discussed in this workshop. As in the first workshop, no consensus was reached, but the majority view in both workshops was that it was not superior. This was an interesting finding, and it was somewhat unexpected. (During the discussions, some participants expressed the view that formal risk assessments sometimes end up being only 'tick box' exercises, and of little value.)

The second workshop ended with an agreement that the topic of formality in QRM was of direct relevance and interest to medicines manufacturers, and that clear regulatory guidance in this area was needed. As at the first workshop, the participants agreed that the topic merited further study and research, and it was suggested that the terminology relating to formality in QRM should be reviewed, as perhaps that was where some of the difficulties in understanding this concept lay.

----- End of Appendix 1 -----