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QRM: a Case for Convergence: a Reminder that Quality Risk Management Must Work With Other Risk Management Systems

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QRM: A Case for Convergence

A reminder that Quality Risk Management must work with other Risk Management systems

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Abstract

This article reflects that Quality Risk Management (QRM) is operating in a different technological environment since the *ICH Q9: Quality Risk Management* [1] guidance was first published in 2005. This paper explores the array of risk management systems that influence operations in a typical modern high-tech manufacturing facility. These 'other' risk management systems, either directly or indirectly, inform both the risk assessments and the control strategies developed by QRM. Convergence is another word for coming together. In order to assure that QRM can fully align and converge within operations, it must also ensure that it can align with these allied risk management systems.

Introduction

2005 was a very different technological landscape than today. The only available tablet was medicinal. Wi-Fi in the home was unheard off – no internet, no Netflix. While the I-Pod was newly available, it was 2007 before the I-phone was launched, and with it the ability to both surf the internet and photograph our surfing all with one pocket size device. Windows XP was the operating system on our desktops, and it could only access Facebook if located on a college campus. CDs were used to back up data. Clouds caused rain showers.

In 2005, the pharmaceutical industry began its journey with Quality Risk Management (QRM) with the publication of a guidance by the International Council for Harmonisation (ICH). This body, formed to enhance convergence across global regulatory requirements, published *ICH Q9: Quality Risk Management*. [1] The objective was to establish the principles and tools to enable the application of QRM in a Pharmaceutical Quality System (PQS). The two primary principles of ICH Q9 are that:

- 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.

When released, ICH Q9 was an innovative document. It places the patient at the heart of quality management. It moved the quality conversation from one of absolutes – rights and wrongs, compliance and non-compliance – to one of balance, where process understanding is upheld as the key competency of good judgement. The attributes of a product that make it safe and effective are highlighted as the critical value of the product. Hazards, that could potentially compromise those attributes, are identified and controlled. At the same time, the document recognises that zero risk is not always attainable, but that it should be as low as reasonably possible. [2]

QRM was designed to sit within the PQS and influence and inform quality controls across the product lifecycle. It was not intended as a stand-alone guidance and was shortly supported by the publication in 2008 of *ICH Q8: Pharmaceutical Development* [3] and *ICH Q10: Pharmaceutical Quality System* [4]. The essence of the trilogy is that the critical-to-quality attributes (CQA's) of a product should be identified early in the development lifecycle and that, with the correct application of the PQS, those attributes should be preserved and protected throughout the remainder of the product lifecycle. In business terms this is referred to as the preservation of value [5]. Any actions taken in response to issues, or any changes made to a process, should have the intent of preserving value, improving control, and reducing risk to product.

As a result of the trilogy, the future of pharmaceutical manufacturing was altered to one of process understanding, control, and improvement. Quality management and process management were intertwined. Management Review, and the role of management in general, became critical to ensuring that the real-world outcomes of control were monitored and fed back to the source of control. Prevention of issues became as important, if not more important, than reacting to them. ICH Q9 was a key influencer of these paradigm changes.

However, 15 years on, the guidance is somewhat dated. The modern PQS is much less site-specific than even a decade ago, residing as it typically does within a global organisation, with advancing technology across a diversified lifecycle. Outsourcing and extended supply chains have become common. In many business sectors, primarily in response to the global recession of 2008, Risk Management has found a more central role in enterprise management and as a result, it too, has evolved. With increasing diversity and complexity, QRM must continue to align and remain central to management objectives.

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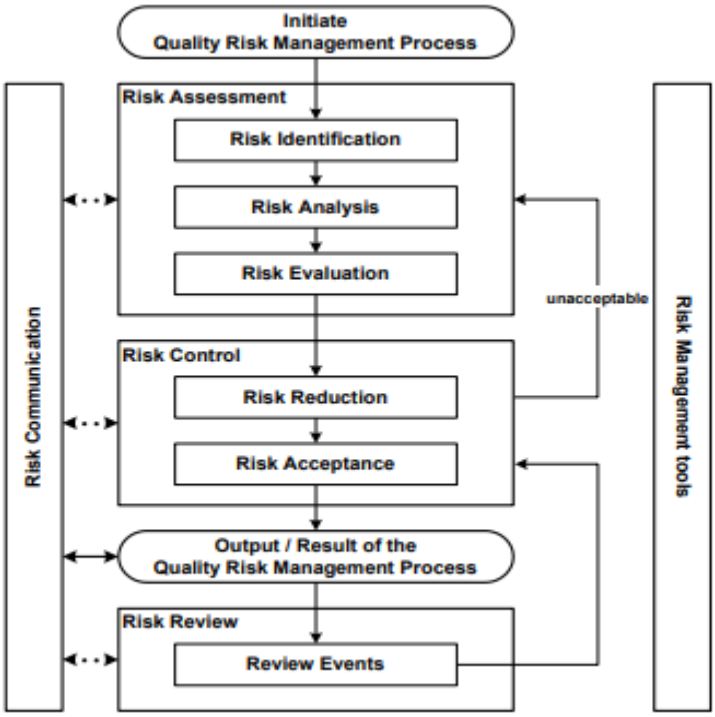

Figure 1: Risk Management Lifecycle from ICG q9

The Current Landscape

In 2017, Yu & Kopcha of the FDA [6], summarised the future of pharmaceutical quality when they stated that the fundamental destination was '*a maximally efficient, agile, flexible, pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight'.*

While this sounds like an ambitious objective, Yu & Kopcha recognised and detailed the substantial progress that had already been made towards this goal including, Process Analytical Technology (PAT) in 2004, Current Good Manufacturing Practices (cGMP) for the 21st Century (2004), *Quality* by Design (QbD) (2009), and Emerging Technology (2017) [3] [7] [8] [9]. The authors concluded that regulatory guidance has delivered on support for innovation and modernisation. Regulatory focus has indeed encouraged a progression from off-line lagging finished product testing to real time process monitoring. This approach has the added benefit of developing process understanding and resolving uncertainties with product and process. This focus supports the pathway to agility and flexibility, as mentioned by Yu & Kopcha.

In Appendix 1, ICH Q10 notes that regulatory relief may be available to organisations that could establish the effectivity of the PQS, in terms of process understanding and control. *ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* [10] offers further regulatory flexibility for organisations with the appropriately scientific risk-based approaches. The ability to demonstrate that innovation, improvement, and change are driven by science based informed decision making is critical. When ICH Q9 was published its focus was to establish a systematic approach to *quality* risk management. It proposed a traditional risk management approach, with the emphasis is on identifying and mitigating risk. ICH Q10 later broadened the scope and included an ambition to support innovation and continuous improvement

However, progress in terms of the application of real time measures, and perhaps innovative and disruptive technology in general, is slow. An oft quoted headline article in the September 3rd 2003 edition of the Wall Street Journal [11] noted that *''the pharmaceutical industry has a little secret: even as it invents futuristic new drugs, its manufacturing techniques lag far behind those of potato-chip and laundry soap makers'*! In 2018, industry publications were still referring to the 2004 FDA PAT guide as an 'aspirational guidance' [12]. Despite the regulatory interventions, modernisation and progress continue to be challenging for established manufacturing operations.

Product and processes technologies are evolving at a wonderous rate. The application of complex systems to simplify processes is paradoxically making systems more difficult to understand. Complex systems are littered with interdependencies that are hard to determine. Organisational literature considers complexity as an important factor in influencing organisations, particularly in the migration from the industrial age (2.0) to the knowledge era (4.0) [13].

The industry must increasingly rely on its innovation partners, the developers of the software, automation, robotic, data analysis, and the detection and measurement systems that it integrates into its complexity. It must also rely on the risk management systems used to design, develop, and manage these complimentary products and services. The industry has been cautious in its approach to this opportunity.

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What are these 'other' risk management systems?

Progress, improvement and innovation in the industry are essential for future competitiveness. However, they also necessitate the integration of technology, information systems, data analysis, automation, and intelligent systems. In this authors opinion, the need for alignment between the approach adopted by QRM in the pharmaceutical sector and the risk management systems of supporting sectors is pivotal to progress.

Process Control Systems

The close connection between product quality and process control is accelerating with the journey to Pharma 4.0. The term Pharma 4.0 is a play on the 2011 German government initiative – Industry 4.0 – which created the concept of the cognitive factory, where systems and equipment communicate and self-optimise [14]. Converging the ability to access, analyse and understand large volumes of multi-variate data to create process understanding with an increased use of automation, robotics and machine intelligence, the move to real time product quality control and release has never been closer or more inviting. The emergence of virtual technology to create simulated processes – known as digital twins- allows process changes, troubleshooting, or improvements to be conceptualised and modelled off-line before implementation in real environments.

All these systems, and the software, robotics, and automation required to support the technologies, are developed in different industry sectors, each of which will have applied a risk management approach to their design and testing. For the industries, including pharma, using these technologies, these processes need to be understood and potentially verified. Life science specialists are unlikely to have the required skills to evaluate the risk-based approach to software development, automation controls, complex algorithms, and modelling. Even with specialist knowledge, this is a challenge within those industries [15] and the subject of intense and continued research. Large scale software systems are typically complex and are often themselves, the output of several converging development processes. While there is no requirement to duplicate these risk management processes – they do need to be verified as appropriate. This confidence is enhanced if the risk management processes used are based on recognised standards and are structured similarly to those of the user.

The software development industry applies and relies on risk management processes throughout the development lifecycle. Many of the standards used in this sector are published by the IEEE (Institute of Electrical and Electronics Engineers) and the ISO (International Standards Organisation). The most common is *ISO IEC IEEE 12207:2017 Systems and software engineering — Software life cycle processes* [16], a software engineering standard that defines the software engineering process, activity, and tasks associated with a software life cycle from conception through to retirement. There are similar supporting standards for hardware design, security systems, etc.

ISO IEC IEEE 16085:2006 Systems and software engineering - Life Cycle Processes-Risk management [17]is currently undergoing an update to align with the enterprise risk management framework described in *ISO 31000:2018 Risk Management Guidelines* [18] The latter being a risk management guide for 'top management' providing a framework for the various risk management systems within an organisation e.g. safety, environment, IT, finance and, hopefully, quality.

Increasingly and at a rapid rate, QRM must accept the need to recognise, rely upon, align, and accept the application of international standards of practice and accredited systems within these specialities. QRM assessments will both rely on the risk controls applied to these systems and build on the risk control strategies developed. Therefore, it is critical to ensure that the language, methods, terminology and framework of the QRM process continues to enable alignment with these standards.

Project Management

While processes and the associated critical control specifications are developed by process designers, the translation to equipment and technical specifications and the resulting procurement decisions are often made by specialist project engineers. In modern large-scale projects, many of the key decisions in relation to process design, and the supporting measurement and monitoring technologies, are made in the project management environment.

Facility design has evolved into a separate expertise, aimed at maximising space and the effectiveness of the process. These engineers will conserve the process value criteria, while seeking to integrate the efficient flow of materials, people and information, and the required work environment, into a single well-functioning system. Furthermore, it is not unusual for

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the construction of a facility to be in progress before the details of the process controls are fully understood, adding a further uncertainty to the process.

Domain	Definition of "Risk"	Additional Definition and Explanatory Notes	Source
Systems Engineering	Risk is the likelihood of an event occurring coupled with a negative consequence of the event occurring.	A "corollary" definition is provided along with the definition of "risk" as follows: - Opportunity is the potential for the realization of wanted, positive consequences of an event.	INCOSE Systems Engineering Handbook, version 3.2.2
Information Security	Risk is the net negative impact of the exercise of a vulnerability, considering both the probability and the impact of occurrence.	The definition to the left was published in 2002. The updated (2012) definition is: - Risk is a measure of the extent to which an entity is threatened by a potential circumstance or event, and typically a function of: (i) the adverse impacts that would arise if the circumstance or event occurs; and (ii) the likelihood of occurrence.	NIST Publication 800-30, Guide for Conducting Risk Assessments, Information Security, U.S. DoC
Reliability and Safety Engineering	Risk is the combination of probability and severity of the failure incident (scenario) occurring.	The definition to the left is from reliability engineering. The definition from safety engineering is: - Risk is the combination of the probability of a failure event, and the severity (fatality, injury, property damage, annoyance) resulting from the failure.	Wikipedia pages for "Reliability engineering" and "Safety engineering" (Aug. 18, 2013)
Risk Management (Safety) **International Community (ISO)**	Risk is the combination of the probability of occurrence of harm and the severity of that harm.	- Harm is injury or damage to the health of people, or damage to property or the environment - A harmful event is an occurrence in which a hazardous situation results in harm - A hazardous situation is a circumstance in which people, property, or the environment are exposed to one or more hazards - A hazard is a potential source of harm	ISO/IEC Guide 51, Safety aspects – Guidelines for their inclusion in standards
Risk Management (General) **International Community (ISO)**	Risk is the effect of uncertainty on objectives.	- An effect is a deviation from the expected — positive and/or negative - Objectives can have different aspects (such as financial, health and safety, and environmental goals) and can apply at different levels (such as strategic, organization-wide, project, product and process) - Risk is often characterized by reference to potential events and consequences, or a combination of these - Risk is often expressed in terms of a combination of the consequences of an event (including changes in circumstances) and the associated likelihood of occurrence - Uncertainty is the state, even partial, of deficiency of information related to, understanding or knowledge of, an event, its consequence, or likelihood.	ISO GUIDE 73:2009, Risk management – Vocabulary
Project Management	Risk is an uncertain event or condition that, if it occurs, has a positive or negative effect on a project's objectives.	- When assessing the importance of a project risk, consider the two key dimensions of risk: uncertainty, and the effect on the project's objectives - The uncertainty dimension may be described using the term "probability" and the effect dimension may be called impact" (though other descriptors are possible, such as "likelihood" and "consequence". - Risk includes both distinct events which are uncertain but can be clearly described, and general conditions which are less specific but may give risk to uncertainty	The Project Management Institute Practice Standard for Project Risk Management, 2009
General / Layperson	Possibility of loss or injury	First English usage: 1661. Origins: French *risqué*, Italian *rico*.	Webster's Ninth Collegiate Dictionary

Table 1: Various Definitions of the word 'Risk' likely to be encountered on an Engineering Program (Stein/Maynard) [19]

While process and product risk management criteria are key, these engineers must balance these requirements with other risk considerations including safety, environment, schedule,

cost, resources, security, capacity, yield, adaptability, reliability, supply chain, ease of maintenance and repair, business continuity etc.

Constraints impacting risk are also inevitable e.g., footprint, planning permissions, costs, resources and schedules. Various solutions will be designed, modelled and revised in the process. In order to design a safe and reliable facility layout, a complete understanding of the contribution to risk from all these drivers must be assessed and understood. [20] [21]. Trade-offs are inevitable and must be informed by a comprehensive, integrated and aligned risk management system. Changes are also expected, and these must be assessed with impact to all the above-mentioned risks. Divergence in risk vocabulary, classification, or assessment methods increases the likelihood that errors or misjudgements will be made.

With over 700,000 members, the Project Management Institute (PMI) is the world's largest not-for-profit membership association for the project management profession. In 2011, the organisation aligned with INCOSE (International Council on Systems Engineering) to address concerns in relation to risk vocabulary. This is exemplified by the various definitions of risk identified. (Table 1) [19]. The confusion extended beyond these definitions and beyond the two sectors identified. The divergence was further complicated by different risk management systems and language within the customer industry sectors (e.g., pharmaceutical, medical device, construction, automobile, etc.) and in the supporting processes (safety, human factors, IT, legal, disaster management, etc) - each having developed their risk management practices, terminology, and publications separately and independently.

To address these anomalies, the PMI-INCOSE Risk Management Collaboration committed to pioneering a systems approach to engineering program risk management using the ISO 31000:2018 Risk Management Principles and Objectives [18] model as a guide to enabling a consolidated approach. Once again, the ISO 31000 standard provided a useful umbrella for alignment. The exercise, did, however highlight the confusion that arises when different frameworks and language is applied.

The objective of the collaboration was to address the problems related to inconsistencies in risk management-related terminology and practices, and to facilitate effective integration of risk management into organizations. The process highlighted the risks associated with inconsistent terminology. The output of this process (which is ongoing) contributed to the 2017 publication of the 6th Edition of the PMBoK® Guide - A Guide to the Project Management Body of Knowledge [22], a

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widely accepted standard in project management and the fundamental text for Project Management Professional certification by the PMI.

ASTM

In 2003, the ASTM (formally known as the American Society for Testing and Materials) established Committee E55. The main objective of this committee was to support the application of Process Analytical Technology (PAT) in the pharmceutical sector with technical guides and standards. The initial structure of E55 included three main subcommittees: E55.01 - PAT System Management; E55.02 - PAT System Implementation and Practice; and E55.91 - Terminology. The committee expanded its scope in 2006 from the implementation of PAT to the much broader Pharmaceutical Manufacturing, again with a focus on the *'development of standardised nomenclature and definitions of terms, recommended practices, guides, test methods, specifications, and performance standards for the manufacture of pharmaceutical products'.*

In 2009, the E55 committee published *ASTM E2476 Standard Guide for Risk Assessment and Risk Control as it Impacts the Design, Development, and Operation of PAT Processes for Pharmaceutical Manufacture* [23]. This standard, since updated in 2016, provides guidance on the assessment of risks in the PAT development process. While focused on one aspect of the process, the application of PAT, the standard is aligned with ICH Q9. This alignment is helpful, as it ensures that the overall application is consistent.

Reliability

Reliability engineering focuses on the equipment, instruments and control systems that are relied upon to protect the product value (CQA's) through process control. These controls are studied to prevent them failing. Potential degradation factors are identified and appropriate preventative actions, such as test plans, calibration schedules, maintenance plans, spare parts, etc are actioned. The goal is to maintain reliability for the lifetime of the control, therefore aging/ reduced performance is a key concern.

Like risk management and, indeed, it does achieve the same objective, it is focused on causal factors and detecting and preventing failure *before* it impacts the process. It is 'ahead' of the

process failure. Its focus is on preventing the risk control system from failing – rather than the process itself. Reliability belongs to a family of risk management techniques that focus on the Layers of Protection [24] around a control point. Since ICH Q8/9/10, process control is placed more centrally to the preservation of product quality. It is increasingly reliant on a range of experts in the supporting disciplines of engineering, automation, and instrumentation.

Increasing in popularity in pharmaceutical manufacturing operations, reliability engineering is designed to address complex systems. It involves the use of many of the common risk management techniques, but also considers design reliability analysis, human factors, predictive maintenance, fault tolerances, operational and maintenance induced failures, failure reporting (FRACAS), measurement and monitoring, chaos and stress studies, etc. It has developed as a discipline within the engineering profession, recognised by both the IEE (Institute of Electrical and Electronics Engineers) and the ASQ (American Society for Quality).

The discipline is also supported by a newly published (2014) family of ISO standards – ISO 55000 [25]. Based on a previously used PAS 55 (Publicly Available Specification), which was widely applied within the energy and transport sectors, the ISO 55000 suite of standards is aimed at assuring that the assets within an organisation support process control, while balancing with safety, capacity, schedules, and costs. Risk management and informed decision making are central to the approach described. These standards are designed to align with both the quality system standards, as described in the ISO 9000 suite of standards, and with ISO 31000.

Combination Products

Innovations in technology do not just apply to processes. Products themselves are evolving and will continue to evolve. The combination product market (drugs and devices) is predicted to grow to a USD 177.7 billion industry by 2024 [26]. Among the products expected to show strong growth are transdermal patches and inhalers.

The devices in these products are designed and developed using a separate risk management framework – ISO 14971:2019 *Application of Risk Management to Medical Devices* [27] . The first edition of this standard was published in 2000, with two further updates culminating in the latest edition in 2019. Published by the ISO, this standard focuses on product risk through

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the entire lifecycle, including manufacturing. During the most recent update of ISO 14971, compatibility with the framework described in *ISO 31000:2018 Risk Management Guidelines,* and with the general definitions therein, was discussed. The advantage to this alignment is that it would allow ISO 14971 to sit within an enterprise risk management framework based on the same vocabulary.

This risk management framework is supported by a glossary of supporting terminology - *ISO/IEC GUIDE 63:2019 Guide to the development and inclusion of aspects of safety in International Standards for medical devices* [26]. Unfortunately, this is not the only glossary of Risk Management Terminology in the ISO lexicon. Currently the pharmaceutical industry draws on the ISO/IEC Guide 51:2014 Safety Aspects – Guidelines for their Inclusion in Standards [25]. While very similar, it is important that these guides remain aligned.

To further demonstrate the continued inter-weave of risk management systems, many medical devices now contain software, which is often required to communicate with other systems such as hospital monitoring systems. This software is typically developed using yet another ISO risk management guide - *ISO/IEC 80001 – Application of Risk Management For IT-Networks Incorporating Medical Devices* [28], written for the management of the safety and security of medical devices connected to IT networks.

For combination products i.e., drug/device combinations, the appropriate risk-based approach is applied to each component during development, with a combined and somewhat duplicating system applied to the resulting combination. This divergent approach can become challenging when simple devices are combined with hazardous medicine e.g. fentanyl patches. In this example, the risk assessment of the device alone may not be comparable to risk to the patient of the combined therapy. Alternatively, low risk medication such as insulin, epinephrine, or asthma medication are, because of the acuteness of the clinical need, heavily dependent on the correct deployment of the device – making the function of the device critical. Independently assessing each element with separate risk management systems may not offer the full control strategy for the treatment. Additionally, in practice, one sector typically adopts an established product from the other and the novelty is in the combination.

When adopting a product partner, the specialists within one sector evaluate the risk-based approach of the other, an approach with which they may be less familiar. While there is much

common ground between the two risk management systems – any divergence must increase the risk of misinterpretation and error.

Agencies, e.g. FDA, that oversee both pharma and the device sectors are familiar with the risk management approach in each sector i.e. pharma or medical device. However, individual product assessors, within CDER (Centre for Drug Evaluation and Research) or CDRH (Centre for Device & Radiological Health), are typically more familiar with the risk approach adopted within their own sector. When a combination product is submitted for review, it is assessed by either CDER or CDRH, based on the dominant therapeutic effect.

As an added complexity, many emerging therapies in the area of tissue, cell, or gene therapies require medical devices to administer the product at the point of care. Some of these devices, such as cell sorters, have been assigned to CBER for review, as the main therapeutic effect is the biological entity. While there is no evidence that the use of separate risk management systems adds to the time or complexity of the evaluation of such products –alignment could not hinder these assessments. Alignment with emerging risk management principles within transfusion medicine, with its added consideration of donor and clinical risk management cannot be ignored either.

Finally, the risk assessment and management of the processes used to manufacture combination products is an intertwine of both the pharma (ICH Q9) and the medical device (ISO 14971) standards – sometimes within an enterprise aligned with ISO 31000. While the Risk Management File required by the ISO 14971 system can accommodate the requirements of ICH Q9, the reverse application imposes additional requirements. To facilitate the further convergence of combination products, including tissue/device combinations, continued alignment of risk management frameworks and terminology is important.

Future 'Combinations'

Every 5 years or so, the 'Big Four' accountancy firms each publish their projection for the future of industry sectors, including the pharmaceutical and life sciences sector [29] [30] [31] [32]. These publications give an insight into the challenges ahead for the industry and the emerging technology trends. Among the predicted *'seismic and disturbing'* shifts to 2030 is the emergence of new therapies based on new technologies such as gene therapies, cell

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therapies, 3D printing, nanotechnologies, and predictive analytics. Nano technologies, tissue engineering, and robotics are envisaged as essential specialty partners to deliver these future therapies. The latter two forces being highly reliant on data powered insights and modelling. Ernst and Young [35] highlighted that both pharma and biopharma needed to develop their own core competencies into the future while developing the pathways to *integrate* innovations from other technology sectors. Assessing the risks involved when combining technologies from external sectors with internal systems must be seamless. In order to avoid creating barriers to progress, the pharmceutical industry must consider frameworks to facilitate such convergences, while preserving the need to apply a bespoke and tailored risk management system that supports the unique concerns of the pharmaceutical, biopharmaceutical, ATMP (Advanced Therapeutic Medicinal Products), and C/GT (Cell & Gene Therapies) sectors.

Conclusion

There are many drivers of innovation and technical and operational complexity in modern pharmaceutical operations and with them many risks to be managed. The manufacture of good quality medicinal product is the core competency of pharmaceutical organisations and QRM, which is designed to enhance the control of the manufacturing process. However, it must align with the wider organisational complexity and integrate with other risk management strategies to achieve its intended goals.

Risk Management Systems, like other processes, are not truly effective when analysed in isolation. A process that has been assessed for one objective e.g. process safety does not necessarily meet the requirements of another objective e.g. quality. The appropriate control of a safety risk may occur at the expense of the optimum control of a product quality risk. These risks must be balanced and manged in a harmonised and holistic manner.

Traditional risk management, with its focus on assessing singular granular parts – one factor at a time – can fail to capture the impact of all the parts moving together. It establishes mitigations for risks as isolated events. The simplification of one complexity (e.g. real time process measurement) may be applied at the expense of increasing another (e.g. human process understanding). The economist Nassim Table [33], noted that a city is not a big village, and that a corporation is not a large small business. Similarly, an automated process is not a manual process with computers attached. It has added layers of complexity, that process understanding alone cannot re-construct. Separating the analysis of the process from

the associated information management systems does not construct the overall risk picture. The integration of these risk management complexities into an overall risk management dynamic is essential and exceptionally challenging [34] This is the responsibility of the manufacturing organisations and cannot be prescribed by the regulatory authorities.

Those 'other' risk management strategies may be internal (e.g., safety, IT, finance) or external (e.g., project management, software development, automation). QRM must both rely on the output of these risk-based approaches and must integrate the controls required into the overall control strategy. The industry cannot seek to rework these assessments, as it has neither the competency nor the resources to do so. But it must be assured that it can rely on the output of these assessments and it must align them within its own operation. Convergence with other sectors is facilitated by using common terms, vocabulary, methods and approach. Aligned risk management systems facilitate the safe management of the complexity of convergent technologies.

It is therefore important that QRM is fully integrated and aligned with an organisation's enterprise risk management system, QRM can identify and preserve product quality at the top management level from the critical and complex decision-making that will most challenge it. QRM places product quality within the hierarchy of values within the organisation. The Enterprise Risk Management system will manage and balance these criteria throughout the lifecycle, ideally protecting them from cost reductions, schedule pressures, resource constraints, etc –all pressures that are primarily controlled outside the PQS. The PQS will manage some aspects of risk control, through procedural controls, change management, or CAPA. Control of risk from other sources e.g., data management, asset management, software, hardware and systems management, security, facility management will be managed by other, and hopefully complimentary, risk management systems.

That processes within the same business enterprise can align to achieve common objectives is important. The alignment of these objectives and the management of the associated risks is the role of the top management team. This is facilitated when all supporting risk management systems have a common framework and use common terminology. Consequentially, the pharmceutical industry should consider the wider adoption of ISO 31000. This is not an industry specific standard. It is a management standard designed to

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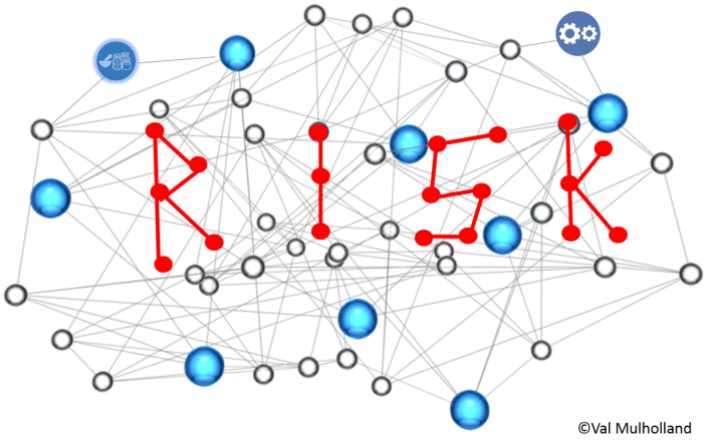
support the interweave of risk management standards at an enterprise level. It sits within the boardroom of organisations, where most key decisions are made

Manville & Ober [45] stated that *'We're in a knowledge economy, but our managerial and governance systems are stuck in the Industrial Era.'* Information, data and knowledge is fundamental to risk management. The rate of change of information technology and its applications is unprecedented. For QRM to be effective, PQS owners should also recognise the need to ensure that the environment in which it operates has an appropriate macro risk management structure. Recognition and alignment with ISO 31000 would provide this cover. While it not required that ICH Q9 formally align with the ISO standard, applicants should recognise its growing application and influence.

Keeping a tool, such as a risk management standard, aligned with technology and modern business approaches is challenging, but critical. It is critical that ICH Q9 remains influential and avoids a divergence in language, approach, or method. Currently the ICH Q9 document is consistent with ISO 31000. It may be wise to preserve this connection.



Bibliography

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

[2] K. Waldron, "Quality Risk Management 101: ICH Q9 in Context," 28 March 2018. [Online]. Available: https://www.pharmaceuticalonline.com/doc/quality-risk-management-ich-q-in-context-0001. . [Accessed Oct 2020].

[3] ICH, "ICH Q8: Pharmceutical DEvelopment," 2008.

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

[5] M. J. Lanning and E. G. Michaels, "A Business is a VAlue Delivery System," McKinsey Staff Paper, 1988.

[6] L. Yu and M. Kpcha, "The Future of Pharmaceutical Quality and the Path to get there," *Int J Pharm,* vol. 528, no. 1-2, pp. 354-359, 2017.

[7] F. a. D. Administration, "Guidance for Industry:PAT A Framework for Innovative Pharmceutical Development, Manufacturing, and Quality Assurance," 2004.

[8] Food and Drug Administration, "Pharmaceutical cGMP for the 21st Century, a Risk Based Approach," 2004.

[9] Food and Drug Administration, "Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernisation, Guidance for Industry," 2017.

[10] ICH, "ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Managment," 2019.

[11] S. Leila Abboud, "New Prescription for Drug Makers: Update the Plants," *Wall Street Journal,* 03 Sept 2003.

[12] J. Orr and G. Reid, "Process Analytical Technology: Meeting FDA's Aspirational Guidance in Continous Manufacturing," 09 July 2018. [Online]. Available: https://www.pharmaceuticalonline.com/doc/process-analytical-technology-meeting-fda-s-aspirational-guidance-in-continuous-manufacturing-0001.. [Accessed 26 Oct 2020].

[13] V. Roblek, M. Mesko and A. Krapez, "A Complex View of Industry 4.0," *SAGE Open,* 2016.

[14] European Commission, "Germany:Industrie 4.0," 2017.

[15] M. Pasha, G. Qaiser and U. Pasha, "A Critical Analysis of Software Risk Management Techniques in Large Scale Systems," *IEEE Access,* vol. 6, pp. 12412-12424, 2018.

[16] ISO/IEC/IEEE, "ISO 12207:2016 Systems and Software Engineering - Software Lifecycle Processes," 2016.

[17] ISO/IEC, "ISO 16085:2006 Systems and Software Engineering - Lifecycle Process Risk Management," 2017.

[18] ISO, "ISO 31000:2018 Risk Management Guidelines," 2018.

[19] J. Stein and D. Maynard, "Risk management @ risk: what are the opportunities PMI and INCOSE should work on first?," in *PMI® Global Congress 2013*, New Orleans, 2013.

https://arrow.tudublin.ie/level3/vol15/iss2/21
DOI: https://arrow.tudublin.ie/level3/vol15/iss2/21/

[20] A. M. Kazerouni, B. Agard and Y. Chinniah, "SIAS 2012 The Application of Risk Assessment to Facilities Planning: A Synthesis of Risk Assessment Methods and Layout Design Models," in *7th International Conference on the Safety of Industrial Automated Systems (SIAS)*, Montreal, 2012.

[21] S. Amri, S. Darmoul and S. Hajri-Gabouj, "Risk issues in facility layout design," in *Sixth International Conference on Industrial Engineering and Operations Management, IEOM'2016*, Kuala Lumpur, 2016.

[22] PMI - Project Management Institute, PMBOK Guide - Sixth Edition, 2017.

[23] ASTM, "ASTM E24779 Standard Guide for Risk Assessment and Risk Control as it Impacts the Design, Development, and Operation of PAT Processes for Pharmaceutical Manufacture," 2016.

[24] V. Mulholland and S. Warreth, "Risk Management tied up with a Bow Tie," *KENX Insight Online Journal,* vol. July, July 2020.

[25] ISO, "ISO 55000:2014 Assett Management - Overview, Principles and Terminology," 2014.

[26] Research & MArkets, "Drug-DEvice Combination Products, MArket Size, Share, & Trends Analysis Report by Product 2018-2024," 2018.

[27] ISO, "ISO 14971:2019 Medical Device: Application of Risk Managment to Medical Devices," 2019.

[28] IEC, "IEC 80001-1:2010 Applicaiton of Risk Managment for IT Networks incorporating Medical Devices - PArt 1: Roles Responsibilities and Activities.," 2010.

[29] Deloitte, "The Future Awakens:Life Sciences and Healthcare Predictions," 2017.

[30] KPMG, "Pharma Outlook 2030: FRom Evolution to Revolution," 2017.

[31] EY (Ernst & Young), "From Participants to Principles," 2018.

[32] P. W. Cooper, "Driving the Future of Health," 2019.

[33] N. Taleb, Antifragile, THings that Gain from Disorder, Penguin Books, 2013.

[34] I. Gorzen-Mitka and M. Okrreglicka, "Managing Complexity: A Discussion on Current Strategies and Approaches," in *22nd International Economic Conference - IECS 2015*, Sibiu, 2015.

[35] V. Mulholland and S. Warreth, "Risk Management Ties up with a Bow Tie," KENX, July 2020. [Online]. Available: https://kenx.org/kenx_insights/risk-management-tied-up-with-a-bow-tie-how-the-bow-tie-tool-could-be-used-to-develop-and-communicate-risk-control-strategies-in-the-pharmaceutical-industry/. [Accessed 27 Oct 2020].

[36] ICH, "Final Concept Paper Q9: Quality Risk Management," 2003.

[37] ISO/IEC, "ISO/IEC Guide 51: 2014 Safety Aspects - Guidelines for their Inclusion in Standards.," 2019.

[38] ISO/IEC, "ISO/IEC Guide 63:2019 Guide to the Development and Inclusion of aspects of Safety in International Standards for Medical Devices," 2019.

https://arrow.tudublin.ie/level3/vol15/iss2/21
DOI: https://arrow.tudublin.ie/level3/vol15/iss2/21/