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Quality Risk Management – an update on the ongoing revision of ICH Q9

Kevin O'Donnell, PhD, Market Compliance Manager, HPRA

"Delivering Value and Resilience using QRM"

OLLSCOIL TEICNEOLAÍOCHTA BHAILE ÁTHA CLIATH
TECHNOLOGICAL UNIVERSITY DUBLIN
PDA Ireland Chapter

Pharmaceutical REGULATORY SCIENCE Team

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QRM – A Fundamental Enabler for the Pharmaceutical Quality System

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Since 2005, when ICH Q9 was finalised, QRM has become increasingly important for the industry and regulators alike, in all areas of activity

- Many initiatives have been undertaken to embed QRM principles and risk-based approaches into day-to-day, as well as strategic, activities.
- ICH Q10 also recognised the importance of QRM, positioning it as one of two 'enablers' to the Pharmaceutical Quality System (PQS), the other being Knowledge Management (KM).
- It stated that QRM and KM will provide *"the means for science and risk based decisions related to product quality."*

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- It stated that QRM and KM will provide *"the means for science and risk based decisions related to product quality."*

- It is interesting now to consider that reference to **'science and risk based decisions'** in ICH Q10, and how Q10 clearly linked QRM and KM as a means to make such decisions.
- A significant part of the ongoing Q9 revision is about decision making and the use of science and knowledge to facilitate that.

Value and Resilience in the context of QRM…

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There are many ways in which effective QRM can add value and bring resilience to both the pharmaceutical industry and regulators alike

- QRM can help inform the design of manufacturing facilities and production processes, so that there is a high level of assurance that good quality medicines and free from contamination
- It can inform the design of equipment qualification and process validation protocols, so that the important aspects of equipment and processes are checked and proven to be robust and resilient
- It can help companies evaluate and monitor suppliers in meaningful ways, to ensure that the materials and services they obtain from suppliers are of the correct quality
- It can help design, evaluate and approve supply chains so that they are resilient to internal and external challenges, where the risks of product shortages and supply disruptions can be minimised
- It can help regulators apply their oversight resources to the highest risk areas, products, companies, etc., and it can help them communicate risk issues more effectively

Value and Resilience in the context of QRM…

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The Covid-19 Pandemic illustrated the importance of resilience in the medicines supply chain, and also the need for flexibility in the regulatory requirements that govern the manufacture and supply of medicines

- How much resilience was there in early 2020? And how easy is that to measure? What is resilience anyway?
- The Oxford dictionary defines it as being able to withstand or recover quickly from difficult conditions.
- The Collins dictionary defines it as being capable of regaining the original shape or position after bending, stretching, compression, deformation… and recovering easily and quickly from shock, illness, hardship, etc.
- Do resilience and flexibility (as in regulatory flexibility) go hand in hand? Are they inter-related?
- At the beginning of the pandemic, the EEA regulatory network quickly realised that regulatory flexibilities were needed to assure the continued supply of critical medicines, and by April 10th 2020, a number of regulatory flexibilities were agreed and published
  - Additional flexibilities were published on April 17th and again on May 26th 2022

Value and Resilience in the context of QRM…

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  - Addition… n on May 26th 2022

Quality Risk Management underpinned many of the flexibilities that were granted… e.g. those relating to….

- The extent of Quality Control testing
- The Qualification of Facilities
- Concurrent Process Validation
- Making Temporary Changes to Quality-related tasks
- Planning on-site vs. distant assessments by regulators

This brings us to the ongoing revision of ICH Q9

The ICH Q9 Revision – Key Milestones

- **In 2018, HPRA initiated discussions with EMA about a revision. EMA was strongly supportive, and a proposal paper was prepared by HPRA**
- **A US FDA colleague and an industry representative then became involved, and in 2018/2019 they assisted the HPRA in refining the proposal**
- **By early, 2019 the formal proposal was made by EC/Europe to ICH for a revision, and it was centred around four specific topics**
- By November 2019, ICH had considered the proposal and decided to proceed
  - *June 2020: Informal ICH Working Group put in place to prepare for the revision*
  - *November 2020: ICH Concept Paper and Business Plan agreed and published*
  - *December 2020: The Expert Working Group for ICH Q9(R1) was convened and the revision work got underway*
  - *Step 3- Public Consultation on the Draft Revised Guideline began in December 2021 and ran for three months*
  - *Finalisation of the revised guideline (Step 4) and of supportive training materials - to be ready by March 2023.*

The revision concerns 6 specific topics

- ***Subjectivity in QRM***
- ***Product Availability Risks***
- ***Formality in QRM***
- ***Risk-based Decision Making***
- ***Risk Review***
- ***Hazard Identification***

Five of the above topics are being addressed by adding new guidance into Q9 and by developing training materials that support the new guidance

One topic, Risk Review, will not have any new guidance written for it, but new training materials are being developed for it

Note: This is a very targeted revision of ICH Q9 – it is not a full rewrite. Most of the existing guidance in Q9 will remain unchanged.

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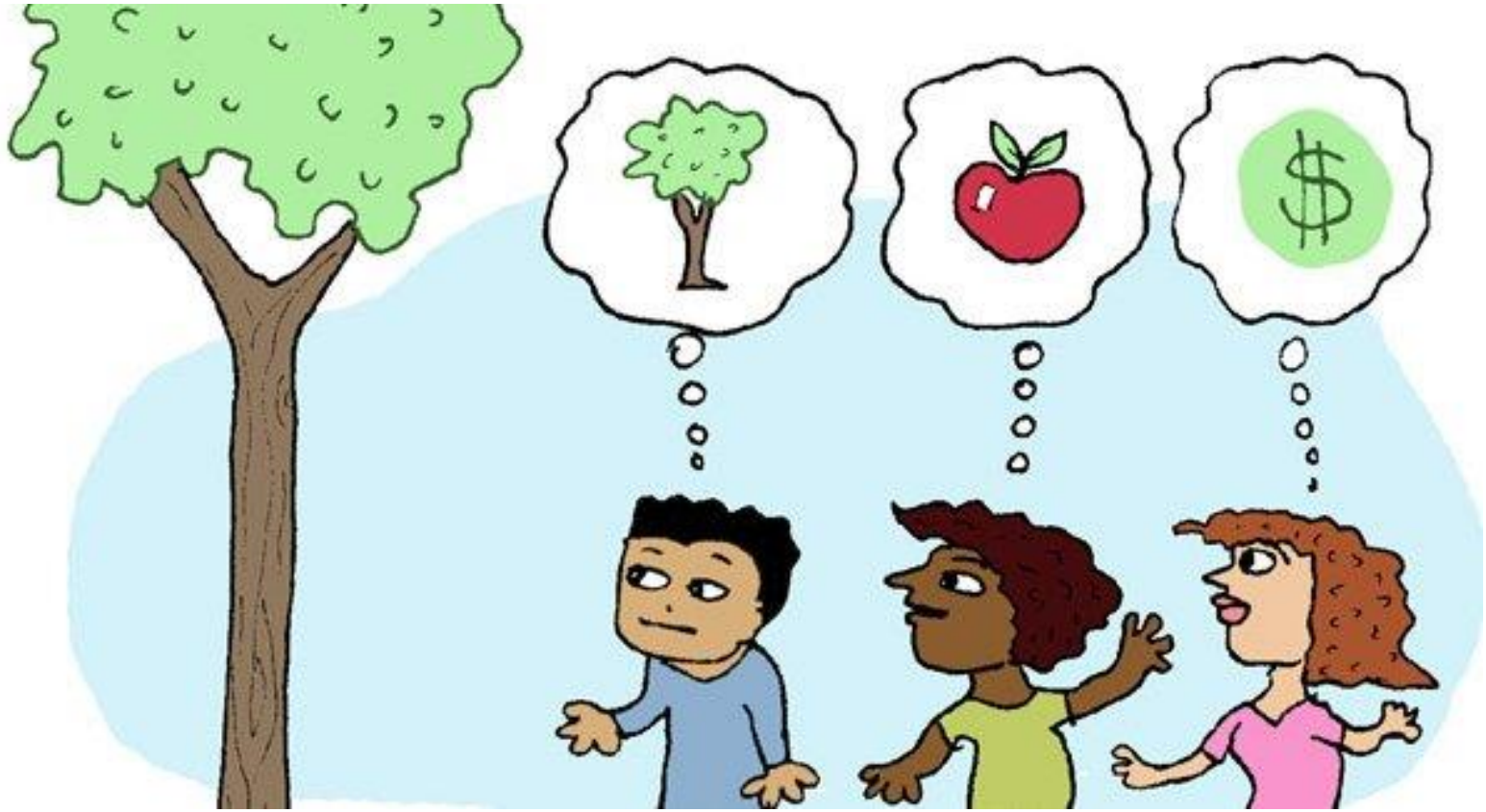
Let's take a brief look at each of the six revision topics

Topic 1: Subjectivity in QRM



Topic 1: Subjectivity in QRM

High levels of subjectivity in risk assessments and QRM outputs is problematic:

- High levels of Subjectivity are not in line with 1st QRM principle of Q9: "*The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient*".
- Subjectivity can relate to:
  - *the risk scoring methods that some risk assessment tools use*
  - *differences in how hazards, risks and harms are perceived by different stakeholders and how risks are assessed*
- While subjectivity cannot be eliminated from QRM activities, it may be controlled using well recognised strategies, including addressing bias and behavioral factors.

- The revision of ICH Q9 and its associated training materials are addressing the above (and other) points.

Subjectivity in QRM cont'd

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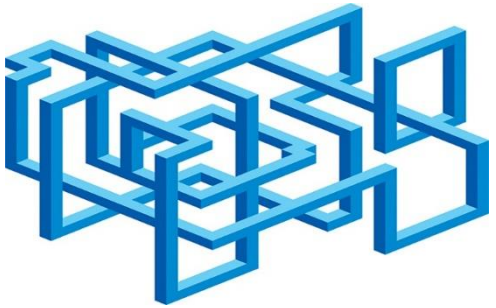
Addressing subjectivity should be beneficial…

- Less subjective risk assessments should lead to more science-based control strategies and validation protocols
- This should lead to fewer quality defects as well as less costly validation activities
- Such improvements in QRM may support the implementation of ICH Q8, Q10, Q11 and Q12, which all expect science and risk-based approaches
  - This demonstrates the ***foundational relevance of QRM***

Topic 2: Product Availability Risks

ICH Q9 is not a supply chain guideline, but quality/manufacturing issues that impact product availability can present risks to patients, and managing these risks is important.

- ICH Q9 already addresses product availability risks, as its definition of harm includes damage *'from a loss of product availability'*.
- Addressing such risks across the lifecycle is important, given the extent of globalization of medicines supply chains, their complexity and fragmentation (high number of actors)



- An increased emphasis in ICH Q9 on managing product availability risks related to manufacturing problems/issues, and on risk-based drug shortage prevention and mitigations, will serve the interests of patients.

Topic 3: Formality in QRM

ICH Q9 states: *"The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk."*

- But what does formality in QRM actually mean?
- A lack of understanding of this has led to confusion and uncertainty in the industry and among regulators
- The revised version of Q9 will seek to clarify what formality in QRM means
- It will discuss degrees of 'formality' and the factors that might be considered when determining how much formality to apply to a given QRM activity
- It will also emphasise that there is flexibility in how much formality may be applied in relation to QRM activities

Formality in QRM cont'd

- Additional clarity on formality may help 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*

- A greater understanding of formality in QRM has the potential to lead to improved outcomes in terms of pharmaceutical quality, medicine availability, and patient protection.

Topic 4: Risk Based Decision Making

- This doesn't just apply to the industry….
- The Covid-19 pandemic illustrated the importance of effective risk-based decision making by regulators in a myriad of areas – e.g. in the assessment and approval of conditional marketing authorisations, in inspection strategies, in pharmacovigilance activities, in granting regulatory flexibilities, etc.

Topic 4: Risk Based Decision Making

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While ICH Q9 refers to decision-making, there is currently a lack of clarity on what good risk-based decision making is, how it might be achieved, and how QRM may improve decision-making generally

- While there is a breadth of peer-reviewed research in this area, the uptake of that research within the pharmaceutical industry may be improved.
- There have been many formal initiatives undertaken by other industries (e.g. nuclear power, aeronautics, the US Coast Guard) to clearly define and develop risk-based decision-making processes and guidance.
- The Q9 revision will seek to provide clarity in this area and address the expected benefits of investing in risk-based decision-making activities.
- This may facilitate access to new medicines for patients, especially for fast-tracked applications, which require robust risk-based decision making.

- Q9 already provides a high degree of flexibility in what QRM tools and procedures may be used when making decisions; this is very positive.

Topic 5: Risk Review

The Q9 revision will provide additional clarity on the expectations relating to keeping risk assessments current and on the implementation of risk reviews

- This will take lifecycle manufacturing performance and quality feedback into account
- Risk Review ties in with the concept of continuous improvement as expressed in ICH Q10 and in the lifecycle management guidelines (ICH Q12/Q14)
- This area is being addressed by developing training materials on this topic

Topic 6: Hazard Identification

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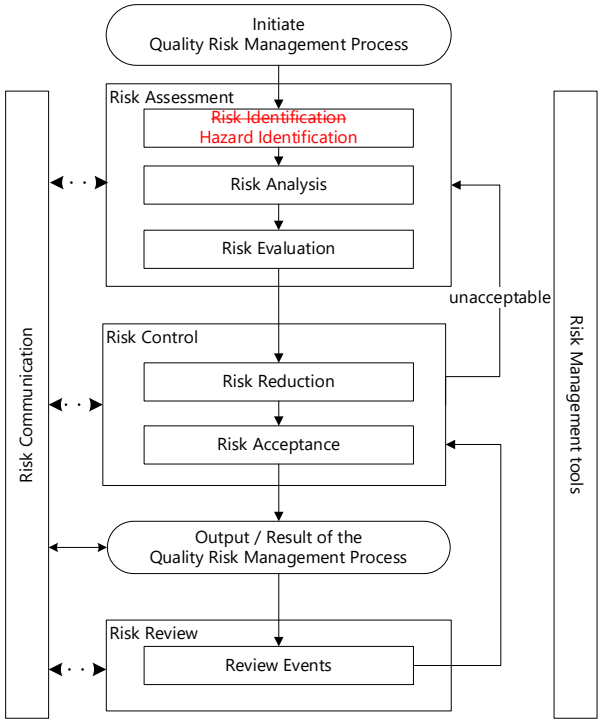
The term 'Risk Identification' is being changed in the revised guideline to 'Hazard Identification'



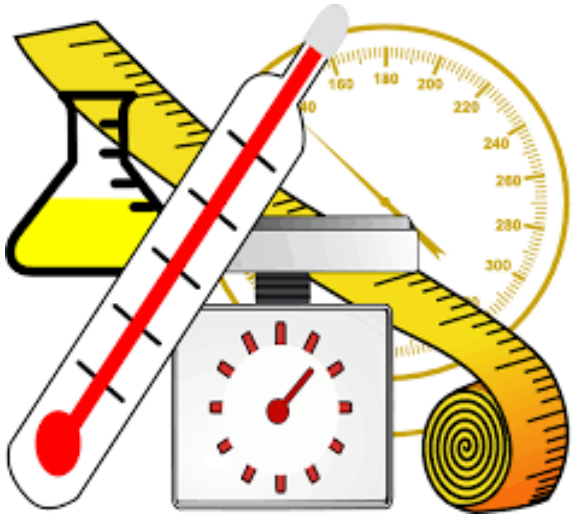
- This is to better reflect the current guidance in ICH Q9 on Risk Assessment…
  - *"Risk assessment consists of the **identification of hazards** and the analysis and evaluation of risks associated with exposure to those hazards…"*
- The figure in ICH Q9 depicting the QRM process is also being changed, to replace Risk Identification with Hazard Identification.

This change will align with the expectation to identify hazards relevant to patients when evaluating risks, and it may improve how hazards are perceived and assessed.

Official ICH Training Materials are being developed on all six revision topics, to support the changes to the guideline

The training materials will help implement the new ICH Q9(R1) guidance, with an emphasis on the 'how'.

The Q9 revision is focused on the application of Good Science in the management of risk



Scientific approaches to QRM are stressed in the ICH Concept Paper for the revision work

- *"Experience from the recent quality defects (e.g. nitrosamines…`)* illustrates the need for **a more scientific approach** by manufacturers to risk assessment and QRM activities…
- "A revised ICH Q9 … could lead to more effective and **science–based control strategies**…, improving manufacturing consistency, lowering costs and reducing the likelihood of quality defects, recalls, and medicine shortages."

New Technologies & Innovation are also an area of focus in the ICH Q9 revision

The ICH Concept Paper indicates that the revision may support *Digitisation and Emerging Technologies* (e.g., new manufacturing technologies, automation, and use of big data, PAT)

- *e.g. "As digitisation is implemented into manufacturing facilities, the application of QRM to the design and validation of production processes, … may become increasingly important."*

*It is of interest that **Quality Defect issues** are referred to in three places in the ICH Concept Paper for the revision*

Despite all our QRM work (Industry and Regulators alike), there are indications that there are still unmitigated risks in our industry as a result of quality defects…

Serious Quality Defects reported to the HPRA, 2002-2020

(Major and Critical Cases only)

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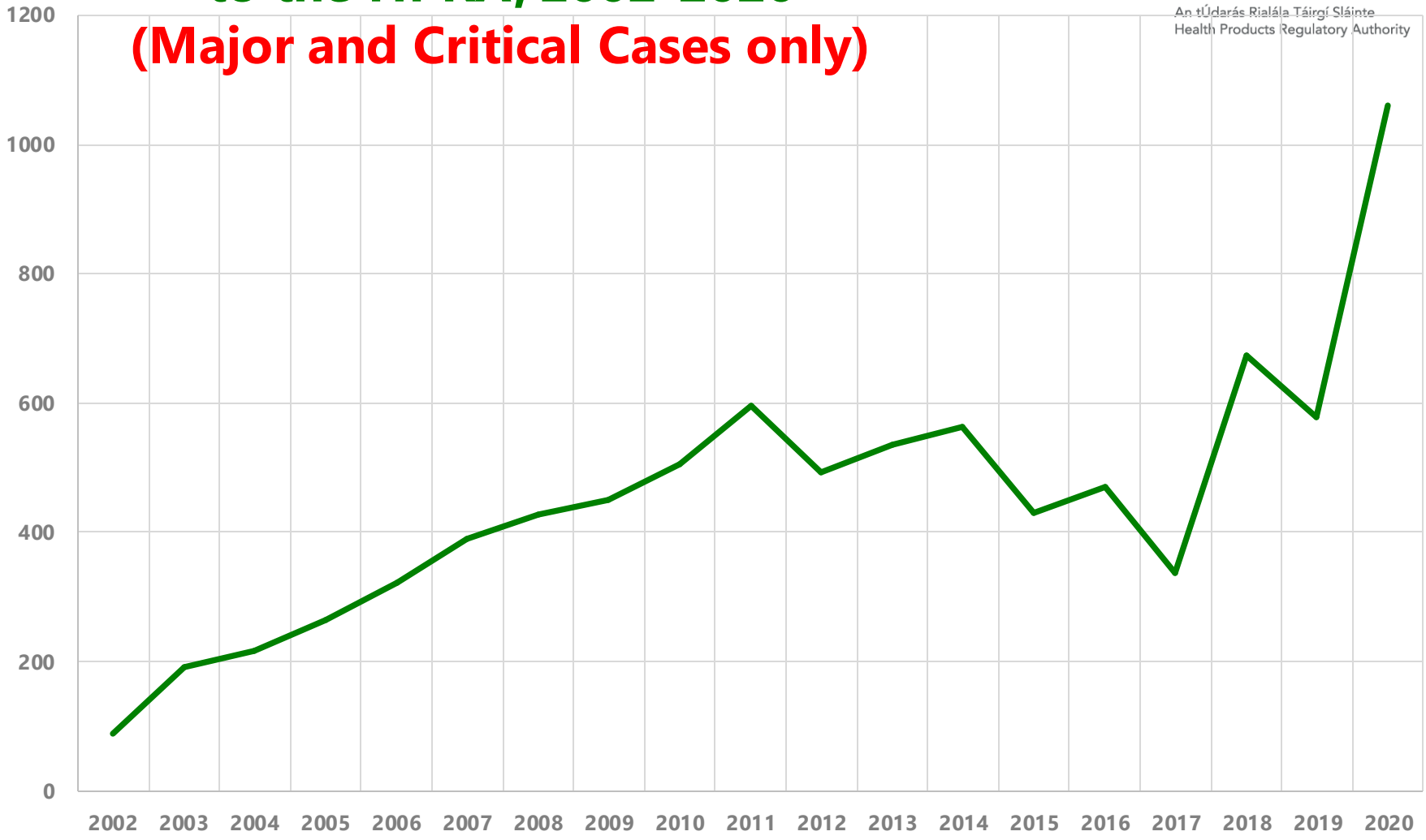

Total Quality Defects Quality Defects reported to the HPRA 2002-2020

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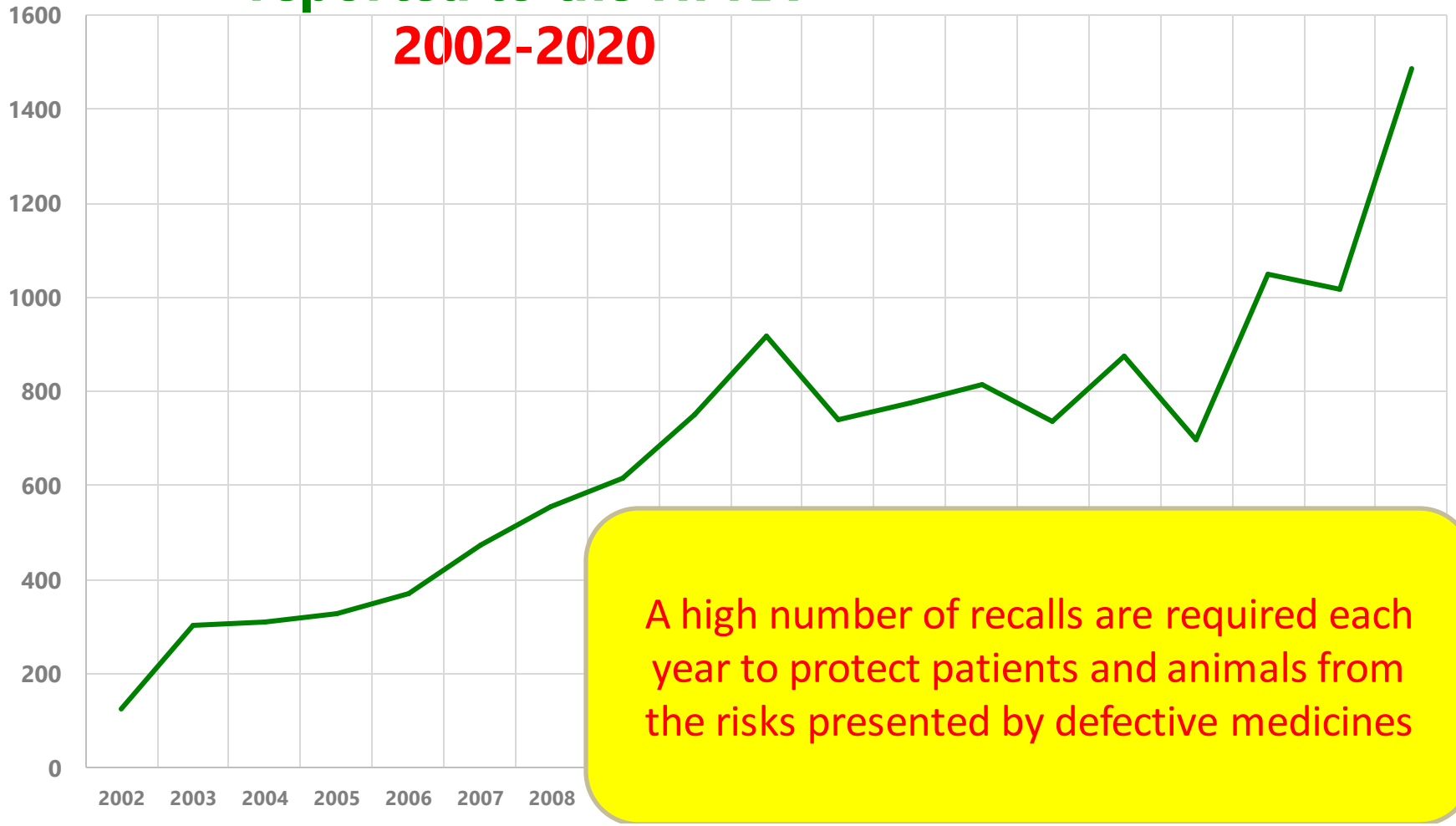

A high number of recalls are required each year to protect patients and animals from the risks presented by defective medicines

Total Quality Defect Reports to 2021

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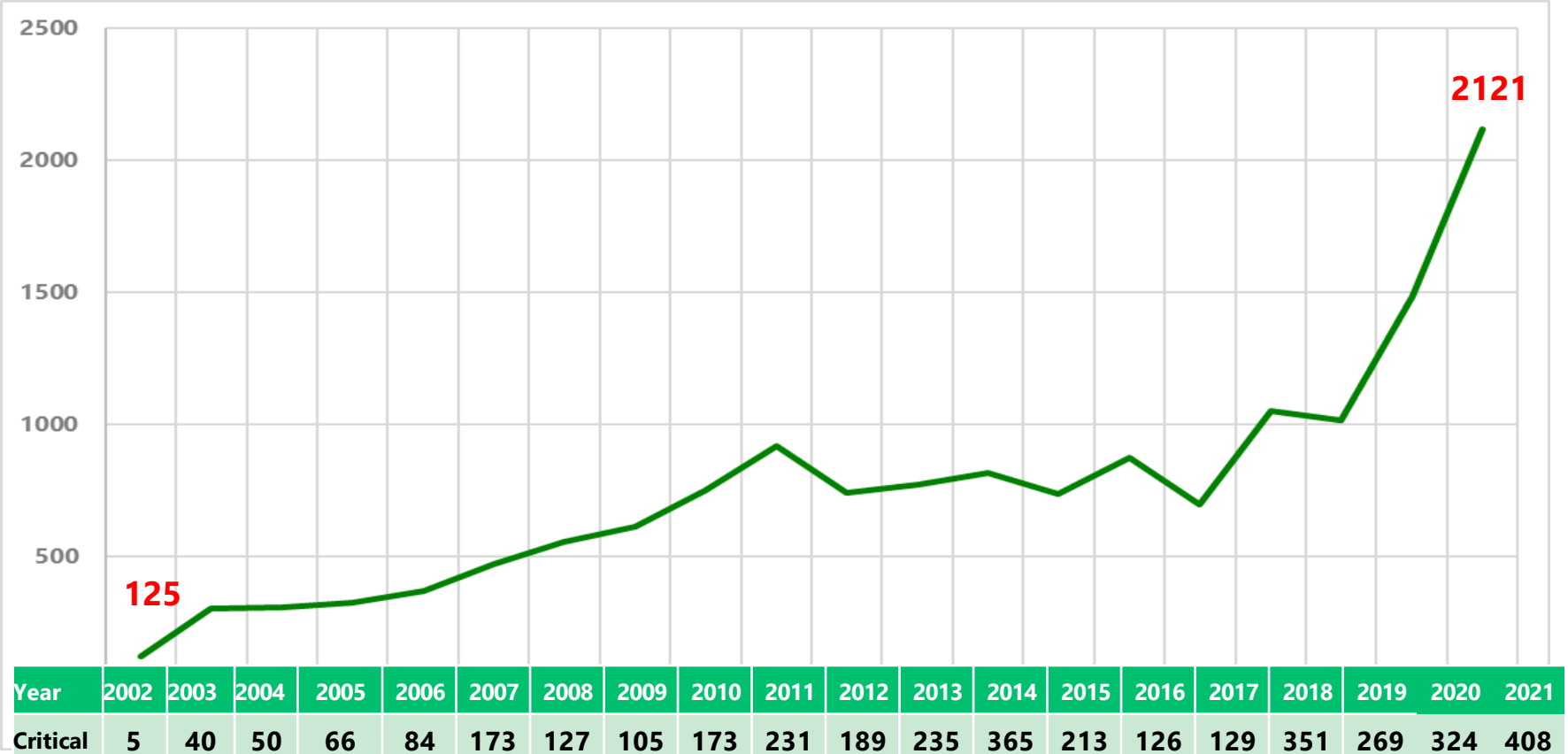

Year	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Critical	5	40	50	66	84	173	127	105	173	231	189	235	365	213	126	129	351	269	324	408
Major	83	152	167	199	238	216	300	345	332	364	303	300	199	218	343	209	323	310	737	1416
Others	37	111	92	62	49	84	128	164	246	322	249	239	252	306	407	360	376	437	425	294
Total	125	303	309	327	371	473	555	614	751	917	741	774	816	737	876	698	1050	1016	1486	2118
Recalls	70	74	85	74	58	97	141	98	168	253	141	109	102	118	216	89	202	132	85	124

Examples of serious Recall issues in the last few years

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- **August 2022: Recall to patient level of three compounded medicinal products due to incorrect product compositions -** in one case, the patient required hospitalisation
- **January 2022: Recall of a Zinc Sulphate capsule product to patient level level –** one pack contained 100 Diltiazem tablets (via a manufacturing mix-up)
- **April 2021: Recall of two Liothyronine / Levothyroxine products to patient level -** due to potential for under-concentration of both actives in the tablets
- **Nov 2020: Recall of a Glucose 50% IV product to hospital level -** due to cracks in the glass vials leading to sterility assurance risks
- **May 2020: Recall of an Investigational Medicinal Product from a clinical trial in children -** due to a product mix-up in different arms of the trial
- **Feb 2020: Patient level recall of adrenaline auto-injectors due to blocked needles and device actuation issues (earlier recall also in 2019)**
- **Aug 2019: Labelling error with an Acitretin product –** a three year pregnancy prevention warning was incorrectly stated as two years on the outer packaging

It is useful to note that vast majority of Quality Defects reported to the HPRA are manufactured using…

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Qualified Equipment

Validated Processes

Trained Staff

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Qualified

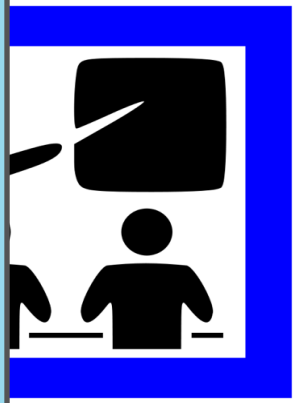
This brings us to thinking about the effectiveness of QRM activities in GMP facilities at this time…

Why are validated manufacturing processes producing defective batches of medicines?

How robust has the hazard identification part of risk assessment been to date?

To what extent has risk assessment been integrated into qualification and validation activities?

How can true risk-based qualification and validation be achieved?



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Going back to the ICH Q9 revision…

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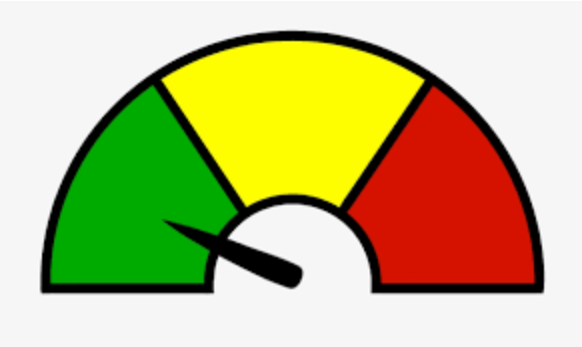
Shifting "the QRM focus from reactive to proactive will enable continual improvement to become a key aspect of the PQS. Thus, this revision of ICH Q9 is of strategic importance."

Ref. ICH Q(R1) Concept Paper, 2020



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Some final thoughts:

Lets go back to ICH Q10…

Consider this little discussed Appendix in ICH Q10:

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- **Potential Opportunities to Enhance Science and Risk Based Regulatory Approaches**

Scenario	Potential Opportunity
1. Comply with GMPs	Compliance – status quo
2. Demonstrate effective pharmaceutical quality system, including effective use of quality risk management principles (e.g., ICH Q9 and ICH Q10).	Opportunity to: • increase use of risk based approaches for regulatory inspections.
3. Demonstrate product and process understanding, including effective use of quality risk management principles (e.g., ICH Q8 and ICH Q9).	Opportunity to: • facilitate science based pharmaceutical quality assessment; • enable innovative approaches to process validation; • establish real-time release mechanisms.
4. Demonstrate effective pharmaceutical quality system and product and process understanding, including the use of quality risk management principles (e.g., ICH Q8, ICH Q9 and ICH Q10).	Opportunity to: • increase use of risk based approaches for regulatory inspections; • facilitate science based pharmaceutical quality assessment; • optimise science and risk based post-approval change processes to maximise benefits from innovation and continual improvement; • enable innovative approaches to process validation; • establish real-time release mechanisms.

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- **Potential Opportunities to Enhance Science and Risk Based Regulatory Approaches**

Scenario	Potential Opportunity
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3. Demo understan quality ris ICH Q8 a	ent;
4. Demo pharmace product a including manageme ICH Q9 and ICH Q10).	ent; processes to maximise benefits from innovation and continual improvement; • enable innovative approaches to process validation; • establish real-time release mechanisms.

The effective management of risk has to potential to deliver such opportunities for the industry!

"Effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks and can beneficially affect the extent and level of direct regulatory oversight."
(ICH Q9)

Finally… what might the Q9 revision mean in practical terms for pharmaceutical companies?

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Do you think the emphasis on managing **Subjectivity in QRM** will result in meaningful changes in how QRM facilitators and team members are trained… as well as in how risk teams operate, and in how risk ratings are assigned?

What about the new guidance on **Formality in QRM**, which refers to *Uncertainty*, *Complexity* and *Importance*? Will this guidance drive more evidence-based risk reduction via more rigorous risk assessments?

Might the focus on **Risk-based Decision Making** lead to renewed efforts to better understand decision making and decision science in general…. and will it lead to formal decision making tools being used more?

Might manufacturing sites get more involved in implementing **drug shortage** prevention strategies and controls?

Will **Risk Reviews** be given more prominence within the PQS, and will they become more value adding?

Finally… what might the Q9 revision mean in practical terms for pharmaceutical companies?

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What about the … s to *Uncertainty*, *Complexity* ar… …nce-based risk

Might the focu… …efforts to better understand de… …nd will it lead to

And will we all do better Hazard Identifications?

Where we will not have another Nitrosamines issue to deal with?

Might manufacturing sites get more involved in implementing **drug shortage** prevention strategies and controls?

Will **Risk Reviews** be given more prominence within the PQS, and will they become more value adding?

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Thank you for your attention.