



Application of Quality Risk Management to Pharmaceutical Operations

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Key Topics of Discussion

- Definition of Quality Risk Management (QRM)
- Overview of PDA Technical Report No. 54
- Importance of QRM
- Regulatory status of QRM
- Practical approaches for QRM
- “Reactive” QRM
- “Proactive” QRM
- Conclusions

Quality Risk Management (QRM) is the identification of risks and their management

- Risk - potential for losing something of value balanced by the potential for gain; or an intentional interaction with uncertainty
- Quantifying risk:

$$\text{Risk} = \text{Probability of occurrence} \times \text{Potential impact or loss}$$

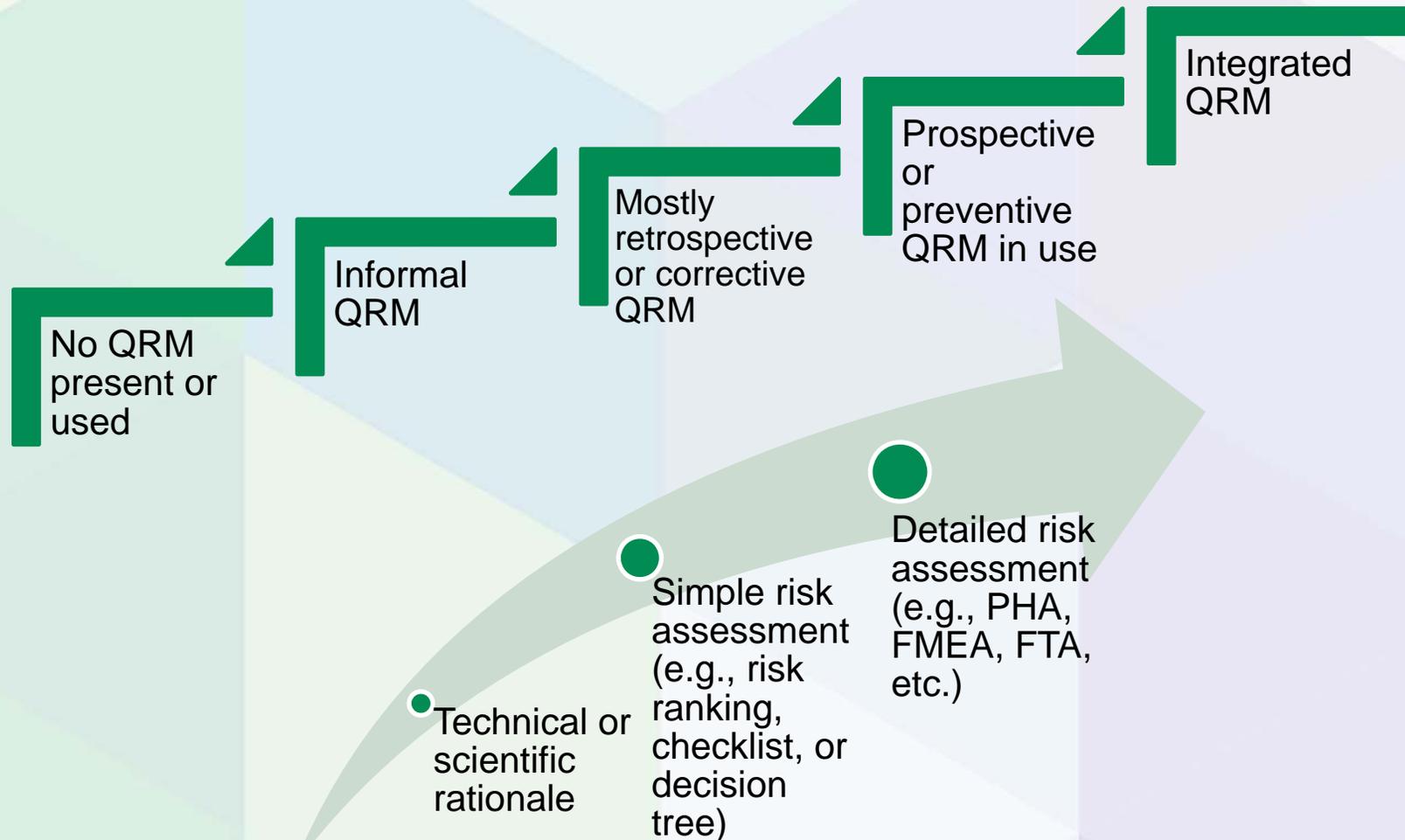
Probability is influenced by an ability to detect or remove

Potential impact or loss is a function of amount at risk \times expected loss

- Risk management - identification and control, management, or mitigation of risks that eliminates or reduces risk to an acceptable level
- Quality risk management - adds the use of scientific knowledge, process/product knowledge, patient impact, and documentation to risk management

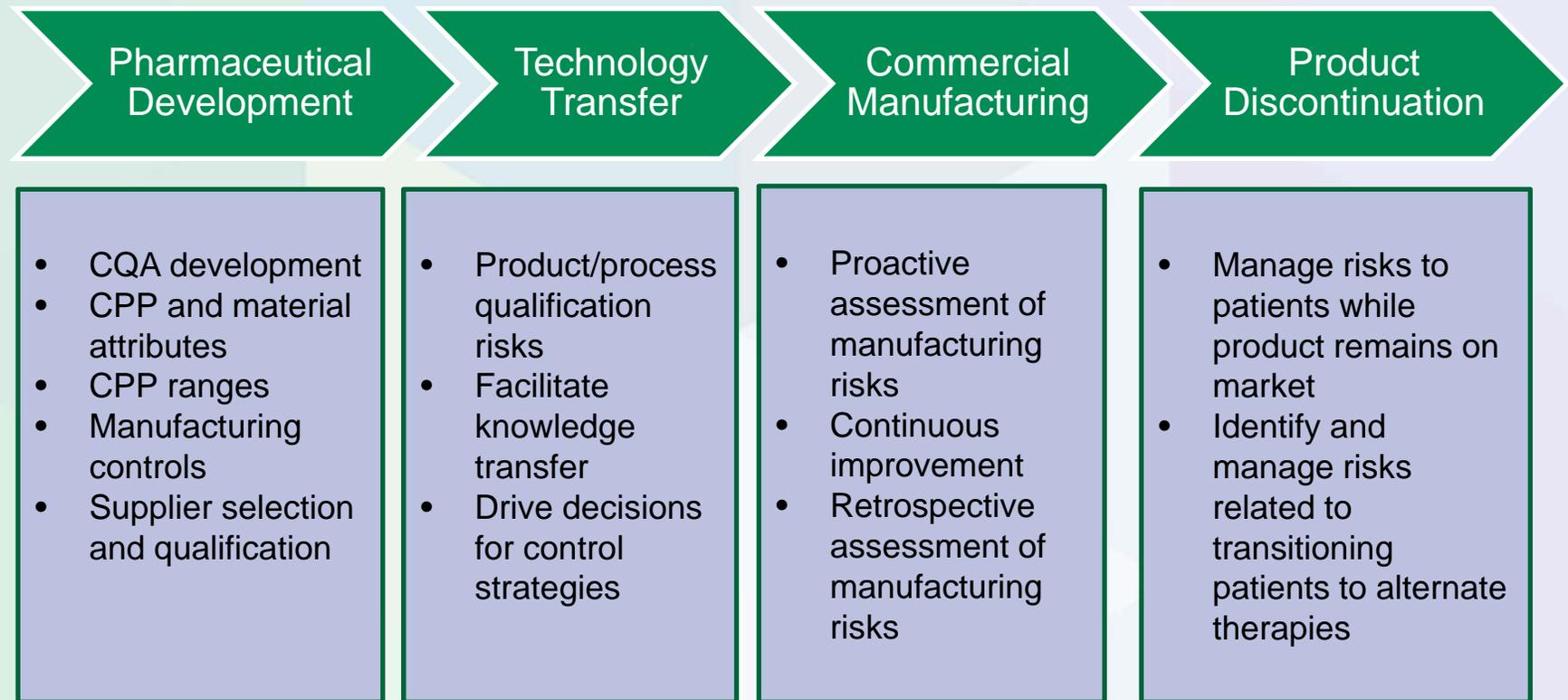
We cannot completely eliminate risks in pharmaceutical operations, so our ability to identify and mitigate these risks is critical.

The TR 54 maturity model describes the progression from no QRM process to one highly integrated into all business functions



PDA's Technical Report No. 54 provides a comprehensive roadmap for establishing and using QRM principles

- TR 54 "Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations", 2012
- Product Life Cycle:



The principles of QRM can be incorrectly applied in pharmaceutical operations

- QRM is NOT an excuse to violate cGMPs
 - Release of a contaminated lot because of a low QRM score
 - Use of QRM to replace root cause analysis
 - I don't need an SOP for that because of the QRM score
- QRM is NOT a shortcut for avoiding the hard work of cGMP compliance
 - Use of QRM to inappropriately reduce process validation studies
 - Use of QRM to justify minimal on-the-job training
 - Use of QRM to cGMP compliance failures

QRM is a tool to facilitate cGMP compliance, not replace it . QRM can be a strong documented ally in demonstrating that we operate in a state-of-control.

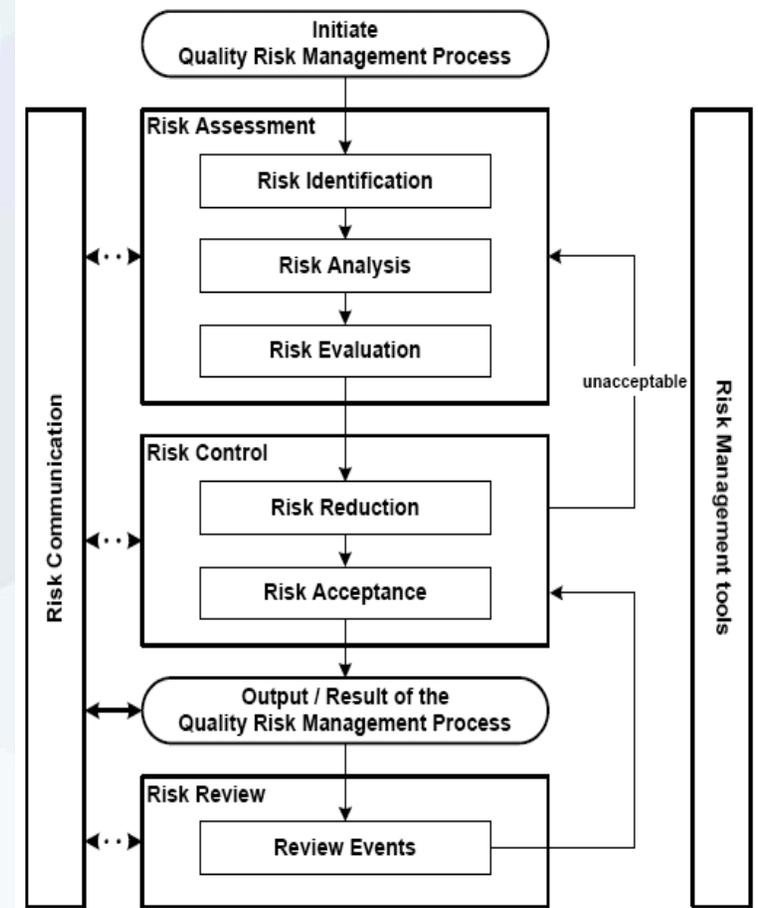
Why is the management of risk important in today's world of pharmaceutical manufacturing?

1. **Not all risks can be eliminated** – thus, we must manage and mitigate those risks that do exist
2. **Not all risks deserve equal attention** – by having a process that ranks and prioritizes risks, we can better utilize our resources and efforts
3. **Not all risks are negative** – by properly assessing and managing risks, we can often drive continuous improvement
4. **Not all risks represent compliance concerns** – global regulatory agencies recognize risk and now consider QRM a science-based tool
5. **Not all risks are readily apparent** – a hidden risk can often pose a greater threat to our business than those we know and can manage

QRM is a key component of a comprehensive Quality System that can improve quality, reduce compliance concerns, and drive continuous improvement.

Global regulatory agencies are increasingly encouraging the use of QRM to manage cGMP activities

- **ICH Q9** – well established and accepted
- **PIC/S Guide to GDP** (June 2014)
“The management should have a formal process for reviewing the quality system on a periodic basis. The review should include... self-assessment processes including risk assessments and audits...”
- **US FDA** – Guidance published based on ICH Q9. Also, documentation on risk assessments increasingly requested in on-site inspections



QRM is broadly accepted and expected by global regulatory agencies. We must now be prepared to show documentation and the associated rationale used.

A number of approaches have been developed to identify and/or quantify risks

- **FMEA** (Failure Mode and Effect Analysis)

An FMEA is a systematic method of identifying and preventing product and process problems before they occur. The FMEA involves identifying and quantifying every potential risk, assessing its impact, and mitigating unacceptable risks. A typical FMEA can consume hundreds of rows in an Excel spreadsheet and take several hundred man-hours to complete.

- **Q9-Style** (can be complex or simple)

- **Simplified systems**

- Likelihood of occurrence (score from 1 – 4)
- Severity (score from 1 – 4)
- Detectability (score from 1 – 4)
- If total score is above 4, specific written action is required

		Probability		
		Low	Medium	High
Impact	High	Yellow	Red	Red
	Medium	Green	Yellow	Red
	Low	Green	Green	Yellow

- **Memo-style** (narrative description of risks, assessment, and mitigation)

Many approaches for quantifying risk exist . The key is that you create a system that can be documented and provides a means for prioritizing your risks.

QRM can be used as a “reactive” tool to assess potential quality issues that have already occurred

1. Assessment of post-marketing issues

- Complaints
- Stability issues

2. Assessment of manufacturing issues

- Potential contamination issue
- Incorrect label

3. Assess the breadth of an investigation

- Extend to other batches or products
- Laboratory issue impact other previous analyses

4. Assessment of adverse trends

- Water results
- Environmental results

In “reactive” events, containment of the issue becomes a key component of the risk assessment. The less contained or limited the issue, the higher the risk potential . Thus, the greater need for mitigation.

QRM can also be used to “proactively” assess cGMP activities to determine the potential for concern

1. Assessment of proposed changes

- Line speed change
- Addition of a third shift

2. Assessment of regulatory actions of experiences of others on your own operation

- Warning Letter items from another firm
- Proposed new regulatory requirements or expectations
- Oversized tablet issue

3. Assessment of new operations

- New tablet press
- Additional automated inspection systems

4. Tool for continuous improvement

- Laboratory flow re-design
- Batch record review/release process

“An effective quality risk management approach can further ensure the high quality of the drug product to the patient by providing a proactive means to identify and control potential quality issues....”

- FDA Guidance on QRM -

A comprehensive “proactive” use of QRM always includes the open-ended question: What could possibly go wrong? Each possibility represents a risk that must be listed, assessed, and mitigated, if needed.

In conclusion, how we can use QRM to positively drive our pharmaceutical operations forward?

1. QRM is here to stay – so, you can expect to be asked in your next inspection to provide documentation for risk management decisions.
2. Do not attempt to use QRM as an excuse to short-cut cGMPs.
3. Don't get overly burdened with what system or process to use for QRM. The key is to formally and intentionally apply it to your operations.
4. QRM can be an effective tool for critical decision-making for “reactive” events and situations. When done well, QRM can provide a much clearer pathway.
5. QRM is an important continuous improvement tool for assessing the potential risks “proactively.”

The proper application of QRM approaches can mitigate the risks we encounter when we intentionally interact with uncertainty.

Thank you!

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