Application of QRM Principles for Requalification Programs

Adam Hall
Sr. Manager, QA Validation
Lonza Pharma and Biotech
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Pharma&Biotech

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Scope of application:

What is meant by "Requalification Program"?

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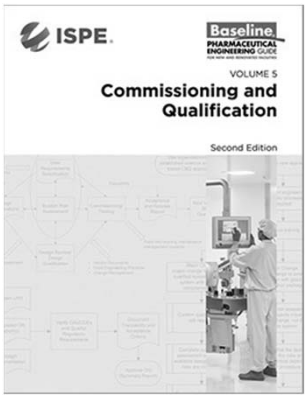
"Requalification"

Preferred terminology seems to change from guidance to guidance, and organization to organization, for what is essentially the same activity:

- **"revalidation"**
- **"requalification"**
- **"validation maintenance"**
- **"periodic review"**
- **…and others**

ISPE Baseline Guide for Commissioning and Qualification (Second Edition) refers to these activities generally as Periodic Review (Chapter 9).



- **"There is a regulatory requirement to maintain qualified systems in a validated state…"**
- **"This chapter describes an approach for periodic review where the frequency of review or requalification is established <u>based on risk</u>, the current level of <u>process understanding</u> and <u>process performance</u>, and <u>regulatory requirements</u>."**

  - *ISPE Baseline Guide for Commissioning and Qualification*, Second Edition, 2019, Section 9.1`

Requalification, for the purposes of this presentation, is the documented, routine qualification activity required to prove that a system or piece of equipment remains in its validated state.

A “Requalification Program” governs what systems require requalification activities, and establishes the cadence of these activities. It also governs historical, or “paper-only,” periodic review.

But which approach is right for which systems?

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Quality Risk Management:

Establish a documented justification based on science and risk.

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What is meant by “Risk-Based” approach?

Is it:

- **Risk acceptance?**
- **Risk denial?**
- **Risk identification and targeted mitigation?**

Requalification is a mitigation to the critical risks identified.

- **It could be a large effort, or next to nothing.**

Know your Process!

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The Requalification Program documents the what and when.

QRM establishes the WHY.

Considerations:

- **Criticality of process step or activity**
  - Direct impact
  - Failure modes and severity
- **Detectability**
- **Probability of Adverse Event**
- **Regulatory Expectations**

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More to consider when trying to demonstrate the state of control for the system or equipment:

- **What can be leveraged from ongoing operations to demonstrate state of control?**

- **Continuous Monitoring?**
- **Periodic Monitoring or Sampling?**
- **Trend Reporting?**
- **Predictive Data Analytics?**

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Common question: Risk Assessment generation can be a long, painful process. Do we really need to do it?

Yes.

Avoid “one-size fits all” approach.

Apparent Pros:
- **Simple**
- **Seemingly Safe / Compliant / “Overkill” approach**

Actual Cons:
- **Wasteful – potential to do too much**
- **Risky – potential to do too little**
- **Not fully compliant without documented justification**

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What do the Regulations say about it?

- **Sometimes determinative, "black or white":**
- **Annex 1 requirements for annual requalification of sterilization:**
  - "All sterilization processes should be validated…"
  - "…The validity of the process should be verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment."
    - PIC/S, P E009-14, Annex 1, *Manufacture of Sterile Medicinal Products*, 2018, Sections 83 and 84

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What do the Regulations say about it?

Other expectations are less prescriptive. Require that organizations develop and justify approach utilizing Quality Risk Management.

Where requalification is necessary and performed at a specific time period, the period should be justified and the criteria for evaluation defined.

- **PIC/S, P E009-14, Annex 15, *Qualification and Validation*, 2018, Section 4.2**

PIC/S
PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PE 009-14 (Annexes)
1 July 2018

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What do the Regulations say about it?

"Periodic revalidation should be considered as some process changes may occur gradually over a period of time, or because of wear of equipment."

"The frequency and extent of revalidation should be determined using a risk-based approach together with a review of historical data."

- **WHO, *Guidelines on Validation*, 2016, Sections 10.33 10.34)**

World Health Organization

GUIDELINES ON VALIDATION

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OK, I did a Risk Assessment.

Am I done?

Two more steps:

- **Document the justification for the execution intervals required.**
- **Look at what the Risk Assessment tells you about your state of control.**
  - Is it good enough? Can it be better? Challenge the status quo.
  - Is there more you can do to improve control, decrease risk to patient, lower costs and reduce equipment downtime?
  - Move from lagging indicator to real time (or predictive)?

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Some Final Thoughts:

- **A properly facilitated and performed risk assessment should identify the failure modes that need to be addressed in order to move from a weaker, slower, more labor intensive mitigation (annual requalification) towards more efficient solution (real time monitoring).**
- **Question and challenge interpretations of guidance from peers, procedures and audit responses. Observe direction of broader industry.**
- **Continue to seek "smarter," automated or engineered solutions, even where regulatory expectations of requalification activities might seem "written in stone."**
- **Example: Air detection probes in autoclaves.**

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Questions?

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