Title:	Periodic Review of Processes and Systems				
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Periodic Review of Processes and Systems

Introduction

This guidance addresses the application of a risk-based approach to:

- Prioritize the systems and processes for periodic review (PR)
- Justify frequency and schedule of PR (if applicable)
- Routine revalidation of processes

The scope of this guidance can be applied to validated test methods, manufacturing processes, sterile processes, equipment cleaning processes, and qualified systems (e.g. equipment, facilities, computer, process control automation and utilities).

The processes of conducting re-qualification and PR are also described.

Validated processes and qualified systems (from this point forward refers to equipment & computer systems) are required to be periodically evaluated to verify that they remain in a validated state. High risk processes (e.g. sterile or aseptic) may also require routine re-qualification and/or revalidation. The application of a risk-based approach allows:

- The prioritization of PR and routine re-qualification/revalidations activities.
- The scientific justification of the PR frequency and routine re-qualification /revalidation frequency (if applicable)

A PR is intended to satisfy the "quality review" referenced in ICH Q7A, section 12.60.

Recommendations & Rationale for Recommendations

1. Scope of the PR

Periodic Review (PR) applies to validated processes and systems.

Examples of the terminology used for critical systems include Direct Impact or critical. Periodic Review of the systems will apply according to the qualification approach used as indicated in Appendix1.

For systems, Appendix 1 provides guidance on the steps to be followed based on the approach used, how the risk assessment of systems is used, where it is documented, how the frequency of the PR is established and when the PR cycle starts.

This determination should be conducted jointly by representatives of the site Quality Team and the System Owner and other potential Experts (e.g., Engineering/Maintenance).

As a minimum this determination assessment should include an evaluation of the system criticality.

In addition, evaluation of the probability of an adverse event and detectability can be used to provide further justification of the level of quality risk associated with a system.
Refer to Appendix 2 (I) for systems risk assessment(RA) examples to determine PR frequency.

For Processes:
The initiation of a periodic review should be clearly defined for each process, and should be based on a risk assessment. There are many considerations that need to be included, some of which are listed below:

- Criticality of the process and associated product(s) – e.g. final product, intermediate, bulk, route of administration.
- Critical quality attributes of the product that are controlled and/or monitored by the system or process without downstream verification.
- Probability of a critical parameter deviation being detected before it could reasonably affect product quality attributes.
- Use of data from the system to demonstrate compliance with a registered process, including batch record, lot release or other GMP records.
- Ability of trending system(s) being used to detect drift that may impact validation status of process
- Frequency of trend data recording and review

A typical risk assessment process is based on the combination of process criticality, probability of an adverse event and detectability of an adverse event. This allows the assignment of an overall level of risk to the process, using either a quantitative numerical scale or a qualitative "High – Medium – Low" scale.

Where there is no requirement for a defined Periodic Review frequency, it may also be possible to justify no fixed frequency and to use trending (for example, using RFT techniques) of existing quality/management systems such as:

- change management
- deviations and failures
- routine checks required as part of process set up or operation

Refer to Appendix 2 (II) for processes RA examples to determine PR frequency.

8. Additional considerations
System documentation

Appendix 2:

(I) Example of Systems Risk Assessments to Determine Periodic Review Frequency

Fluids Autoclave
System criticality –High – used to terminally sterilize parenteral product

Probability of an adverse event – Low – mechanical equipment is robust, process control is simple, utility supply is consistent and has had no unplanned interruptions in the previous 3 years. Historical data shows no operational issues for the last 10,000 sterilization cycles.

→Risk classification is Medium.

Probability of detection – High – independent, dual temperature probes monitor product and drain temperatures to verify sterilization cycle performance. Probes are routinely calibrated monthly. The type of probe used has shown no out-of-specification drift or failures between calibrations in the previous 5 years of use on site. Independent pressure transmitter monitors chamber pressure. The type of transmitter used has shown no out-of-specification drift or failures between calibrations in the previous 5 years of use on site.

→Risk priority is Low.
Periodic Review frequency defined as 5 years, with the additional justification of the routine revalidation program for the sterilization process.

WFI System
System criticality – Medium – used for cleaning of equipment before sterilization.

Probability of an adverse event – High – historical records show one pump failure resulting in microbiological contamination of the system and a further system microbiological deviation in the past 6 months (approximates to at least one adverse event every 100 days).

→Risk classification is High

Probability of detection – Low – component failures are typically detected very quickly, however microbiological failures are not detected immediately due to the sample incubation time.

→Risk priority is High
Periodic Review frequency defined as annual

(II) Example of Processes Risk Assessments to Determine Periodic Review Frequency
Below is an example of periodic review frequencies, based on a qualitative overall level of risk:

Low Risk – Frequency maximum 5 years.
Medium Risk – Periodic review should be conducted at least every 3 years; actual frequency should be assigned and justified based on process usage.
High Risk – Annual periodic review is recommended.

Example: Manual cleaning of aseptic product filling set-up

