Guidance Number 40:

Appendix 1:

Example of Periodic Review Content

1	Introduction & System or Process Background/Description*	This will include verification of the system description (Has the system description changed? What is the system composed of?). In case of a process, has the process changed? Any change of use of the system or process change that may impact the system qualified status or process validated status and any outstanding actions from Qualification/Validation Reports, previous PR and system audits/assessments. If no changes have occurred, previously approved descriptions of the system/process may be referenced.
2	Change Management*	Evaluation and trending of the changes to the system/process, including consideration of the impact of multiple changes (cumulative or repetitive effect) to the system/process and their combined effects on qualification/validation.
3	Deviations/Non Conformance, Incidents, and Investigation reports*	Evaluation and trending of the number and significance of any deviations (frequency and reasons) associated with the system/process, along with any outstanding corrective actions. Any system/process fault/incident logs should be included and the impact of deviations and incidents on the stability and reliability of system/process performance and system qualification/process validation should be considered. This should include review of the potential cumulative impact of multiple deviations.
4	Maintenance & Calibration* (only applies to Systems PR)	Evaluation of the frequency of any unplanned repairs or repetitive failures and the significance of the fault and any outstanding corrective actions. Consider the impact of faults on the stability and reliability of system performance. Confirmation that planned maintenance activities critical to product quality and patient safety have been carried out as scheduled. Calibration review should include assessment of the impact of any out-of-calibration reports.
5	Performance Trends*	Where applicable, performance trends for systems/processes will be assessed. Any repeat or prolonged observances, trends outside normal operation and any gradual trends that may be drifting towards an out-of-control situation will be documented and assessed for impact on the qualified/validated state.
6	New regulatory requirements	Evaluation of impact of new requirements is a continuous/ongoing process as new standards are issued; if a process for maintaining validations/qualifications to current regulatory and company standards is in place, it should be referenced. Document and confirm that the current validation/qualification is considered updated. If new requirements have been established, determine if additional testing or validation/requalification is required (make reference to applicable change control).

* - indicates where another quality system or document may be referenced to meet all or part of the review requirement

Appendix 2:

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

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

- Criticality – high, (product type, any contamination is direct into final dosage form)
- Probability of an adverse event –medium (manual cleaning process)
- Detectability (risk of non-detection) – low to medium (dependent on ability to

100% visually inspect)

Overall level of risk is high; annual periodic review recommended.

Example: Secondary packaging process for a solid dose blister product

- Criticality – medium (oral solid dose, secondary packaging)
- Probability of an adverse event – low (automated equipment)
- Detectability (risk of non-detection) – low (process monitored by barcode checks of packaging materials, in-line checkweigh and vision system)

Overall level of risk is low; five-yearly periodic review recommended