4.5.4 Periodic reviews shall be conducted within the time interval not to exceed 5 years.

4.5.5 In the absence of a risk-based schedule, the periodic review shall default to no more than 2 years.

4.5.6 Periodic review of validated process is not required as the evaluation of deviations, changes and process trends is covered and combined with the Annual Product Records Review.

4.5.7 The results of the periodic review shall be documented, reviewed and approved by the site validation committee.

4.5.8 The review may result in the need for additional studies (e.g. supplemental validation or revalidation).

4.5.9 For processes with systems with lower risk, a periodic review with evidence that the process or system is consistently producing product meeting its specifications fulfils the need for revalidation.

4.5.10 For system that has not been impact assessed, its impact will be assessed to determine whether the system is a direct impact, indirect or non-impact system prior to periodic review.

5.0 PROCEDURE

5.1 Periodic Review of System

A system's first periodic review will cover the time period from the completion of the system's most recent full validation to the review date. Subsequent reviews then cover the time period since the completion of the most recent periodic review.

During the periodic review, the following will be evaluated:

- Review of system description, including complete listing of critical subsystems /components (e.g. equipment, hardware, software).
- Review of the cumulative and/or repetitive effect of all changes (e.g. Change Controls) to include an assessment of whether further action is warranted.
- Review of all deviations (e.g. Deviations, Incidents) including frequency and reasons, to determine whether there is a trend away form the qualified state.
- Review of appropriate maintenance and calibration records (as applicable) to determine whether the system has been properly maintained.
- Review performance trending, if applicable (e.g. system logs).
- Review system against applicable regulatory, GMP and Site requirements established since the last periodic review or qualification.

5.2 Periodic Review Report

The criticality of a system is a quantitative measure of the severity of the impact of an adverse GMP / product quality event occurring in the system that would affect GMP regulatory compliance and/or the critical quality attributes of any relevant products. When assessing the criticality of a system, the system impact on product quality may include:

5.4.1.1 Direct product contact.
5.4.1.2 Production of any excipient or ingredient.
5.4.1.3 Cleaning, sanitisation or sterilisation.
5.4.1.4 Preservation of products status.
5.4.1.5 Generation of data / records used to reject or accept product.
5.4.1.6 Control of a process without independent verification.

Based on this assessment, the criticality level of the system may be defined:

Low – minor negative impact, no direct effect on patient, no long-term GMP regulatory compliance effect.

Medium – moderate impact, possible long-term effect on patient, short to medium term GMP regulatory compliance impact.

High – very significant impact, direct and immediate effect on patient, long term GMP regulatory compliance effect.

5.4.2 **Probability of an Adverse GMP / Product Quality Event**
The probability is a measure of the probability of an adverse GMP / product quality event occurring. This should take into account the complexity of the system, its robustness and its frequency of use. The probability should be assigned based on an estimate of how often an adverse event would expect to occur, as below:

Low – one adverse GMP / product quality event in 10,000 operations

Medium – one adverse GMP / product quality event in 1000 operations.

High – one adverse GMP / product quality event in 100 operations.

Risk Classification:

		Probability of an Adverse GMP / Product Quality Event		
		Low	Medium	High
System Criticality	High	2	1	1
	Medium	3	2	1
	Low	3	3	2

5.4.3 **Probability of Detection**
The probability of detection is an indication of how likely it is that an adverse GMP /product quality event would be detected. For example, routine calibration may

