responsibilities for both the technical and cGMP compliance review of the design should be clearly mandated.

It is crucial to start off with a User Requirement Specification (URS) for the project. It ensures that the user has defined exactly what is required, by specify operating and output requirements, any critical control requirements and any internal and regulatory standards, which may apply. All Requirement Specification documents should be approved by appropriate stakeholders including the quality group for GMP compliance, and used as primary referenced document in the design review process. See **SOP VAL-030.**

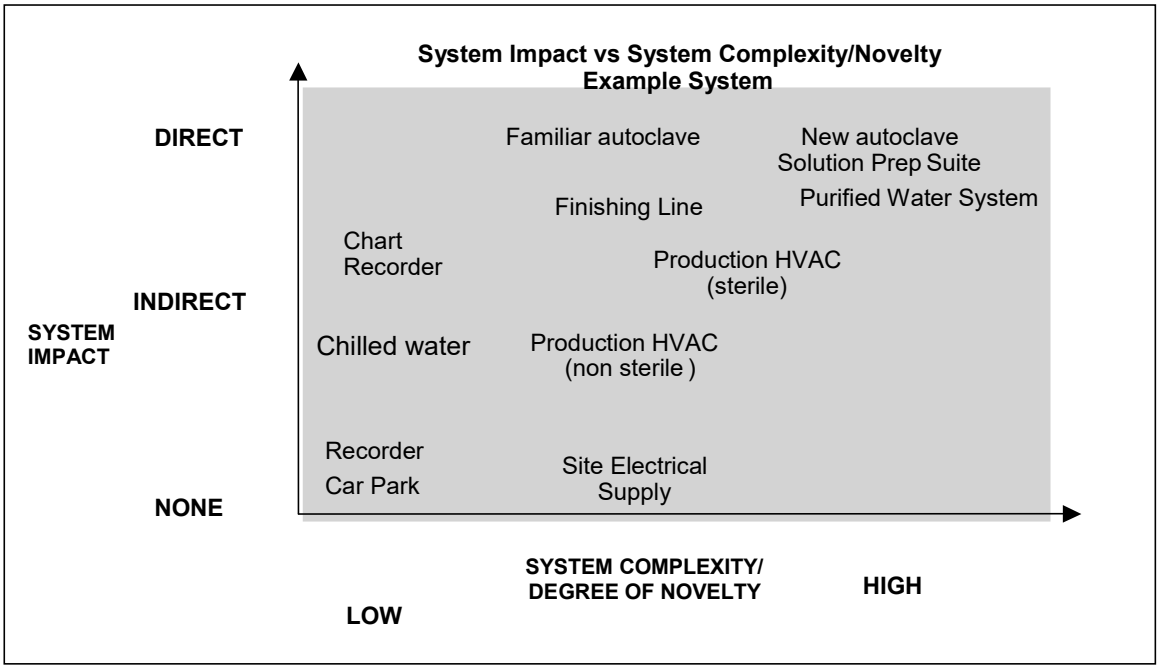
Once compiled, this information will provide the project team with a basis for discussions and clarification of the system through the design phase of the project and to enable functional specification to be drawn up and reviewed.

2.1. Design Qualification Process

The Design Qualification process should address the following points:

- What will be reviewed? (*Documented in Validation Plan or DQ protocol)*
- What methods or approach will be followed? (*Documented in Validation Plan or DQ protocol)*
- List of documents to be reviewed and consulted *(Documented in Audits report or in design review minutes)*
- List of members involved in the DQ review session *(Documented in Audits report or in design review minutes)*
- Conclusions and actions required (*Documented in DQ protocol)*

The level of Design Qualification applied to any design should be based on a consideration of the complexity and novelty (to the user) of each system, and the impact of each system on the product quality. (See **SOP** VAL-045**.**, section 3.1 and 3.2 for a list of questions assess whether an Item/Function has a "Direct or Indirect Impact" on the quality of a product/process).



Highly complex, "Direct Impact" system, warrant a greater degree of scrutiny than simple, familiar system of no impact.

2.2. Selecting a Design Qualification Review Method

The Project Manager or Project Coordinator will determine the most appropriate review method, based on the system impact, complexity and novelty. Below are few approaches that may be applied during the Design Qualification, but not limited to:

- Review the Functional and Project Specifications against the URS and manufacture literature.

- Will an alarm system be activated if air pressure differentials are outside limits?
- Have dust and process extracts been considered in the air balance?
- Will the critical openings be protected by interlocked doors?
- Do the specifications for the upper acceptable limit for particles of defined size meet cGMP?
- Do the specifications for the upper acceptable limit for viable organisms meet cGMP?
- Will ductwork be clearly identified?
- Are the commissioning tests clearly explained?
- Will commissioning method statements be provided?
- Are the validation tests clearly explained?
- Will all instruments be calibrated?
- Will all instruments be calibratable?
- Will calibration certificates be provided?
- Will the design facilitate maintenance?
- Will the design facilitate cleaning?
- Will as-built drawings be provided?
- Will manuals covering operation be provided?
- Will manuals covering maintenance be provided?
- Will the cleaning method be clearly specified?

The responses to these aspects should be documented in detail and a list of deficiencies, remedial actions and issues for resolution produced.

5. Appendix 2 – HAZOP

HAZOP refers to a formal and structured **Haz**ard and **Op**erability study. It is a systematic and detailed study following a preset agenda and involving a team with a variety of backgrounds and responsibilities. It involves an examination of the possibility and consequences of deviations from normal or acceptable conditions in an attempt to ensure all possible EHS risks and risks to product quality are foreseen and addressed.

For each operation or activity associated with the system a list of possible deviations is considered. For each possible deviation, the severity and likelihood of the deviation is assessed and, if warranted, the issue is listed as a problem to be solved. A list of *keywords* is used as prompts for the HAZOP team. The key words used in a HAZOP will vary depending on the nature of the system under analysis. However, if a keyword is not relevant it will take little extra time to dismiss it. Whereas, if a keyword is left out, the risk of missing a deviation is increased. Refer to section 5.2 for an HAZOP example.

5.1. Keywords

Variable	*Guide Word*
Timing	Start too early/late, Stop too early/late, Duration, Sequence
Position	Too High, Too Low, Too Far, Too Close, Wrong Orientation
Direction	To one side, Upwards, Downwards, Reverse
Speed	Too Fast, Too Slow
Flow	High, Low, Zero, Reverse, 2 phase
Level	High, Low
Pressure	High, Low, Vacuum
Temperature	High, Low
Humidity	High, Low

6. Appendix 3 – Failure Mode Effect Analysis (FMEA)

The principle of FMEA is to consider each mode of failure of each component in turn and determine the effects. The FMEA can be undertaken from the perspective of system operation, product quality or EHS but not all three at once. For example, a component whose failure will cause significant downtime, but has little effect on the product, will have high severity consequences for system operation but not for product quality.

The Table below is a sample Assessment.

Function	Failure Modes	Failure Cause	Failure Detection Method	Effect of Failure	Failure Probability	Detection Probability	Severity Factor
One function	Several failure modes	Several causes for each mode?	Are each of these causes detectable	Consequences / severity of failure?	How probable is this failure cause?	How sure can we be of detecting the failure cause?	What level of risk does this represent?
				A (1-3)	B (1-3)	C (3-1)	AxBxC

The severity factor score will highlight the major risks and the priority in addressing them. For example; a failure that has low severity consequences, that is unlikely to occur and has a high probability of detection has a severity factor of 1 (1x1x1). Whereas, a frequent, undetectable failure of severe consequences has a severity factor of 27 (3x3x3).

7. Appendix 4 - Risk Assessment on Product Quality

Risk Assessment on Product Quality evaluates the impact of the system on product quality on areas that have a Direct and Indirect function. The key product quality attributes to be considered are:

- Identity
- Safety
- Efficacy
- Purity

The risk assessment process allows for early actions to be implemented during the implementation phase to reduce and eliminate risk during the project life cycle.

7.1. Overall Approach

1. The first step is the determination of whether the system function or sub-function represents a risk when assessed against a series of GxP criteria. (See **SOP** VAL-045. section 3.1 and 3.2.)
2. Having determined that a particular function or sub- functions may have a direct and Indirect GxP associated with it, the assessment should proceed to identify the various risk scenarios. It is useful to consider for each event what is the likely effect will be (note that each event may have more than one effect).
3. For each Event consider the ***likelihood*** (frequency or probability) of it occurring. Assign a ranking to the likelihood of low, medium or high. Where the likelihood is unable to be estimated, assign a ranking of high. The GAMP4 suggested method of frequency ranking is
    - **Low** – The Frequency of the event occurring is perceived to be once per ten thousand transactions (1 in 10,000).

