

Risk Management Analysis Techniques For Validation Programs

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Introduction

In recent years, the subject of quality risk management has become a major focus of the Food and Drug Administration (FDA). On April 9-11 2002, the FDA held a public meeting in Washington, D.C. The purpose of the meeting was for the public to comment on the following three FDA concept papers:

Premarketing Risk Assessment, Risk Management Programs, and Risk Assessment of Observation Data: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment.¹

It is only matter of time before the FDA and other regulatory agencies will expect the same quality risk assessment to be applied to all areas of the biotechnology and pharmaceutical industry.

Quality Risk Management

Quality risk management is not a new concept. It has been used in the medical device and other industries for many years, and is now becoming more accepted within the pharmaceutical and biotechnology industries. For example, Failure Mode and Effect Analysis (FMEA) techniques have been around for over 30 years. It's only recently, however, that FMEAs have gained widespread acceptance outside the safety area, thanks in large part to QS-9000.

The purpose of this article is to discuss several risk assessment techniques, and how they can be utilized to support the development of user requirement specifications, commissioning, and validation activities. Before a risk assessment technique can be utilized in any quality assessment, it is first important to understand each technique and how to implement them into your system. There are many

different risk management tools however, this article will be based on those most commonly used in the healthcare industry. The following is a list of the most commonly used risk management tools, and a brief description of their practical usages:

- Cause and Effect
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Failure Modes and Effect Analysis (FMEA)

Cause and Effect

Cause-and-effect diagrams were developed by Kauro Ishikawa of Tokyo University in 1943, and thus, are often called Ishikawa Diagrams. They are also known as fishbone diagrams because of their appearance (in the plotted form). Cause-and-effect diagrams are used to systematically list the different causes that can be attributed to a problem (or an effect). A cause-and-effect diagram can aid in identifying the reasons why a process goes out of control.

A fishbone diagram is one technique used to illustrate cause-and-effect. The following is an example of a fishbone diagram technique:

FISHBONE DIAGRAM TECHNIQUE

1. **The diagram, like other problem solving techniques, is a heuristic (verify) tool.** As such, it helps users organize their thoughts and structure the quality improvement process. Of course, the diagram does not provide solutions to quality problems.
2. **The final diagram does not rank causes according to**

their importance. Put differently, the diagram does not identify leverage points, that when manipulated, will significantly improve the quality of the process at hand.

- The diagram is a very attractive tool.** On the face of it, it is easy to learn and apply. However, it is a mistake to approach it without mastering at least some organizational learning skills, such as working together with others, seeking the truth, being open to different ideas, and seeing others who might oppose you as colleagues with different ideas. Without such skills, internal politics can dominate the process (e.g., the most powerful opinion dominates; team members bring to the diagram construction process a political agenda).

Fault Tree Analysis

A Fault Tree Analysis (FTA) is a deductive, top-down method of analyzing system design and performance. It involves specifying a top event to analyze (such as a sterilization process), followed by identifying all of the associated elements in the system that could cause that top event to occur.

FTA is a top down approach to failure mode analysis. It assumes a system level failure, and identifies critical failure modes within that system. The undesirable event is defined, and that event is then traced through the system to identify possible causes. One event is addressed at a time, and all pos-

sible causes of that event are considered. The analysis proceeds by determining how these system-level failures can be caused by individual or combined lower level failures or events. The tree is continued until the subsystem at fault is determined. By determining the underlying causes, corrective actions can be identified to avoid or diminish the effects of the failures. FTA is a great “lead-in” to robust experimental design techniques. For example, the following is a top down approach to understanding a basic sterilization model (See Figure A)

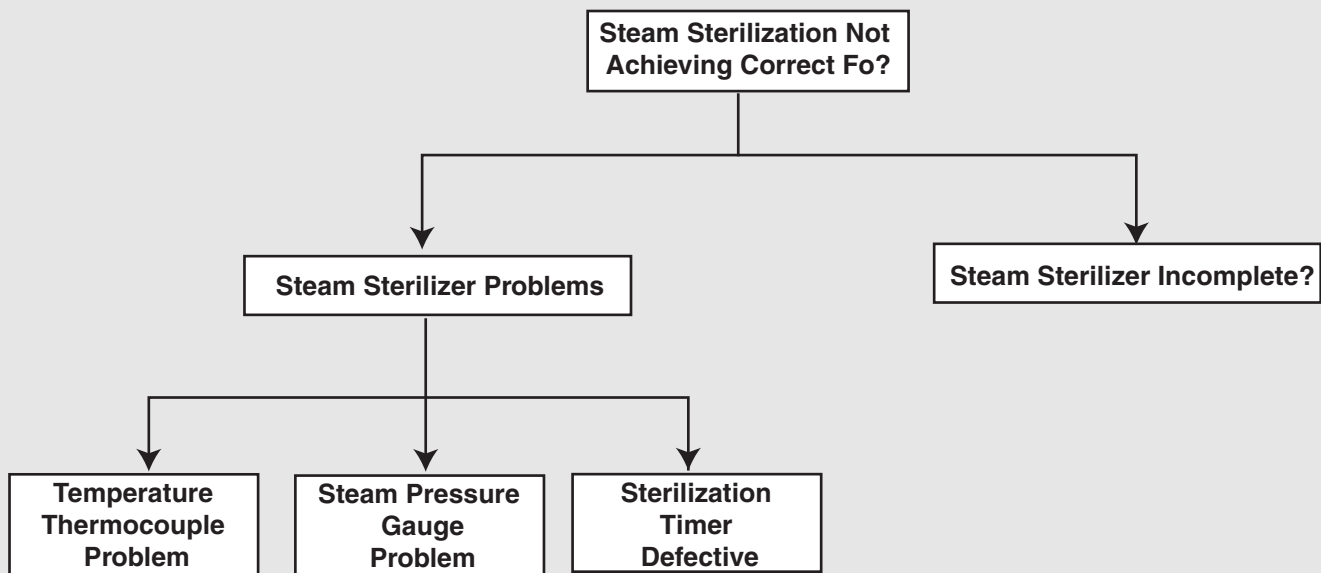
Hazard Analysis and Critical Control Points (HACCP)

HACCP is a management system in which product safety is addressed through the analysis and control of biological, chemical, and physical hazards from raw material production, procurement and handling, to manufacturing, distribution, and consumption of the finished product. For successful implementation of a HACCP plan, management must be strongly committed to the HACCP concept. A firm commitment to HACCP by top management provides company employees with a sense of the importance of producing safe products. While HACCP is traditionally used in the food industry, one can see the value of using this technique in determining the critical control point in the manufacturing of biological or pharmaceutical drugs.

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Figure A

A top down approach to understanding a basic sterilization model



Failure Mode and Effect Analysis (FMEA)

Potential Failure Mode and Effect Analysis (FMEA) have recently emerged as a powerful tool for avoiding costly product performance failures. Both product/design FMEA and process FMEA can help you improve product reliability, and reduce design and manufacturing costs. FMEA is a bottom up approach to failure mode analysis. It is an inductive process, which is performed after the detailed design phase of the project. It is used to evaluate a design or process for possible failure modes. FMEA considers each mode of failure of every component of a system, and ascertains the effects on system operation of each failure mode in turn. The failure effects may be considered at more than one level. For example, the subsystem and the overall system may be considered. This technique helps eliminate poor design and process features. FMEA is complementary to each stage of a product design, development, and validation.

HHS Publication FDA 90-4236 states, "Failure mode effect analysis (FMEA) should be conducted at the beginning of the design effort and as part of each design review to identify potential design weaknesses. The primary purpose of FMEA is the early identification of potential design inadequacies that may adversely affect safety and performance."

FMEA is a method to evaluate possible ways failures can occur in a design, process, system, or service. FMEA uses teams to improve the design, product, process, and/or service.

A second tool, process FMEA, helps in analyzing manufacturing processes and identifying the processes that are important for manufacturing a trouble-free, functioning product. The intent is to identify and correct known or potential failure modes that can occur during process development. It has the greatest impact in the early stages of process design, before any machines, tools, or facilities are purchased. This level of analysis is completed before setting the final product design and, therefore, before production begins. After identifying the critical processes, corrective actions and appropriate process controls, such as Statistical Process Control (SPC), are evaluated and implemented. Process FMEA can also be used to define important process variables (as compared to product variables) to maximize the application success of SPC. Process FMEA's should be living documents.

FMEA cause and effect should be used during process validation to determine "worst-case" conditions.

FOLLOWING IS A LIST OF THE FMEA OBJECTIVES:

- Improve productivity and yields
- Improve product reliability through improved design control
- Reduce waste and rework in both product design and manufacturing processes
- Improve manufacturing process reliability and reduce process variability
- Change the focus of your engineering and manufacturing efforts from "putting out fires" to improving product design and manufacturing
- Reduce design and manufacturing costs
- Predict potential, unavoidable design and manufacturing problems, and implement corrective actions
- Reduce product development and design cycle times
- Comply with FDA GMP regulations

The next section of this article will describe how to implement FMEA methodology into your risk assessment program

How to Implement a FMEA Methodology into Your Risk Assessment Program

Every company is unique therefore, it will require different methods when developing and implementing a risk management program. This section of the article will focus on developing a risk assessment program from the early stages of process development, developing a user requirement specification for equipment and utilities, new facility construction and commission, and into manufacturing process and routine process monitoring. While there are many different risk assessment methods, this section of the article will be dedicated to developing and implementing FMEA and developing User Requirement Specifications (URS).

Early Stage Process Development Using Design FMEA

A FMEA is systematic method of identifying and preventing product and process problems before they occur. FMEAs are focused on preventing defects and contamination problems, enhancing safety, and increasing customer satisfaction. Usually, FMEA's are conducted in the product design or process development stages, however, FEMAs can be performed on existing processes and products.

Design FMEA

Design FMEA is used to analyze product design before they are released to manufacturing. A design FMEA focuses on failure modes caused by design deficiencies.

Process FMEA

Process FMEA is used to analyze manufacturing processes. A process FMEA focuses on failure modes caused by deficiencies or potential problems with the actual process.

FMEA PROCESS STEPS

The following are general steps that should be followed:

1. Select the team.
2. Review the process
3. Set up initial brainstorming meeting.
4. Construct a FMEA worksheet. (*See Figure 1*)
5. Prioritize the steps, define the definition of key terms, and agree on the criteria for ranking severity, occurrence, and detection.
6. Investigate and evaluate available information.
7. Team approved action(s). Assign appropriate personnel to each corrective action.
8. Complete and document corrective actions, as required.

Selecting the Team

It is important to select team members who have different familiarity with the product and process. Team members must understand customer expectations and be knowledgeable of the system, its controls. The success of FMEA in selecting a team leader who will be responsible for setting up meetings, ensuring that the team has resources to support FMEA, and managing to the successful completion of the FMEA. Depending on whether the FMEA is design or process, different team members will be required. Representatives from the following list should be chosen dependent upon the nature of the project.

- Research & Development
- Manufacturing
- Regulatory Affairs
- Engineering
- Quality Control
- Quality Assurance
- Project Management

Review the Process

To ensure that everyone on the FMEA team has the same understanding of the process that is being worked on, the team should review all the necessary documentation relating to the product. If the team is conducting a process FMEA, a detailed flowchart of the operation should be reviewed.

The documentation will assist the FMEA in understanding all the requirements and issues related to the process and/or product.

Set up Initial Brainstorming Meeting

Once the team has an understanding of the process (or product), team members can begin planning for potential failure modes that could affect the manufacturing process or the product quality. A brainstorming session will uncover all ideas. Team members should come to the brainstorming meeting with a list of their ideas regarding the process or product.

Most manufactured products and manufacturing processes are complex, therefore, it is best to conduct a series of brainstorming sessions, each focused on a different element (for example; process, personnel, methods, procedures, components, equipment, materials, and the environment) of the product or process.

Once the brainstorming is complete, the ideas should be organized by category. The team must decide the best categories for each group, as there are many different ways to form group failure modes. The type of failures e.g., materials, mechanical, and personnel can be used to categorize a grouping. The type of failure can indicate the stage of the product or the process point at which the failure is most serious. Grouping the failures will make the FMEA process easier to analyze.

For accuracy and completeness, it is important to record all decisions made during the brainstorming meeting. The development of standardized assessment forms to capturing valuable information is one tool that is very effective in accumulating information.

Failure Modes

A failure mode is a physical description of a defect, condition, or characteristic related to the specific function, component or operation identified. List the potential effects of each failure mode. There may be several of these for each item identified in the list below:

Figure 1

FMEA Team Start-Up Worksheet

FMEA Number: _____ Date Started: _____

Date Completed: _____

Team Members: _____

Team Leader: _____

1. Are all affected areas represented?
YES NO Action: _____

2. Are different levels and types of knowledge represented on the team?
YES NO Action: _____

3. Is the customer involved?
YES NO Action: _____

4. Who will take minutes and maintain records? _____

FMEA Team Boundaries of Freedom

5. What aspects of the FMEA is the team responsible for?
(FMEA Analysis) (Recommendations for Improvement) (Implementation for Improvement)

6. What is the budget for the FMEA? _____

7. Does the project have a deadline? _____

8. Do team members have specific time constraints? _____

9. What is the procedure if the team needs to expand beyond these boundaries?

10. How should the FMEA be communicated to others? _____

11. What is the scope of the FMEA?
Be specific and include a clear definition of the process or product to be studied:

START WITH KNOWN FAILURE MODES:

- Customer complaints
- Process control reports
- Validation failures
- Test results
- Product quality data

Potential Effects (System and End User)

Effects are any conditions that can occur in the early process development phase, clinical setting, and/or manufacturing conditions, potentially brought about by a failure mode, if it were present in the product used by the customer. In the case of process FMEAs, also include potential effects on subsequent operations in the manufacturing process. There may be several effects for each failure mode.

Assigning Severity, Occurrence, and Detection Ratings

In most FMEA, the rating is based on a 10-point scale, with one (1) being lowest and ten (10) being highest. *Figure 2* is an example of a typical ranking system for Severity, Occurrence, and Detection.

It is important to establish clear and concise descriptions for the points on each of the scales, so that all team members have the same understanding of the ratings. The scales should be established before the team begins the ranking of the FMEA.

In a typical ranking system, each of three ratings (severity, occurrence, and detection) is based on a five-point scale, with one (1) being the lowest rating and five (5) being the highest. This ranking method was selected because it best suited the process analysis.

Severity

Severity ranking is an assessment of the seriousness of the effect, assuming the affected product is actually being used. This is depicted using a numbering scheme. The Severity is estimated on a scale of one through five. *Figure 3* may be used as a reference for scaling. There will be a severity rank for each effect identified.

Potential Causes of Failure

For each failure mode, list all the possible mechanisms and causes that could bring about the failure. There may be

more than one cause for each failure mode.

• Design FMEAs

The focus is specifically on design weaknesses and deficiencies, or possible customer use/misuse situations that could lead to the failure.

• Process FMEAs

The focus is on process aspects, controls, variables, or conditions that can result in the failure.

Occurrence

Occurrence is the probability that the cause listed will happen and create the failure mode described. Historical data on this or similar designs/processes may be used to estimate how often an occurrence will transpire. The probability of occurrence may be defined on a scale from one to five. There is an occurrence rank for each cause identified. (*See Figure 4*)

Detection

Detection ranking is specific to “Current Controls.” A ranking score of one is assigned to represent the combined impact of all controls identified for a given cause. If there are no controls for a cause, assign a high rank (5) in the detection column for that cause.

• Design FMEAs

Detection is based on the ability that routine testing and inspection will detect the failure or cause of the failure prior to manufacturing.

• Process FMEAs

Detection is based on the probability that the process controls/inspections identified will prevent or remove the cause prior to manufacturing or customer use.

Risk Priority Number (RPN)

The Risk Priority Number, (RPN), is a measure of the overall risk associated with the failure mode. The RPN is obtained by multiplying the rating for severity, occurrence, and detection. It will be a number between 1 and 125. The higher the number, the more serious the failure mode will be. Each failure mode may have several RPNs, because there may be multiple effects (i.e., severity, occurrence, and detection ranks) and, therefore, several combinations of those numbers.

Severity x Occurrence x Detection = RPN
 5 x 5 x 5 = 125

Figure 2**A typical ranking system for Severity, Occurrence, and Detection.**

Rating	Severity	Occurrence	Detection
10	Dangerously High	Very High: Failure is almost inevitable	Absolute Uncertainty
1	None	Remote: Failure is unlikely	Almost Certainty

Figure 3**A severity rank for each effect identified.**

Severity Level	Description	Ranking
Very High	Any failure that could reasonably result in a safety issue (potential harm to worker or customer) and/or may result in a regulatory issue.	5
High	Major failure that may render the system inoperable or result in significant reduction in performance or quality of the product	4
Moderate	Moderate failure likely resulting in reduction in performance or quality of the product. These failures are noticeable to the end user, and are likely to generate a moderate level of dissatisfaction or complaints from the customer.	3
Low	Minor failure, not noticeably affecting functional quality, however, may generate complaints due to annoyance. For example, cosmetic defects and increased maintenance.	2
None	Minor failure, unlikely to be noticed by customers or generate complaints.	1

Figure 4 For Client Review Only. All Rights Reserved. Advanstar Communications Inc. 2005**An occurrence rank for each cause identified.**

Probability of Failure	Description	Ranking
Very high	Failures occur regularly and one could reasonably expect the failure to occur for each component or during each process step.	5
High	Failures occur on a frequent basis. These failures do not occur every time, however, they do occur at a rate to produce significant concern to the product quality and performance.	4
Moderate	Failures occur only occasionally, however, at a rate that does not significantly impact production, but can be a nuisance.	3
Low	Failures occur rarely. These failure rates create few production problems.	2
Remote	A failure of the component or system is extremely unlikely.	1

Figure 5**A detection rank for each failure identified.**

Probability of Failure	Description	Ranking
None	No detection methods in place to prevent the release and use of the product or process. Detection of problems are not feasible.	5
Low	No intentional inspection techniques in place; however, the failure is such that it may render the product useless upon receipt.	4
Moderate	Indirect inspection techniques on various aspects of the product/process, such that an abnormality could reasonably result in a true failure occurring.	3
High	Statistical sampling inspection techniques in place to directly look for the failure.	2
Very high	100% inspection techniques in place to directly look for the failure	1

Prioritize the Failure Modes for Action

As a general guideline, RPN numbers with a severity of three (3) or greater, and an overall RPN of 50 or greater, should be considered as potentially critical, and actions should be taken to reduce the RPN. However, this threshold number may vary from process-to-process, and the project team must make the final decision.

Pareto analysis can be applied. The top 20% of the ranked RPN numbers should account for approximately 80% of the anticipated frequent failure modes. These 20% should be a top priority in corrective action.

RECOMMENDED ACTIONS

- To reduce severity: change design or application/use.
- To reduce occurrence: change process and/or product design.
- To improve detection: Improve controls as a temporary measure. Emphasis should be on prevention e.g., develop controls with alarms.

By ranking problems in order, from the highest risk priority number to the lowest, you can prioritize the failure modes. A Pareto diagram is helpful to visualize the differences between the various ratings, and to assist in the ranking process. The FMEA team must now decide which items to work on first. Usually, it helps to set a cut-off RPN, where any failure modes with an RPN above that point are attended to.

Those below the cut-off are left alone for the time being. For example, an organization may decide that any RPN

above 50 creates an unacceptable risk.

Once a corrective action is determined by the teams, it's important to assign an individual or group to implement the required action. Selection should be based on experience and expertise to perform the corrective action. It's also important to assign a target completion date for the action item. This will help in insuring the timely close of any problem.

Reassessing the Risk Mode after Corrective Action

Once action has been taken to improve the product or process, a new rating for severity, occurrence, and detection should be determined, and the resulting RPN calculated. For failures modes where action was taken, there should be significant reduction in the RPN. If not, that means the action did not reduce the severity, occurrence, and detectability. The final RPN can be organized in a Pareto diagram and compared with the original. You should expect at least a 50% or greater reduction in the total RPN after the FMEA.

After the action has been implemented, the severity, occurrence, and detection ratings for the targeted failure modes are re-evaluated. If the resulting RPN is satisfactory, you can move onto other failure modes. If not, you may wish to recommend further corrective action.

Use the example of a typical FMEA worksheet that appears on the prior page.

The FMEA risk assessment method listed above is just one example of how implementing a risk management tool

Description of FMEA Worksheet

System _____
 Subsystem _____
 Component _____

Potential Failure Mode and Effects Analysis (Design FMEA)

FMEA Number _____
 Prepared By _____
 FMEA Date _____

Team Lead _____
 Core Team _____

Key _____
 Date _____

Revision Date _____
 Page _____ of _____

Item / Function	Potential Failure Mode(s)	Potential Effect(s) of Failure	Severity	Potential Cause(s)/ Mechanism(s) of Failure	Occurrence	Current Design Controls	Detectability	RPN	Recommended Action(s)	Responsibility & Target Completion Date	Action Results				
											Actions Taken	New Sev	New Occ	New Det	New RPN
Coolant containment in Product. Poor hose connection	Crack/break. Burst. Bad seal. Poor hose material	Leak	3	Over pressure	3	Burst, validation pressure cycle.	2	18	Test included in prototype and production validation testing.	John Scientist 2/27/04 Jim Engineer 5/1/04	Install durable hose material with pressure interlock to prevent over pressure. Validated new design	3	1	1	3
<p>Write down each failure mode and potential consequence(s) of that failure.</p> <p>Severity - On a scale of 1-5 rate the Severity of each failure (5= most severe).</p> <p>Occurrence - Write down the potential cause(s), and on a scale of 1-5, rate the likelihood of each failure (5= most likely).</p> <p>Current Design Controls</p> <p>Detectability - Examine the current design, then, on a scale of 1-5, rate the Detectability of each failure(5= least detectable). See Detectability sheet.</p> <p>Recommended Action(s)</p> <p>Responsibility & Target Completion Date</p> <p>Actions Taken</p> <p>New Sev</p> <p>New Occ</p> <p>New Det</p> <p>New RPN</p>															
<p>Risk Priority Number - The combined weighting of Severity, Occurrence, and Detectability. RPN = Sev X Occ X Det</p> <p>Response Plans and Tracking</p> <p>Corrective Action Implemented New RPN assigned</p>															

can decrease the potential for quality problems. The next topic will cover establishing risk management for systems that require validation.

User Requirement Specification Procedure — Getting Started

This section of the article will describe how to develop a URS system for direct and indirect impact systems. However, before a detail URS document can be developed, a system impact assessment process should be performed for each system. *Figure 6* is a brief overview of how to perform an equipment impact assessment.

Equipment Impact Assessment

An equipment impact assessment should be performed on any system or equipment before they are purchased, re-

ceived, installed, commissioned, and validated. However, before URSs and protocols can be developed, a component impact assessment should be performed on that system.

In order to decrease the cost and potential delays in a project, Good Engineering Practices (GEP) should be implemented. The ISPE Baseline Commissioning and Qualification guideline defines Good Engineering Practice as follows:

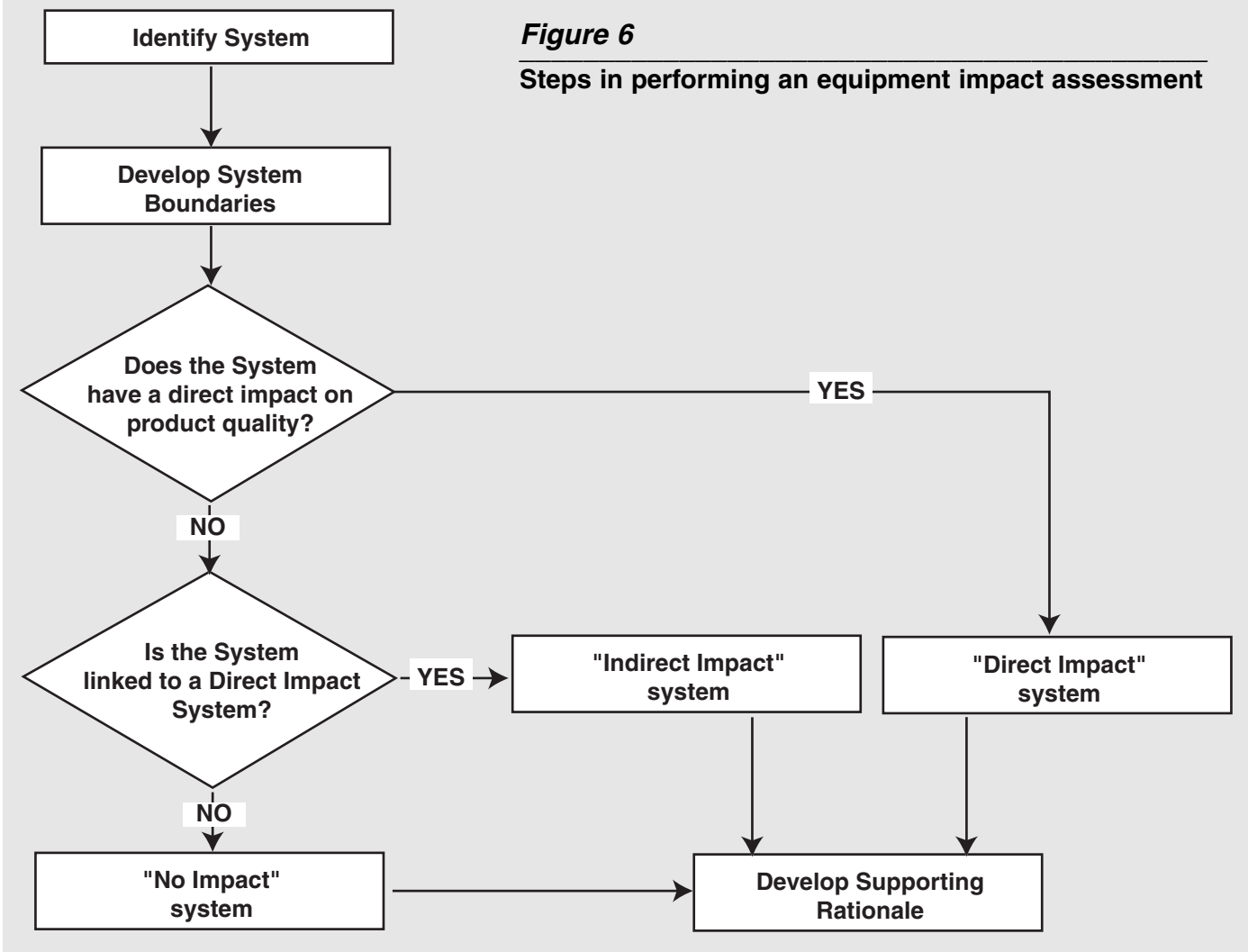
“Established engineering methods and standards that are applied throughout the project life cycle to deliver appropriate cost-effective solutions”²

The proper design and selection of system can be critical to any manufacturing operations. By implementing GEP, the risk of problems occurring during the design and selection can be decreased substantially.

“Direct Impact” systems are expected to have an impact on product quality, whereas, indirect impact systems are not expected to have an impact on product quality. Both systems will require commissioning; however, the “Direct Impact”

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Figure 6
Steps in performing an equipment impact assessment



system will be subject to qualification practices to meet additional regulatory requirements of the FDA and other regulatory authorities.

See *Figure 6* for an outline of the impact assessment process based on the ISPE's Commissioning and Qualification guidelines.

Benefits Impact Assessment

Execution of an impact assessment accomplishes the following:

- Provides classification of a system as either Direct Impact, Indirect Impact, or No Impact based on the system's effect on product quality
- Identifies systems that, if improperly, designed or installed, could present a risk to product quality

System Impact Procedure

You must first identify the system and enter system name and system number, on the system impact assessment Table 1. This information can usually be obtained from the P & ID drawings or other system documentation.

- Complete the system description section with a general narrative of the system and its major components, design, operation, functional capabilities, and critical functions.
- Mark on the system P & ID drawing(s) to clearly identify the system boundaries and all components of the system included within the boundary.
- Specify system boundaries by inserting a horizontal or vertical line at the boundary. These lines should be placed to clearly identify whether or not the adjacent component is part of the system.

To help in establishing the system boundary, utilize the following general guidelines (there may be exceptions to these guidelines):

- If the component number of a valve etc. is labeled as part of the main system being assessed, then it generally will be part of that system.
- The control system I/O for a given system will become part of that system.
- Disposable flexible piping connectors and/or portable tanks etc. should not be highlighted as part of the system, and should be noted either on the drawing or in the comments section of the form, so it is clear that they were not highlighted on purpose.

Complete the impact assessment challenge table (See next page). Use the seven listed challenges to evaluate the system and place an "X" in the appropriate "Yes" or "No" block.

Classify the system as "Direct Impact," "Indirect Impact," or "No Impact" on the system classification line.

- If the response to any of challenges numbers one through six is "Yes," the system shall be classified as a "Direct Impact" system.
- If the response to challenges numbers one through six is "No," but the response to challenge 7 is "Yes," the system shall be classified as an "Indirect Impact" system.
- If the response to challenges numbers one through seven is "No," the system shall be classified as a "No Impact" system.

Complete the system classification rationale section with a brief explanation as to why the classification was assigned. This is to ensure understanding by subsequent reviewers and approvers as to why the classification was chosen.

Attach the P & ID's to the system impact assessment table, fill in the page numbers, and fill in the "prepared by" and date fields.

Impact Table 1 is a system impact assessment for nitrogen air distribution system used in the operations of manufacturing process.

Component Criticality Assessment Process

After you have established that a system is direct or indirect, you then perform a component impact assessment. However, this is usually performed after the impact assessment is performed, and URSSs have been developed. The component criticality assessment process requires the Piping and Instrument Drawings (P&IDs) and system instrument list be reviewed in detail.

The components within "Direct Impact," "Indirect Impact," and in some cases "No Impact" systems should be assessed for criticality. This is suggested to ensure that systems previously judged to be "Indirect Impact" or "No Impact" in the early, high-level assessment, have not subsequently acquired a critical function, as the detailed design has progressed to conclusion.

Applicability of any of the following listed criteria to a given component will provide an indication that the component is critical:

- 1) The component is used to demonstrate compliance with the registered process
- 2) The normal operation or control of the component has a direct effect on product quality
- 3) Failure or alarm of the component will have a direct effect on product quality or efficacy
- 4) Information from this component is recorded as part of the batch record, lot release data, or other GMP-related documentation
- 5) The component has direct contact with product or product components

- 6) The component controls critical process elements that may affect product quality without independent verification of the control system performance.
- 7) The component is used to create or preserve a critical status of a system

Evaluation of each criticality of components within each system with respect to their role will assure product quality.

After the impact assessments have been performed, the qualification phase of the systems can be performed. The use of risk assessment methods, as described above, can assist in developing validation protocols that are logically designed to insure proper qualification of a system.

Table 1

Impact Assessment Challenge Table

Impact Challenge Table		Yes	No
1.	Does the system have direct contact with the product (e.g., air quality) or direct contact with a product contact surface (e.g., CIP solution)?	X	
2.	Does the system provide an excipient, or produce an ingredient or solvent (e.g., water for injection)?		X
3.	Is the system used in cleaning, sanitizing, or sterilizing (e.g., Clean Steam)?		X
4.	Does the system preserve product status (e.g., Nitrogen purge for air sensitive products)?		X
5.	Does the system produce data that is used to accept or reject product (e.g., electronic batch record system, critical process parameter chart recorder, or release laboratory instrument)?		X
6.	Is the system a process control system (e.g., PLC, DCS) or contain a process control system that may affect the product quality, and there is no system for independent verification of control system performance in place?		X
7.	Is the system not expected to have a direct impact on product quality, but does support a Direct Impact System?		X
<p>System Classification: (Direct Impact, Indirect Impact, or No Impact): This system was defined as "Direct Impact" because it meets the requirements based on the above risk assessment criteria.</p>			
<p>System Classification Rationale: The function of the nitrogen air distribution system is to provide a continuous overlay of product. Since nitrogen air does impact status, the system impact is considered "Direct." The problem with nitrogen quality is that it will have a direct impact on product quality.</p>			

Applying Risk Management When Developing User Requirement Specifications for Systems

Based on my experience, most companies have not yet developed a risk assessment system for their validation program. They normally rely on industry standards or previous experience to determine which type of qualification protocols (Installation, Operational and Performance) need to be developed. Most often, they have either developed an ultra conservative or minimalist approach in assessing the types of qualification protocols required for a system. Each approach can be very costly and time consuming for a company. If you take an ultra conservative approach, it will add additional cost and time to the project. By taking a minimalist approach, it could also be very costly and/or time consuming, especially if an inspector notes GMP deficiencies in the validation program.

For years, equipment qualification was an activity that was addressed, if at all, only after equipment was designed, purchased, and installed. Companies view the generation, execution, and detail of this documentation as a “black box”; it’s something they need for compliance, but do not fully understand. The development of User Requirement Specifications (URS) is usually one of the most critical elements in the compliance documentation process.

What is a URS? A URS is a detailed document used to specify the requirements of the user for individual aspects of the facility, equipment, utility, and system, in terms of function, throughput, operation, documents, and applicable qualifications need.

How do you develop an appropriate URS? The following is an example of how to develop an acceptable URS, and applying a risk assessment to determine the type of qualification needed for a particular piece of equipment using a ranking tool.

The URS documents the design qualification and rationale equipment selection. The URS describes critical installation and operating parameters and performance standards that are required for the intended use of the equipment, and provides the basis for qualification and maintenance of the equipment. The URS should be prepared by the equipment owner in collaboration with representatives of departments that will participate in qualification and maintenance of the equipment, and departments that will be affected by the operation of the equipment.

In order for a URS system to be successful, you will need to develop a procedure that describes in detail the function of the URS. While a URS is not necessary, it will

probably raise the level of success when qualifying a system. The URS procedure should have forms, which must be completed by the end user, and reviewed and approved by the various functional groups. The URS is usually submitted to the purchasing department as part of the purchasing specifications. The following is an example of a method for developing a URS with a validation risk assessment.

The use of risk assessment methods can assist in developing validation protocols that are logically designed to insure proper qualification of a system.

Equipment Description Section

The equipment description section of the URS is used to describe design specifications. The following is a brief overview of that section:

- Description: Briefly describe the equipment type, size, capacity, etc. Include manufacturer and model, if known.
- Location: Indicate where the equipment will be installed and/or used. Include room number, floor footprint, lab bench, etc., as applicable.
- Contact Person: The end user or other individual who will coordinate the commissioning process.
- User Department: The department that is responsible for the equipment.
- Other Affected Departments: Departments whose activities will be affected by operation of the equipment, or who will be involved in the selection, installation, operation, qualification, and/or maintenance of the equipment.
- Intended Use: Describe the intended use of the equipment in relation to cGMP operations or processes.
- Functional Requirements: Describe critical functions that the equipment must perform to support the intended use.
- Calibration Requirements: Describe calibration specifications and schedules for instrumentation and controls associated with the equipment.
- Maintenance Requirements: Describe preventive main-

Table 2**Component Impact Assessment**

A. Quality Impact	Score
No impact: Equipment will not be directly or indirectly associated with cGMP activity.	0
Minimal impact: Equipment indirectly affects cGMP processes or procedures. (Non Direct Product Impact)	1
Potential Impact: Equipment performs or directly supports a cGMP process or procedure; failure could potentially affect product quality. Equipment failure could negatively impact operational efficiency or costs. (Indirect Product Impact)	2
Direct Impact: Equipment is an essential component of a cGMP process or procedure, or is in direct contact with drug substance or drug product. Equipment failure could result in loss of product; safety hazard; damage to materials; equipment or facility; or negative inspection findings. (Direct Product Impact)	3
B. Quality Risk Management	Score
No risk control necessary.	0
Failure of the equipment would be detected immediately and be corrected before affecting a cGMP process or procedure.	1
Failure could not go undetected. Systems and procedures are in place to detect negative impact on product quality safety or purity before a significant loss of productivity.	2
Failure could potentially go undetected and cause failure of other processes or procedures.	3
C. Technology Risk	Score
Very simple system; minimal chance of failure.	0
Commonly understood technology, rugged equipment; low probability of failure.	1
Somewhat complex equipment, generally reliable technology, components and/or controls.	2
Highly complex and/or sensitive equipment, sophisticated technology, unique components or processes.	3
D. Technology Risk Management	Score
Control and repair possible without impacting cGMP activities.	0
Equipment requires minimal training, simple maintenance procedures; back-up, repair, or like-for-like replacement is readily available.	1
Requires trained operators and maintenance technicians. Backup systems, repair, maintenance, and replacement are readily available.	2
Operators and maintenance technicians must be highly trained. Maintenance, repair, or replacement requires specialized and/or time-consuming effort. Backup systems, repair, maintenance, and/or replacement are not readily available.	3

tenance tasks and schedule. Identify any additional maintenance requirements to ensure that the equipment continues to operate as required.

- **Qualification Requirements:** Describe qualification requirements to ensure that the equipment remains in a validated state.

System Requirements Definition Section

Identify the specific attributes that are necessary for the equipment to satisfy the requirements for the equipment's intended use. Provide acceptance criteria and acceptable ranges that can be verified to document that the equipment is appropriate for its use, and capable of functioning reliably, as required. This section provides the basis for qualification protocols, and for ongoing maintenance and calibration procedures. List only those characteristics that will provide specific evidence relevant to the equipment's intended use. Include the following requirements, as appropriate:

- **Procurement:** Identify any special shipping, delivery, preliminary testing, certification, or other requirements for acquisition of the equipment, as necessary.
- **Installation:** Identify requirements for installation, operating environment, and support utilities. Indicate any qualification testing and/or documentation required for utilities or peripheral equipment prior to installation of the subject equipment.
- **Operation:** List the critical operating parameters and ranges, capacity requirements, etc., that are required for the intended function. Do not include measures that do not affect the required functionality of the equipment.
- **Performance:** Identify measurable product or results that are required when operating the equipment under expected conditions. Include operating limits and ranges, and worst-case scenarios that may be encountered during normal use.
- **Safety Features & Controls:** Identify safety features and controls that the equipment and installation must supply.
- **Instrumentation, Operating Controls, and Peripherals:** Identify the required instrumentation, control components and peripheral equipment that monitor and control the equipment. Provide necessary operating ranges, sensitivity, and calibration requirements.
- **Consumables:** Identify consumables required for operation of the equipment. Identify whether supplied by manufacturer or user.
- **Documentation:** List the documentation that will be supplied with the equipment, and that must be created

by the company or vendors. Include manuals, factory acceptance test, site acceptance, commissioning documents material construction, parts lists, drawings, government inspections, certificates, SOPs, etc.

- **Training:** Indicate training requirements for operators and maintenance personnel. Identify any special certifications, educational, or physical requirements, for operation or maintenance of the equipment.

Systematic Risk Assessment for System Qualifications

The risk assessment section discusses the potential impact on cGMP operations associated with use of the equipment, and the steps that will be taken to reduce those risks. Identify conditions that could lead to failure of the equipment, and the effects of failure on cGMP operations. Evaluate the degree of risk to product quality, company operations, and safety of personnel and equipment. During the risk assessment, it's important to perform an impact assessment on the system. Impact assessment is the process by which the impact of the system on product quality is evaluated, and the critical components within those systems. The risk assessment for systems should fall within three categories: direct product impact, in-direct product impact, and no direct product impact.

By performing a design impact assessment, companies can reduce the scope of the systems and component subject to qualification, and allowing appropriate focus to be placed on the components that may present a potential risk to the product.

The following is one example of how applying risk assessment for a validatable system can be beneficial in developing a scientific rationale, and justification for selection of the different types of qualification needed to support a system. Summarize risks and associated controls in an impact/complexity analysis, as follows:

- **Impact Analysis:** Rate the impact of the equipment on product quality, safety and purity, and on safety of personnel and equipment. Evaluate the systems in place to control those risks.
- **Complexity Analysis:** Describes the technological risks and controls associated with the equipment. The complexity analysis evaluates the risk of failure due to technical sophistication of the equipment, and the relative difficulty of maintaining the equipment in a state of control.

Table 3**Validation Requirements**

Risk Score	Qualification Requirements	Validation Maintenance Requirements
0	Document installation and commissioning	<ul style="list-style-type: none"> • Documentation maintained by Users or Facilities Department.
1 to 3	IQ	<ul style="list-style-type: none"> • Installation, commissioning, maintenance, and change control documentation maintained by QA.
4 to 6	IQ/OQ	<ul style="list-style-type: none"> • Operate, maintain, and calibrate according to written SOPs. • Document preventive and corrective maintenance and calibration according to SOPs • Apply change control procedures according to SOPs and change control programs.
7	IQ/OQ/PQ	<ul style="list-style-type: none"> • Perform operation, maintenance, calibration, and performance verification procedures according to written procedures. • Document preventive and corrective maintenance and calibration according to SOPs. • Apply change control procedures according to SOPs and change control programs.

- **Risk Score:** This section is a calculation used to evaluate the overall risk of the equipment by combining the individual impact and complexity scores in the following formula:

$$(A + B) \times (C + D)$$

Where: A = Quality Impact
 B = Quality Risk Management
 C = Technology Risk
 D = Technology Risk Management

Validation Requirements

Identify the qualification requirements for the equipment based on the impact/complexity analysis as shown in the following table. For smaller, less complex system qualifications, protocols can be combined into I/OQ or IQ/OQ/PQ protocols. Any additional information to support and justify the validation requirements should be included.

Conclusion

The implementation of a risk assessment program within a firm can decrease the cost and time it takes to perform a system qualification. Spending the time upfront performing a risk assessment will save a company a great deal of cost

and time in the long run. Most project cost overruns and delays have been contributed to not performing “Good Engineering Practices and Risk Assessment at the beginning of project. Also, implementing a risk assessment program within “firms” Quality Function will insure that the final product quality will be achieved. □

About the Author

David W. Vincent has over 24 years experience in the health care industry with 15 years in field of validation. He has BS degree in Industrial Microbiology and Mechanical Engineering Technology degree; he has consulted for many companies, national and international. Mr. Vincent has expertise in many areas of Quality Assurance, Regulatory Affairs, and Validation, including BLA submission preparation, facility and equipment design review, process development and validation, project management, and utility and process equipment qualification. He has been involved in the various aspects of bringing many new drug manufacturing facilities on-line, from design concept and engineering, through construction and start-up, to the qualification/validation, and licensing phases. He has presented many training seminars and written many articles regarding validation topics. He teaches Vali-

ation Program for Pharmaceutical, Biotechnology and Medical Device Industries "RA 776" at San Diego State University (SDSU) for their Regulator Affairs Master Degree program. Currently, he is the CEO of Validation Technologies, Inc. a nationwide Validation Services Company.

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Article Acronym Listing

cGMP:	current Good Manufacturing Practice
FDA:	Food and Drug Administration
FMEA:	Failure Mode and Effect Analysis
FTA:	Fault Tree Analysis
GEP:	Good Engineering Practices
GMP:	Good Manufacturing Practice
HACCP:	Hazard Analysis and Critical Control Point
ISPE:	International Society of Pharmacological Engineers
P&ID:	Piping and Instrument Drawing
RPN:	Risk Priority Number
SOP:	Standard Operating Procedure
SPC:	Statistical Process Control
URS:	User Requirement Specification

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