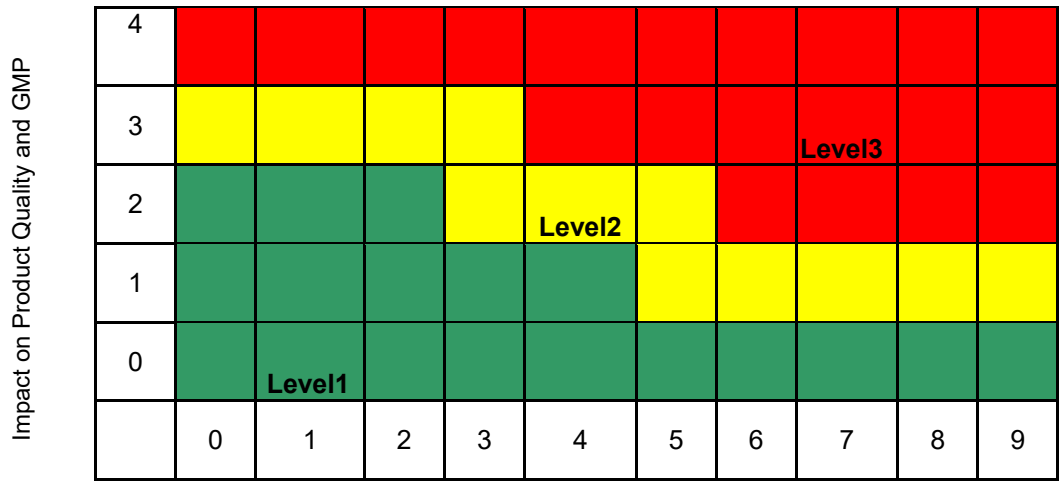
Standard Operating Procedure
Title: Quality Risk Management Techniques

Applicable to Risk Events:	Quality concern Investigations such as **Deviation, Complaint, Out-of-Specification.** The tool can also be used for any other quality and compliance issues where a risk assessment is deemed to be necessary
Risk Assessment Tool:	Risk Ranking and Filtering – Method 1
Entry on Risk Registry:	Not Applicable
Assessment Frequency:	Each time a Deviation, Complaint or OOS investigation is processed
Reference SOPs:	*QMS-035 Deviation Management System* *QMS-055 Product Complaint Procedure* *LAB-055 Laboratory Out Of Specification Investigation Procedure*
Template Location:	**#:\QA\RISK ASSESSMENTS\Risk Assessment Templates**

Following risk matrix can be used effectively to assess risks derived from a quality incident such as Deviation, Complaint or Out of Specification investigation. The matrix is based on two variables. On the vertical axis the variable is the impact of risk event on the product quality and GMP. The horizontal axis represents the probability of recurrence of risk event and delectability of the event if occur again.

Risk Matrix:



Probability = Probability of recurrence + Probability of detection

Risk Levels

For the ease of assessing risk any deviation / complaint / OOS event can be classified into one of the three levels 1, 2 & 3 based on the magnitude and seriousness of an event.

Level 3: Critical (High Risk, shaded by red colour)
A risk event that might creates immediate and significant risk to product quality, user safety or data integrity or a combination/repetition of major deficiencies that indicate a critical failure of systems

Level 2: Serious (Medium to high Risk, shaded by yellow colour)
A risk event that might potentially creates significant risk to product quality, user safety or data integrity or could potentially result in significant observations from a regulatory agency or a combination / repetition of “other” deficiencies that indicate a failure of system(s).

Level 1: Standard (Low Risk, shaded by green colour)

Observations of a less serious or isolated nature that are not deemed Critical or Major but require correction or suggestions given on how to improve systems or procedures that may be compliant but would benefit from improvement (e.g. incorrect data entry).

Risk Ranking of "Impact on Product Quality and GMP"

From all the information collected from the quality investigation and other evidences QA has to rate the impact of the risk event on product quality and GMP from 0 to 4.

0 – No impact on the quality
1 – Low risk for impact on quality
2 – Risk for impact on quality
3 – Probable impact on quality
4 – Risk for customer or production outside regulatory file

Rating of "Probability of Risk Event Recurrence and Ease of Detection"

QA has to determine this variable and rate it by assessing two separate parameters. The first parameter is the "Probability that the event will occur again". Here the rating can be given from 0 to 3.

0 – This risk event will probably not occur again
1 – Risk event may occur again (seldom)
2 – The risk event will probably occur again (from time to time)
3 – The risk event will probably occur again (often)

The second parameter is the "Probability that the event will be detected if it will occur again". Here the rating can fall between 0 to 6.

0 - The risk event will definitely be detected again
2 - The risk event will probably be detected again
4 - The risk event is at risk of not being detected
6 - The risk event will probably not be detected.

After assigning the weights for both the parameters, total probability could be determined by adding the rate of "Probability that the risk event will occur again" and "Probability that the risk event will be detected if it will occur again".

Total probability rank = Probability of recurrence + Probability of detection

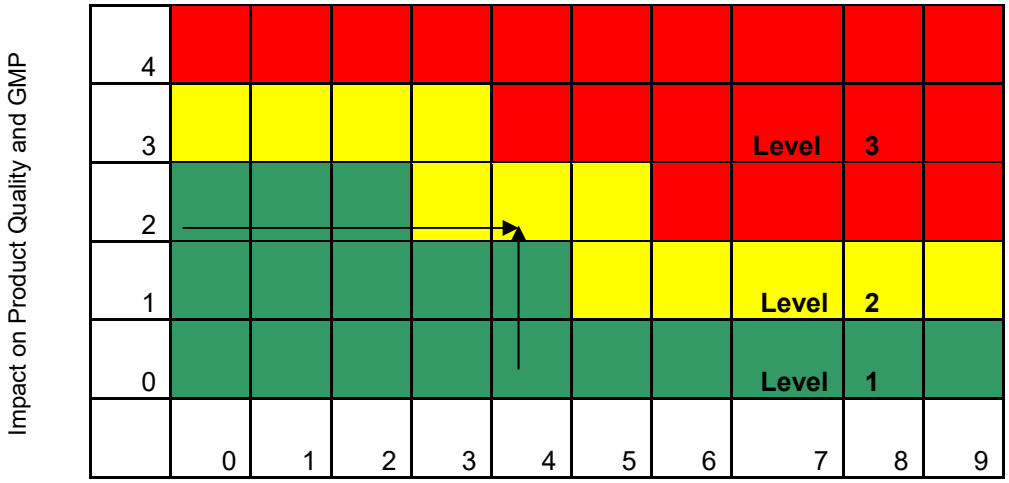
An Example

For instance after an initial investigation on a deviation if QA would find the,

"Impact on Product Quality and GMP" scored **2**,

"Probability that the deviation will occur again' scored 2 and "Probability that the deviation will be detected if it will occur again" scored 2. Than, the total probability score will be 2+2 = **4**.

Plotting this rating for both the variables will assess the risk as **level 2** class. This example is depicted in the following figure.



Next Step after Assessing Risk

QA Associate or Laboratory Supervisor conducting the risk assessment should enter a statement on the investigation report of the finding. The statement should have the minimum information as follows.

(Taken from the example above)

"Based on the available information the deviation can be assessed as follows:
Impact of Product Quality and GMP: ***2*** *(enter a brief rational)*
Probability of recurrence: ***2*** *(enter a brief rational)*
Probability of detection: ***2*** *(enter a brief rational)*
Total probability: ***4 (2+2)***
Overall Risk Level: ***2"***

QA Associate should find out the threshold actions associate to Risk Level 2 and close the investigation.

Risk Level Thresholds:

Level 3: High risk. The risk event is at high risk category. Immediate notification to management required. **QA Manager is** to review and approve the investigation. The issue may be escalated to Site Quality Review Team. Disposition decision may lead to product rework, reject or recall.

Level 2: Medium to High risk. An investigation is needed to find the root cause and possible CAPA. Cross functional investigation may be necessary. **QA Manager** is to review and approve the investigation as part of Disposition Decision. Investigation can be approved and closed when all corrective actions have taken place.

Level 1: Low risk. No corrective action is necessary. The risk event does not necessitate a cross functional investigation. QA Associate may approve and close the investigation. Management notification may not be required.

Standard Operating Procedure
Title: Quality Risk Management Techniques

Appendix 2: **Risk Ranking and Filtering – Method 2**

Applicable to Risk Events: Risk Assessment as part of **Change Management.** The tool can also be used for analysing a manufacturing process to identify high risk steps / critical parameters.

Risk Assessment Tool: Risk Ranking and Filtering – Method 2

Entry on Risk Registry: Next available number taken from the Risk Registry

Assessment Frequency: Varied. As required.

Reference SOPs: *QMS-065 Manufacturing Rework Procedure*

QMS-125 Change Management System

Template Location: **# :\QA\RISK ASSESSMENTS\Risk Assessment Templates**

Risk Overview:

Risk Event Information	
Risk Title:	*[Enter a short title of the risk]*
Issue/Event:	*[Detail the issue / event that necessitates this assessment]*
Risk Question:	*[Formulate the most appropriate risk question for which this assessment is justified. For example "what are the potential risks associated with changing the frequency of weighing device performance verification testing from the current schedule (e.g. daily) to an alternate, longer period"]*
Scope:	*[Enter the scope of this assessment]*

Facts/Arguments Which Form the Basis of this Assessment:

[Enter all background information and arguments associated with this risk event]

Severity Ranking Scale:

Rank	Description	
	User Safety / Product quality	**Regulatory Compliance**
1	No Adverse Event / No quality impact	No Action Taken
2	Reversible Minor Health Issue / minor quality impact	Discussion Point
3	Reversible Major Health Issue / difficult to maintain quality	Observation / Mandated Recall
4	Permanent Health Issue / critical quality compromised	Warning Letter
5	Death / escalate to recall	Consent Decree

Probability Ranking Scale:

Rank	Description
1	No Chance of Occurrence
2	Chance of Occurrence is Remote
3	Occurrence is Unlikely
4	Occurrence is Probable
5	Occurrence is Definite

Threshold Interpretation:

Risk Score	Actions
(1 - 4)	Low Risk. No specific action is necessary to close the investigation
(5 – 9)	Medium Risk. Some actions may be necessary to control the assessed risks.
(10 – 25)	Medium to High Risk. Product quality Risk is medium to high level. Failure to take appropriate Actions could lead to product reject or recall.

Risk Evaluation Matrix:

Probability Score ↑						
	5	5	10	15	20	25
	4	4	8	12	16	20
	3	3	6	9	12	15
	2	2	4	6	8	10
	1	1	2	3	4	5
		1	2	3	4	5
	Severity Score →					

Once the individual risk factors have been ranked, the Total Risk Score is calculated using the values assigned for probability and severity. The Total Risk Score is calculated as shown below.

Probability x Severity = Risk Score

Risk Analysis:

Function	Sub Function/s	Assessment of Risk			Mitigation Measures
		Severity (S)	Probability (P)	Risk Score (S*P)	
[Enter the broad area of function / system that appears to be a risk]	*[Divide each function into several related sub functions that is identified to be a risk and must be assessed]*	*[Enter severity score taken from the severity rank scale]*	*[Enter probability score taken from the probability rank scale]*	*[Multiply severity and probability score to get risk score]*	*[List the possible corrective and preventive actions in order to mitigate the risk factor]*
	Rational: *[Explain the rational for scoring decision]*				

Actions to be Undertaken:
[Enter the list of actions identified during assessment]

Actions to be undertaken	Responsible person	Due date

Summary:

[Enter a brief summary of the assessment. Enter the rationales for all identified risk factors which are assessed and actions taken as mitigation measures]

Authorization:

	Name	Sign	Date
Completed by:			
Approved by:			

Appendix 3: **Quality Risk Assessment for Critical Instrument Calibration Frequency**

Applicable to Risk Events:	Critical Instrument Calibration Interval Change
Risk Assessment Tool:	Failure Mode and Effect Analysis (FMEA)
Entry on Risk Registry:	Yes
Assessment Frequency:	Assessed individually for each critical instrument which needs calibration
Reference SOPs:	*Equipment Installation Procedure* *Equipment Notification Form*
Template Location:	**# :\QA\RISK ASSESSMENTS\Risk Assessment Templates**

The impact of an instrument calibration failure from the standpoint of probability, severity, and detect ability may be determined through the integration and factoring of multiple parameters associated with each criterion as illustrated in the following Table.

Probability

The probability (or likelihood) of instrument failure may be attributed to:

a) Design and construction,
b) The environment it is exposed to, and
c) How it is used.

Knowledge of the effects of design and construction can be gained through a review of the maintenance history of the instrument, comparing it to similarly designed instruments, and by knowing the age of the instrument (period of time in use). For each of these parameters, if the data and relevant information is not known, the risk should be assumed to be high.

The following criteria may be used to determine risk ranking for failure probability.

1. **History**
   There are three (3) possible scenarios illustrated in table where instrument history may be used to determine risk ranking for failure probability.

   Specifically,

   (i) Availability of recorded history of an instrument in its current location,
   (ii) Availability of history of identical instrumentation of the same make and model in the same area, and \
   (iii) Availability of history of similar instrumentation in a similar environment. Risk ranking is determined by the length of recorded history available for an instrument, the number of available instruments for use in data gathering, and the typical interval between observed failures (mean time between failures, MTBF). When the number of instruments in place combined with the use history (e.g. >2 years) is sufficient to have observed most, if not all potential modes of failures (MTBF is long i.e., >24 months), the risk should be considered low.

   The absence of historical records, lack of identical or similar instruments to benchmark, and if the MTBF is <24 months would indicate a higher risk. If there is less than 2 years of historical records, and the number of identical or similar instruments is considered less than sufficient, i.e., <3 and <10 for identical and similar instruments, respectively and the MTBF is >24 months, then the risk should be considered medium.

2. **Environment**
   The environmental situation can be divided into sub-categories as illustrated in Table**.** For purposes of risk assessment, the environmental sub-category with the highest risk determines the risk ranking for failure probability.

3. **Range of use**
Instruments designed around transducers need to be used within their design range. Instruments are more linear and predictable in the middle of their range. Exposing instrument inputs that are outside of the design range may create conditions of non-linearity that are not readily apparent. Risk ranking is determined by the potential range excursions and exposure to conditions that may take the device to the edge of its range or beyond.

4. **Age**
The age of the instruments can be an indicator of the technology. Certain technologies are more prone to breakdown as they reach the end of their operational expectancy. Self correcting, digital instruments have only been around for a few years. Older analog instruments are subject to component aging, drift, and non-linearity. Additionally, older digital instruments may have firmware that is not current, or failing power supplies that do not allow for proper circuit performance. Risk ranking is determined by the instrument length of service; brand new (infant mortality) or very old (aging components) instruments have the highest risk.

Severity

There are several factors that may define the severity (or consequence) of instrument failure. The list includes, but not limited to:

- Human safety
- Environmental safety
- GMP (or GxP) compliance
- Production impact
- Cost
- Energy consumption

Detectability

Being able to immediately detect an instrument Out of Tolerance (OOT) condition may mitigate the impact of such condition upon the system, process or even the product to which it is associated or used. Immediate detection is determined by whether the system or process utilizing the instrument is automated or manual and whether there are other instruments or tell-tale parameters that occur as a direct result of incorrect instrumentation. **Refer to Detectability section of the Table below.**

Systems or processes that are equipped with automation features or components that make it easier to detect OOT conditions should have a reduced risk in detect ability ranking. Systems that have additional instruments or detectable parameters that are frequently observed/compared will enable timely identification of OOT conditions, thus resulting in lower risk.

Risk Assessment Based on FMEA

Probability of Instrument Failure (MTBF = mean time between failures)				
	Risk Level → **Numeric Ranking →**	**Low** **(1)**	**Medium** **(2)**	**High** **(3)**
History	This instrument (The intent is to use history as an indicator of probability)	Have more than 2 years of records, history shows low rate of calibration OOT (Out of tolerance) (MTBF >24 months)	Have less than 2 years of records, history shows low rate of Calibration OOT	Have no historical records or records show MTBF <24 months
	Identical Instrument (make and model)	Have 3 or more identical instruments (MTBF > 24 months)	Have 1 or 2 identical instruments (MTBF > 24 months)	Have no identical instruments to benchmark
	Similar Instruments (The concept is to determine if there are instruments of similar design and functionality utilized in the intended environment that may yield performance data for use as a predictor, i.e. show low risk based on demonstrated reliability)	Have several (e.g.10) similar (in type, technology, range) instruments in similar environments (MTBF > 24 months)	Have a few similar instruments in similar environments (MTBF > 24 months)	Have no similar instruments in similar environments
Environment	Temperature and Humidity (both operating and storage conditions)	Temperature and humidity are stable and are within manufacturer's recommended range	Temperature and humidity vary, but always stay within manufacturer's range	Temperature and humidity are not known or may exceed manufacturer's range
	Power line / electrical Disturbances	Instrument is non-electric	Instrument is battery powered or well-filtered and protected from power disturbances and lighting	Instrument is located in an electrically "noisy environment or may be susceptible to sags, surges, spikes, and severe electro-magnetic interference (EMI)
	Dust / Dirt / Chemical Wash down	Instrument is located in a clean, dry, area that does not get washed down	Instrument is in a protected cabinet, or removed for area wash down. light dust and no chemical exposure	Instrument is in an exposed, dirty environment subjected to frequent wash downs or chemical exposure
	Vibration and shock	Instrument is permanently mounted in a stable environment	Instrument is portable and moved frequently or may be exposed to occasional vibration or shock	Instrument is subjected to severe shock and vibration
	Physical Damage	Instrument is kept in *a* segregated or protected area	Instrument is located in a moderate traffic area and potentially susceptible to	Instrument is located in a high traffic area and susceptible to contact with

			contact with equipment or personnel in transit	equipment or personnel in transit
Range of use	Range of inputs the instrument is subjected to	Instrument is operated at a single fixed setting in the middle portion of its designed functional range	Instrument is operated at multiple settings throughout the middle 80% of its functional range	Instrument is operated at multiple settings across the entire functional range or at a fixed setting at the upper or lower knit of the functional range
Age	Infant mortality (startup failure) or aging components	Instrument has been in service for >3 months but less than 5 years	Instrument has been in service for less than 3 months or greater than 5 years	Instrument has been in service for over 10 years
Severity of Instrument Failure				
	Risk Level ⟶ **Numeric Ranking ⟶**	**Low** **(1)**	**Medium** **(2)**	**High** **(3)**
User Safety	Instrument's criticality to plant safety	Instrument is not part of a safety system	Instrument is part of a safety system, but is redundant (secondary)	Instrument is a primary component of a safety system; no redundant instrumentation is deployed
Environmental	Instrument's criticality to operating environment	Instrument is not part of an environmental system	Instrument is part of an environmental system, but is redundant (secondary)	Instrument is a primary component of an environment system; no redundant instrumentation is deployed
GMP / Product	Impact of performance failure on product quality	Instrument is part a "Non impact" system. Failure to conform with performance specifications / expectations would not adversely impact the quality & product	Instrument is part of a 'indirect impact'** system or an 'indirect component' of a 'Direct impact' system; failure to conform with performance specifications / expectations could adversely impact product quality, however, there is 100% testing/verification downstream in the process	Instrument is a 'Direct Impact' component in a 'Direct Impact' system with no downstream verification or testing, failure to conform with performance specifications / expectations could adversely impact product quality.
** **Note**: Indirect Impact system can be defined as instrument performance which does not directly impact the product quality but may lead to violation of GMP down the line.				
Production	Impact of performance failure on operational efficiency	Failure to conform with performance specifications / expectations would not adversely affect production speed or efficiency	Failure to conform with performance specifications / expectations would adversely impact the speed and/or the efficiency of the operation	Failure to conform with performance specifications / expectations would cause a halt to production

Cost	The Intent is to quantify the additional cost incurred by instrument performance failure	Performance failure results in no additional cost	Performance failure can be mitigated with minor additional resources	Performance failure results in major damage, additional failures or the need for product rework or rejection
Energy	Impact & performance failure on energy consumption	Performance failure has no effect on energy efficiency and consumption	Performance failure causes a minor increase in energy consumption, or loss of efficiency	Performance failure causes a major increase in energy consumption or major loss of efficiency

Note: A severity ranking of Zero (0) is possible. There are some potentially calibrated instruments that will have no impact if they are out of tolerance and are candidates for removal from the calibration program and subsequent categorization as “No calibration necessary” or “For reference only”. Instruments in this category should be clearly labeled in the operation.

Detectability of Instrument Failure

	Risk Level → **Numeric Ranking →**	**Low** **(1)**	**Medium** **(2)**	**High** **(3)**
Automatic Operation	Automated verification critical product characteristics/parameters	100% or continuous online inspection/analysis (PAT) of critical attributes/parameters; redundant stage release testing	Periodic online inspection/analysis of critical attributes/parameters redundant stage release testing	No automated online inspection/analysis of critical attributes/parameters, no stage release testing.
Manual Operation	Human interventions or audits to verify resulting product quality	100% or continuous online inspection/verification of critical attributes/parameters; with or without stage release testing	Periodic online inspection/verification of critical attributes/parameters, with stage release testing	No inspection/verifications during the process and no stage release testing

FMEA Ranking Criteria and Failure Scores using a Three Point Ranking System

Numerical Ranking	**Probability of Risk** (Table I) Criteria used: Instrument history, environment, range of use, & age	**Severity of Risk** (Table II) Criteria used: Impact on human safety, environmental, GMP / Product, production, cost, energy	**Detectability of Risk** (Table III) Criteria used: Automatic / Manual operation, Operator verification	**Maximum Risk Score**
1	**Low**	**Low**	**Low**	**1**
2	**Medium**	**Medium**	**Medium**	**8**
3	**High**	**High**	**High**	**27**

Risk illustration:
To assign the appropriate level of risk, a simple Low, Medium, High model with a corresponding numerical designation of 1, 2 and 3 will be used. Each criterion (probability, severity, detectability) can therefore have a numerical rating of 1, 2 or 3 that will determine the risk score. The risk score for each failure mode is obtained by multiplying the individual scores for each criterion. **For example:**

Probability x Severity x Detectability = Risk Score

Recommended frequency for Instrument Calibration Intervals change – The frequency selected will all be relative to the risk score resulting from the assessment.

Low score will justify broader or less frequent calibration verification from the established guidance table.

High risk score will require adherence to the calibration table or perhaps Team review to tighter than published guidance.

Example only: Change of calibration frequency period based on risk score

Risk Score Examples	Overall Risk Description	Suggested Calibration Frequency Interval change
01	**Negligible**	Consider extending calibration interval up to 36 months
02	**Very Low**	Consider extending calibration interval up to 24 months
03-06	**Low**	Consider extending the calibration interval x 2 (up to a maximum of 24 months) (i.e. 6 months ⟶ 12 months)
08	**Medium**	Consider extending the calibration interval by a factor of 1.2x to1.5x (up to a maximum of 18 months) (i.e. 3 months ⟶ 4 months. 1 2 months ⟶ 1 8 months)
09-12	**Med / High**	Maintain the same calibration interval. (re-evaluate the risk score in 12 months)
18	**High**	Consider shortening the calibration interval by a factor of x 0.5 (i.e. 12 months ⟶ 6 months)
27	**Very high**	Consider shortening the calibration interval to a very short period (i.e. 3 months) and consider re-engineering the instrument system to reduce the risk score

Examples of Instrument Calibration Interval Change Request

The sample risk assessments below are to serve as “examples” only and used as illustration of the approach. Actual situation requires a team assessment and review of site coordinator.

Example: #1
Instrument: Temperature Transmitter
Application: Temperature transmitter on a circulation loop for ‘WFI. Temperature is always maintained at 85^0 C. Transmitter is located in a protected area that does not get washed down. Temperature transmitter is rated to handle the sanitizing temperatures for the system.

Basis for change:

Instrument Type	Instrument class. Critical Y or N	Associated System	Probability of Occurrence	Severity of Failure	Detect ability of Failure	Risk Score (Failure Mode)	Recommended Calibration Period (months) from table	Basis for change calibration interval: Medium probability of failure, medium severity and medium detect ability. Cautiously extend the interval by a factor x1.5
Temperature Transmitter	Y	WFI	2	2	2	8 (Medium)	6 months	9 months

Example: #2
Instrument: Pressure Indictor
Application: Pressure indicator on a large reactor vessel. Need to assure positive pressure in the reactor, but maintain pressure below tank safety rating. Tank is washed down, goes through vacuum pressure cycles, and occasionally goes over-pressure (blows the relief).

Basis for change:

Instrument Type	Instrument class. Critical Y or N	Associated System	Probability of Occurrence	Severity of Failure	Detect ability of Failure	Risk Score (Failure Mode)	Recommended Calibration Period (months) from table	Basis for change calibration interval: High (or unknown) probability of occurrence, medium severity and high detect ability risk. Consider shortening the calibration interval based on the calculated risk (high)
Pressure Indictor	Y	Reactor	3	2	3	18 (High)	12 months	6 months

Example: #3
Instrument: Humidity Transmitter
Application: Ambient humidity sensor in a conditioned room. ***This transmitter is an alarm point only***. The Building Management System (BMS) controls the temperature and humidity and a chart recorder records them, providing very easy detect ability of failure.

Basis for change:

Instrument Type	Instrument class. Critical Y or N	Associated System	Probability of Occurrence	Severity of Failure	Detect ability of Failure	Risk Score (Failure Mode)	Recommended Calibration Period (months) from table	Basis for change calibration interval: Since it is low probability and easily detected, consider increasing the calibration interval to 24 months.
Humidity Transmitter	**Y**	**Packout Room**	**1**	**3**	**1**	**3 (Low)**	**12 months**	**24 months**

Appendix 4: **Supplier Quality Risk Assessment Process**

Applicable to Risk Events: New supplier approval process; Periodic review of supplier quality performance
Risk Assessment Tool: Failure Mode and Effect Analysis (FMEA)
Entry on Risk Registry: Yes
Assessment Frequency: Assessed individually for each critical supplier

Risk Assessment

The risk assessment tool described here is intended to determine the risk posed by each hazard (material supplier) by evaluating five quality risk factors associated with severity, probability and detectability. The quality risk factors are detailed in **Table 1.**

Severity is the measure of the consequences (impact) that a defect or failure borne of the material supplier (hazard) may have on the operation/products. Severity in the risk assessment tool is measured by the intended purpose of the material.

Probability is a measure of the likelihood that the identified risk will occur, or recur and is measured by supply chain complexity, supplier quality system effectiveness, quality knowledge and non-conformance detection by Site.

There is also a specific question on the location of the supplier which assigns additional risk to locations in which
there is a lack of robust pharmaceutical GMP quality system orientation and/or a lack of robust regulatory oversight.

Detectability is a measure of the ability to detect harm and is measured by some of the previously mentioned risk factors (e.g., non-conformance detection by Site).

Risk Analysis and Evaluation

The risk analysis and evaluation is performed by Site for a given supplier and the material(s) procured for use by the site.

The Purchasing team responsible for procurement of the material/product should complete the Supplier Quality Risk Assessment based on analysis of their quality experience and knowledge of the supplier and supply chain(s) for the material(s) supplied. All completed supplier Quality Risk Assessment must be reviewed and approved by Quality Assurance Manager.

For suppliers providing multiple materials, the highest risk category should be assigned. The Supplier Quality Risk Assessment is completed as described below using the Quality Risk Evaluation Form described in **Table 2**.

1. Read the questions in sequential order (i.e., a→b→c, etc.) and determine the first lettered question that can be answered with a "yes".
2. Enter the corresponding quality risk value from the Answer column into the Quality Risk Score column.

3. After completing all five risk factors, sum the individual Quality Risk Scores to calculate the Total Quality Risk Score.

4. Complete the Supplier Quality Risk Evaluation by comparing the Total Quality Risk Score to the following Risk Levels and assign the supplier the corresponding Risk Level:

Table 1: Supplier Quality Risk Factor Information

Quality Risk Factor	General Consideration for Data Gathering
Intended Purpose	• What is the intended purpose of the material?
Supply Chain Complexity	• Where is the material manufactured and handled, and what are the regulatory requirements and quality oversight? • Is the supply chain known and how complex is the supply chain for the material? • What is the method of transportation and who has Control / oversight? • Is the supplier located in a region where there is a lack of robust pharmaceutical GMP quality system orientation and or a lack of robust regulatory oversight?
Supplier Quality System Effectiveness	• Does the supplier has a formal Quality System and is it effective? • What is the audit history at the supplier? • How responsive is the supplier to requests from Site? • Does the supplier have quality system controls over transportation and handling?
Non-Conformance Detection by Site	• What testing is done by Site on the material? • Are there non-conformances detected by the end user that should have been detected by the supplier? • Do the economics of the material make it subject to fraudulent activities (value of material, demand exceeds supply. disproportionate pricing)? • How capable is Site-performed testing in detecting product quality problems?
Quality Knowledge	• Does the supplier accept Site terms in a Quality Agreement? • Does the supplier comply with the Quality Agreement? • Have there been repeat non-conformances detected by Site that the supplier should have detected? • Does the supplier have outstanding. significant adverse regulatory events, impacting the site of interest? • Does the supplier have experience in supplying the pharmaceutical industry?

Threshold interpretation

Risk Level	Total Quality Risk Score
High Risk	≥ 64
Medium Risk	Between 37 and 64
Low Risk	≤ 37

Table 2: Supplier Quality Risk Assessment Form

Supplier Name:	**Supplier Location:**
Material/s Purchased:	**Prepared By:** **Date:**

Comments:

***Instructions**: Read the questions in sequential order and determine the first question that can be answered with a 'yes'. Enter the corresponding qualify risk value in the Quality Risk Score row. After completing all five sections, sum the individual Quality Risk Scores to calculate the Total Quality Risk Score. Complete the Supplier Quality Risk Evaluation by comparing the Total Quality Risk Score to the high, medium and low risk level ranges to determine the Supplier Quality Risk Level*

		Answer
1. Intended Purpose		
a.	Is the material a finished Drug Product, Active Pharmaceutical Ingredient (API), excipient for a parenteral product or does it have specific tiled regulatory requirements?	If yes. High Risk. enter **5**
b.	Is the material a non-sterile excipient, primary packaging, regulated printed packaging, registered starting material or reagent contributing to significant molecule structure?	If yes. Medium Risk. enter **2.5**
c.	Is the material a solvent used in processes, secondary packaging or non registered material?	If yes. Low Risk, enter **0.5**
Quality Risk Score: *(i.e. medium / high / low)*		
2. Supply Chain Complexity		

Is the material manufactured and/or handled in a region where there is a lack of robust pharmaceutical GMP quality system orientation and/or a lack of robust regulatory oversight?	If Yes, High Risk, enter **54** If No, enter **0**
a. Is the supply chain complex with more than three sites involved in the manufacture, finish and/or handling of the material with limited quality oversight of the supply chain? **OR** b. Is the supply chain not completely known?	If yes. High Risk. enter **20**
c. Is the supply chain complex with more than three sites involved in the manufacture, finish and/or handling of the material with adequate quality oversight of the supply chain? **OR** d. Does the supply chain contain two or three sites involved in the manufacture, finish and/or handling of the material with limited quality oversight of the supply chain? **OR** e. Is the method of transportation not under Site control or oversight?	If yes. Medium Risk Enter **10**
f. Does the supply chain involve a single manufacturer that ships the material directly to Site?	If yes. Low Risk. enter **2**
Quality Risk Score: *(i.e. medium / high / low)*	
3. Supplier Quality System Effectiveness	
a. Does the supplier lack a formal Quality System (e.g. ISO or similar)? **OR** b. Does the supplier Quality System either lack effectiveness or the effectiveness is unknown? **OR** c Is the supplier new to Site, have no previous Site Audit history or has a Conditionally Acceptable rating? **OR** d. Is the supplier unresponsive to requests from Site? **OR** e. Does the supplier lack effective quality system controls over transportation and handling?	If yes. High Risk, enter **25**
f. Does the supplier have a Quality System but it lacks a pharmaceutical cGMP/ICH orientation? **OR** g. Does the supplier Quality System have areas of limited effectiveness? **OR** h. Is there an Acceptable Site quality audit rating with unresolved Critical and Major Findings allowed? **OR** i. Is there inconsistent history of responsiveness to Site requests?	If yes. Medium Risk Enter **12.5**

j. Does the supplier Quality System have an established history of being consistently effective? **AND** k. Is there an Acceptable Site quality audit rating with **No** unresolved Critical and Major Findings?	If yes. Low Risk, enter **2.5**
Quality Risk Score: *(i.e. medium / high / low)*	
4. Quality Knowledge	
a. Is the supplier not willing to accept Site terms in a Quality Agreement where required? **OR** b. Are there significant deviation(s) from an established Quality Agreement? **OR** c Over the past four years or six lots have there been repeat non-conformances detected by Site that the Supplier should have detected? **OR** d. If in a regulated industry, is the supplier known to have outstanding, significant adverse regulatory events, impacting the site of interest? **OR** e. Does the supplier have no background in supplying the pharmaceutical industry?	If yes. High Risk. enter **25**
f. Over the past four years or six lots has there been no more than one non conformance detected by Site that should have been detected by the supplier? **OR** g. If in a regulated industry, does the supplier have no demonstrated regulatory audit performance and cannot therefore be readily assessed against industry /regulatory standards?	If yes, Medium Risk, enter **12.5**
h. If in a regulated industry, does the supplier have a reliable history of good regulatory compliance and acceptable audit outcomes? **OR** i. Is the supplier a well-respected supplier to the pharmaceutical industry?	If Low Risk. enter **2.5**
Quality Risk Score: *(i.e. medium / high / low)*	
5. Non-conformance detected by Site	
a. Are there non-conformances detected by the end user that should have been detected by the supplier? **OR** b. For Drug Products. API and excipients, is there no specific ID or potency testing performed by Site (i.e. testing for impurities, identification testing using methods with high selectivity and specificity, etc.)? **OR** c. Do the economics of the material make it subject to fraudulent activities (value of material, demand exceeds supply, disproportionate pricing)?	If yes. High Risk enter **25**

OR d. Is the material subject to the potential contamination with known adulterants to improve the apparent activity or potency of the pharmaceutical ingredient. **OR** e. Is it difficult to detect product quality problems?	
f. Is there an inspection process performed, including testing that can provide a high assurance of non-conformance detection? **OR** g. Is the supplier sometimes able to detect product quality problems?	If yes, Medium Risk, enter **12.5**
h. Is a specific ID or potency test performed at Site along with all registered tests? **OR** i. Is the supplier routinely able to detect product quality problems?	If yes, Low Risk, enter **2.5**
Quality Risk Score: *(i.e. medium / high / low)*	

Total Quality Risk Score: *(Sum of five risk scores detected above)*	**Comments:**

Supplier Quality Risk Evaluation:

- ☐ Low Risk (≤ 37)
- ☐ Medium Risk (Between 37 to 64)
- ☐ High Risk (≥ 64)

Appendix 5: **Risk Assessment Process to Establish External Supplier Quality Audit Frequency**

Applicable to Risk Events: Establishing Ext. Supplier Quality Audit Frequency

Standard Operating Procedure

Title: Quality Risk Management Techniques

Risk Assessment Tool: Risk Ranking and Filtering
Entry on Risk Registry: Yes
Assessment Frequency: Assessed individually for each Supplier
Reference SOPs: *QMS-080 GMP Audit Procedure*

Template Location: **# :\QA\RISK ASSESSMENTS\Risk Assessment Templates**

Risk Assessment Process

1. **Collect and organize relevant information**.
The following represents suggested data to gather prior to performing the assessment:

- Listing of material suppliers, materials sourced and where used
- Prior audit records
- Performance data related to material (lots rejected/finished product issues related to material
- Correspondences with supplier related to changes in operation or process Regulatory inspection records for material supplier, if available.

2. **Identify the Risk Question**
The Quality Risk Management (QRM) process is guided by the establishment of a risk question that identifies the scope, sought outcome and areas of focus (risk factors) for the assessment. For example:

"How should supplier audits be prioritized and scheduled as a function of their risks to product safety, quality and market share (business)

OR

"What are the patients, product quality and business risks associated with materials / components /services used in the production of medicinal products in relation to their supplier's audits and how could these audits be prioritized and scheduled to minimize such risks?"

3. **Determine the Potential Risk Factors and related Hazards.**
In order to determine the potential risk factors and related hazards, one might need to answer:

a. *What are the risk factors* (e.g. patient safety, regulatory compliance and business) from which each scenario must be viewed to ensure that all potential or related hazards are identified?

- What are the sources of potential harm related to each risk factor?
- Could the material sourced have a potential impact on patient safety?
- Could the material sourced have a potential impact on product quality and conformance to registered specifications?
- Could the supply of the material have an adverse impact on the business?

b. *What are the related hazards?*
For the purpose of prioritizing the external supplier audit schedule, each material supplier represents a potential risk to the finished product(s) in which the material(s) sourced are used, therefore, all material suppliers can be viewed as hazards for the purpose of this assessment.

Table 1: Examples of Risk Factors and Severity (this list is not all inclusive)

Hazard	Risk Factor	Severity
		General / Specific
Material Supplier	Quality/ Regulatory	**a.** Type of material/component/service
		1. APIs

	compliance	2.	Labelling/Inserts
		3.	Raw Materials (e.g., Excipients, Processing Aids, Solvents, Gases, Lubricants, Cleaning Agents)
		4.	Packaging Materials, Primary and Secondary
		5.	Service providers such as contract laboratories, calibration, HEPA certification and gamma
		6.	Distributors/Warehouses/Brokers
	Business	**b.**	Number of products involved/volume of material involved (quantity and/or cost)

Table 2: Examples of Risk Factors and Probability (this list is not all inclusive)

Hazard	Risk Factor	Probability	
Material Supplier	Quality / Regulatory compliance	a.	cGMP/regulatory compliance supplier history
		b.	Licenses, inspection and audit outcomes
		c.	Certifications and/or accreditations
	Quality / Regulatory compliance	d.	Quality audit type and number of findings, open/closed
	Business	a.	Volume (lots consumed per years or number of times service used per year)
		b.	Length of time supplier has been used for material/service
		c.	Service history delays, complaints, deliveries on time and/or scheduled

4. **Define the Risk Assessment Scales for Probability and Severity**
In order to perform an assessment of the risk posed by each hazard (material supplier) the probability and severity characteristic of each hazard must be defined. Severity and probability scales must first be defined by determining the range of possibilities and differentiations for each as indicated below:

a. **Severity:** Severity is the measure of the consequence (impact) that a defect or failure borne of the material supplier (hazard) may have on your operation/products.

Assessing the severity requires an understanding of how the material supplier might impact the risk factor. For example, when looking at material suppliers and their potential impact on finished product quality, an API supplier may be assigned a higher severity scale than a tertiary packaging supplier since the API may impact potency or dissolution of the finished product, whereas a shipper has no impact on product performance.

Table 3: Examples of Severity Scale

Severity			Scale
General	Quality/Regulatory compliance	Business	

Type of material/ component/ service	Minor excipients (<20%)	The materials have 0% to 50% production impact	**1**
	Tertiary Packaging		
	Major excipients (20%)	The materials have 50% to 80% production impact	**3**
	Secondary packaging		
	API/critical excipients (e.g. antimicrobial agent/preservative)	The materials have 80% to 100% production impact	**5**
	Sterility Assurance (HEPA Certification, sterilizing filters, irradiation, etc.)		
	Labelling/Inserts		
	Primary packaging (product contact)		

b. Probability

Probability is a measure of the likelihood for a "harm" to occur. The probability as it relates to materials' suppliers could be based the following questions:

- What is the historical performance of an individual material supplier (hazard)? Since the last audit, what has the material supplier's performance been?
- How many material suppliers' lots have failed to meet specifications upon receipt or have been linked to nonconforming finished product (Product Quality)?
- How often have there been supply issues where material that meets specifications was not available to meet the production schedule demands (Business)?
- What is the material supplier's regulatory inspection history and last audit outcome?

Table 4: Examples of Probability Scale

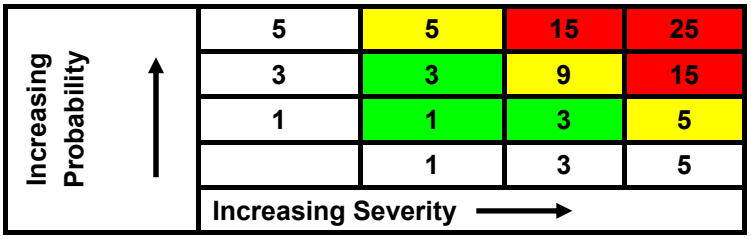
Hazard	Risk	Probability	Scale

	General	Quality / Regulatory	Business	
Material Supplier	cGMP/ regulatory compliance supplier history	Supplier has been inspected within the last six months. • There have been few or no observations • Observations have been responded to and/or responses have been accepted	The materials have been in stock	**1**
		Supplier has been inspected • There have been some (more than 5) Mandatory Action Required observations, • Observations have not been responded to and/or responses have not been accepted	The materials have been short stocked	**3**
		Supplier has been inspected There have been many (more than 10) Mandatory Action Required observations • Observations have not been responded to and/or responses have not been accepted • Supplier has been issued a warning letter or has been placed under a consent decree. **OR** Supplier has never been inspected	The materials have been back ordered	**5**

5. **Define the Risk Evaluation Matrix and Determine the Action Thresholds**
Prior to completing the risk assessment using the scales established for severity and probability. An evaluation matrix must be constructed to aid in evaluation of the total risk scores (severity x probability) derived for each hazard.

An example of a risk evaluation matrix and corresponding action thresholds is shown below. In this example the values in the green boxes (risk scores 1-4) represent low risk and could be audited every 5 years. The values in yellow (risk scores 5-14) represent medium risk and could be audited every 3 years. And the values in red (risk 15-25) are high risks to be audited annually.

Risk Evaluation Matrix



Threshold Interpretation:

Risk Score	Risk Category	Audit frequency
Score (1 – 4)	Low Risk	Audit every 5 years
Score (5 – 14)	Medium Risk	Audit every 3 years
Score (15 – 25)	High Risk	Audit every year

6. Assess Probability and Severity Scale for Each Supplier and determine the severity and probability score for each material supplier (hazard) based on the available data gathered in Step 1.

For example, the supplier of HDPE bottles, Ajax, has a probability score of 3, taking into account that this supplier has been inspected by Site, there have been as many as 7observations and the observations have not been responded to and/or responses have not been accepted by Site as indicated by Table 4.

In addition, the HDPE bottles are used as primary packaging components which correlates with a severity score of 5 as indicated in Table 3. Table 5 summarizes examples of the executed assessment for the Ajax supplier.

To continue with the risk assessment, all material suppliers shown in Site Supplier List will be assessed as previously indicated. Table 6 summarizes examples in how the Suppliers Quality Audit Prioritization and Frequencies can be reported.

Table 5: Examples of Assessment of Probability and Severity

Risk Factor		Potential Hazard		Risk Analysis		Risk Evaluation
		Name	Material /Service	Severity (S)	Probability (P)	Risk Score (S*P)
Patient	Adverse Reaction	Ajax	HDPE Bottles	3	4	12 (Medium)
	Lack of Efficacy	ABC	IFC's	2	1	2 (Low)
Compliance	Non conformance with filed product formulation	Acme	Labels	5	5	25 (High)

Table 6: Examples of Ext. Supplier Audit Prioritization and Frequency Report

Hazard (Supplier's List)		Risk Assessment Scale Results				Risk Control
Name	Material/ Service	Severity (S)	Probability (P)	Total Risk (S*P)	Risk Category	Proposed Audit Frequency
Ajax	HDPE Bottles	3	4	12	Medium	Every 3 years
ABC	IFC's	2	1	2	Low	Every 5 years
Acme	Labels	5	5	25	High	Annual
Astro	Boric acid	1	1	1	Low	Every 5 years
Steritech	Irradiation	5	1	5	Medium	Every 3 years

Appendix 6: **Engineering Project Evaluation**

Applicable to Risk Events: New engineering project evaluations

Risk Assessment Tool: Failure Mode and Effect Analysis (FMEA)
Entry on Risk Registry: Yes
Assessment Frequency: Assessed individually for engineering projects when required
Reference SOPs: *Equipment Installation Procedure*
Equipment Notification Form

Template Location:

Appendix 7: **Process, Cleaning and Computer Validation Projects**

Applicable to Risk Events: Validation of high risk steps / critical process parameters.
Risk Assessment Tool: Failure Mode and Effect Analysis (FMEA)
Entry on Risk Registry: Not required
Assessment Frequency: Assessed individually for each critical process parameters
Reference SOPs: *Guidance for the Use of Risk Assessment in Validation*
Risk Assessment for Computer and Automated Systems

Template Location: