instrument might affect release of the product lots in question. The extent to which the instrument would impact the product is a good indicator of risk. A more conservative extension of the calibration interval can then be made, if appropriate.

Recommendations & Rationale for Recommendations

Risk Assessment Tool -Failure Mode and Effects Analysis (FMEA) is the tool of choice that is recommended for calibration interval change analysis. Its use enables identification of potential failure modes and assignment of numerical ranking using probability, severity and detectability of the risk (Tables I, II, III, respectively). Risk Assessment -Identification, analyses, and evaluation of potential risks

The impact of an instrument calibration failure from the standpoint of probability, severity, and detectability may be determined through the integration and factoring of multiple parameters associated with each criterion as illustrated in Tables I -III. This section will provide additional narrative description in support of the contents in each table which contain guidance on how these parameters can impact the risk of experiencing an out-of-tolerance (OOT) condition for an instrument.

- **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.
Refer to **Table I** below.

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

- . **Severity**
  There are several factors that may define the severity (or consequence) of instrument failure. The following brief narrative description for each factor will supplement the guidance provided in **Table II** below.

  1) Human safety – Direct threat to human safety defines the most severe consequence of calibrations OOT. If an instrument reading (or alarm) is the main protection against severe or potentially fatal injury, such as breathing air, oxygen level, or lethal compounds monitor, then severity is potentially high. Depending on whether an instrument is a primary component in a safety system, or part of a redundant system, will determine the severity of this risk.

  2) Environmental safety – Instruments that prevent or alarm on conditions of hazardous chemical release are examples of this risk. Whether these instruments are the sole indicator of environmental releases or an instrument has back-up or redundancy, will determine the relative severity of risk due to environmental safety.

  3) GMP (or GxP) compliance – Typically, evaluation is made during Commissioning & Qualification to determine the GMP impact of systems and components. If an instrument's performance is integral to demonstrating compliance with product specifications, then the risk severity is based on whether the data derived represents the sole measure of an attribute or whether the attribute is further assessed through another measure or test later in the process.

     Instances wherein an attribute is further characterized by testing performed further down in the process may determine a lower severity ranking than instruments that determine compliance to specs without further verification.

  4) Production impact – Yield and throughput can be optimized through reduction in production process variability as determined through instrument readings. If an instrument is determined to have an impact on production, then maintaining calibration accuracy is important and should be reflected in the severity ranking.

  5) Cost – This represents the potential damage to machines or facilities that may result from an instrument or alarm reaching an OOT condition. The cost to repair or replace damaged assets may be avoided by maintaining instrument accuracy. It is a good practice to determine the effects of instrument OOT on potential damage to other assets.

     Whether the calibration OOT causes additional expense relative to cost of repair or replacement of damage assets or its impact could be reduced through use of minor additional or other resources, will determine the severity risk ranking.

  6) Energy consumption -One specific consequence of instrument OOT could be increased energy consumption. When machines are not operating optimally, frequently they require increased energy consumption. Examine the OOT consequence in light of increased energy consumption (requires additional heating, cooling, fuel, or electricity) to determine the appropriate severity ranking.

- **Detectability**
  Being able to immediately detect an instrument 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 **Table III 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 detectability 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.

Table III: **Detectability of Instrument Failure**

Table III

Detectability of Instrument Failure

	Risk Level → Numerical Ranking →	Low (1)	Medium (2)	High (3)
Automatic Operation	Automated verification of 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 inspection/verification of critical attributes/parameters; with stage release testing	No inspections/verifications during the process and no stage release testing

- **Risk Acceptance:**
  Once the probability, severity, and detectability of instrument failure are individually assessed and agreement is reached on the risk associated with each instrument, a site should then define the level of risk it is willing to accept. The FMEA ranking criteria can be used to assign numerical ratings and complete the overall risk evaluation. See **Table IV**.

Examples of Instrument Calibration Interval Change Requests

The sample risk assessments below are to serve as "examples" only and used as illustrations of this approach. Actual situations require a Team assessment and review of local and site conditions.

Example #1:

Instrument: Temperature Transmitter

Application: Temperature transmitter on a circulation loop for WFI. Temperature is always maintained at 85 deg 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	Inst. Class Critical?Y or N	Associated System	Probability of Occurrence	Severity of failure	Detectability 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 delectability. Cautiously extend the interval, by a factor of x1.5
Temperature Transmitter	Y	WFI	2	2	2	8 (medium)	6 months	9 months

Example #2:

Instrument: Pressure Indicator

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	Inst. Class Critical?Y or N	Associated System	Probability of Occurrence	Severity of failure	Detectability 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 Indicator	Y	Reactor	3	2	3	18 (high)	12 months	6 months

