- Risk to patient

The quality risk management approach as applied to the identification of deviations vs. events
illustrated in this guidance not only identifies the different risk factors to consider when performing the evaluation but also demonstrates a simple tool (depicted in tabular format) for determining how to group potential risks into low, moderate, or high categories. For the purpose of this evaluation, two risk factors, probability and severity, will be examined for each perceived risk associated with the defined risk scenario.

Recommendations and Rationale
Risk Question
In this case the criticality of an issue drives the creation of the risk question. Our risk question becomes, "*what are the potential risks associated with identifying an issue as a deviation which requires investigation vs. event which requires notification only*"?

Risk Assessment Tool
Given the nature of the data to be used for the assessment, the Risk Ranking and Filtering method has been selected to aid in the assessment of risks associated with categorizing the issues. Risk Ranking and Filtering (RRF) focuses on two separate
risk factors, probability and severity, associated with each potential risk relevant to an issue.

Risk Assessment
Identification, analysis, and evaluation of potential risks. The potential risks associated with the identification of deviations vs. events were derived through completion of a brainstorming exercise and are listed below:

Regulatory expectations– the formalized requirements pertaining to investigations should be reviewed and understood to determine the potential risk of non-compliance. Risks may vary from one market to another, it is suggested that the expectations for the most stringent market served be used for the assessment of a minor regulatory deviation when multiple markets are involved. Note that repeat deviations, albeit minor in nature, may require a variation to be submitted as recommended by EMEA position paper on QP discretion.

cGMP expectations – the unwritten expectations that are generally accepted as "standard practice" should be considered. Many times these expectations are verbally expressed by regulatory inspectors during facility inspections. As with Regulatory expectations the assessment should be based on the most restrictive GMP expectations.

Direct impact system – it is expected that the site has performed and documented an assessment of all systems. The impact classification is utilized in this assessment**.**

Direct product quality impact – this encompasses all factors that could have a direct impact on product quality such as out of specification result, stability failures, foreign matter, etc.

Risk to patient – this encompasses all factors that could be harmful to the patient such as cross contamination of product, mislabeling, etc
For each of the above stated risks related to the identification of deviations vs. events the individual risk factors or components must be assessed. As identified previously, each potential risk has an associated probability and a severity. The probability represents the likelihood of the risk being realized while the severity is a measure of how much impact it would have if it did occur.

Risk Level	Probability	Severity
Moderate (3)	**Regulatory** – Some requirement exists to investigate non critical events. Not included in regulatory filing. **GMP** – It maybe considered an industry standard to conduct investigations on this type of events. **Direct impact system** – It is an indirect impact system. **Direct product quality impact – there may be** an indirect product quality impact. **Risk to patient** – It may present a moderate risk to the patient. e.g., Blister pack not formed correctly.	**Regulatory/GMP** – May result in a comment/minor observation during a regulatory inspection. **Direct impact system** - May have a GMP impact as it is an indirect impact system (if impact is mitigated with secondary system then severity moves to low). **Direct product quality impact** – May indirectly impact product quality (if impact is mitigated with secondary system then severity moves to low). **Risk to patient** - May result in an indirect risk to patient (if impact is mitigated with secondary system then severity moves to low).
High (5)	**Regulatory** – A formal requirement exists for investigating this type of events. Included in regulatory filing. **GMP** – It is an industry standard to conduct investigations on this type of events. **Direct impact system** – It is a direct impact system. **Direct product quality impact** –It has a direct impact to product quality. **Risk to patient** – It has a direct risk to patient.	**Regulatory/GMP** – May result in a FDA-483/major or critical observation during a regulatory inspection. **Direct impact system** – Results in impact as it is a direct impact system (if impact is mitigated with secondary system then severity moves to moderate). **Direct product quality impact** – Impacts product quality. **Risk to patient** – May result in a direct risk to patient.

* QAR: Quality Assurance Report or Deviation Report

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 Acceptance

After the Total Risk Score has been calculated for each individual potential risk it must be assessed against an evaluation matrix to determine the acceptability of the existing risk or, conversely, identify the need for reduction of the risk through implementation of controls, where possible. The evaluation matrix is to be devised based on a site's willingness to accept different levels of risk.

Table II and the related Interpretation section represent an example evaluation matrix.

Table II: Risk Score Evaluation Matrix

Increasing Probability ↑	5	5	15	25
	3	3	9	15
	1	1	3	5
		1	3	5
Increasing Outcome Severity →				

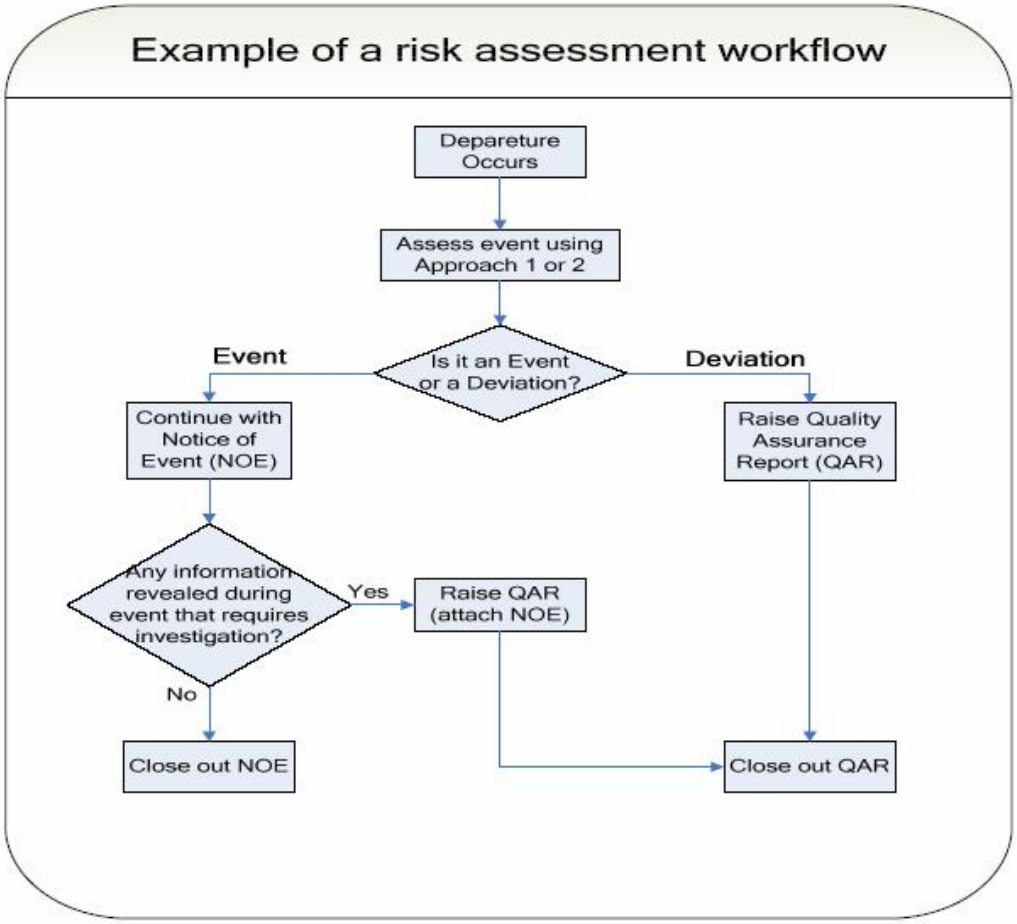
Event	Probability/mitigation	Severity/mitigation	Risk score	Classification
data	available, documentation errors trended and reviewed			
Deviations from SOP with no impact to product	3- Potential to affect all systems	1- No impact to product quality. No risk to patient.	3 - Low	Event
In-process Control missed	3- Direct impact system. GMP standard to document and evaluate in-process control results.	1- In-process data available for other intervals which comply with acceptance criteria. Product tested to final release specifications.	3- Low	Event
Excursions from process manufacturing descriptions	5- Process parameters are filed	1 – No impact to patient	5 - Moderate	Deviation from regulatory filing
Equipment Out of Calibration	3- Indirect impact system. May have an indirect impact on product quality. GMP standard to investigate.	3- May result in a comment or minor observations during a regulatory inspection. Mitigated when calibrated equipment is OK and product quality is sustained.	9- Moderate	Deviation
Labeling Issues	5- Specifications are filed.	3- May result in indirect risk to patient. Can be detected/mitigated at several points within the company and distribution channel.	15- High	Deviation
OOS	5- Specifications are filed	3- OOS may impact patient and OOS product not released to market	15 - High	Deviation
Stability failures	5- Stability specifications filed	5 – Product is in dating and in the market	25 - High	Deviation
Foreign Matter/ Contamination	5- Direct impact, GMP standard to investigate, potential for introducing foreign matter from various sources: raw materials, environment, people and equipment.	5- Impacts product quality. May result in a direct risk to patient. If product is released, may result in customer complaints and major observation during a regulatory inspection, and/or recall.	25 - High	Deviation

Approach 2
Individual risk assessment approach
Depending on the individual site preference, the system could be designed in a manner that assesses each issue to determine the criticality.

Risk Assessment
This can be achieved by creating a list of questions to be answered for each issue. The questions should be formulated using the same areas that the System Assessment described above used, i.e. regulatory expectations, cGMP expectations, system impact, product quality impact, risk to patient

- this encompasses all factors that could affect the safety, purity, or identity of the product.

Risk Control and Review



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