Regulatory Basis:
FDA Quality Systems Regulations

Reference: FDA CFR - Code of Federal Regulations Title 21

General Discussion
Often times, deviations that occur during the handling, manufacturing, testing or distribution of materials/products have little or no impact on product quality or to its registration filing. The purpose of this guidance is to provide a process for assessing if a deviation does or does not impact the product quality or its filing through the use of a Quality Risk management (QRM) tool.

A deviation with no impact to product quality or to regulatory filings is classified as an ***event*** and thus does not require to be investigated while those that impact product quality or regulatory filings are classified as ***deviations.***

Accordingly, the following definitions for Events and Deviations apply:

Deviation - A departure from approved procedures, formulas, specifications, or parameters that has an impact or potential impact to product quality, GMP regulated systems, or regulatory filings. These are typically documented in a Quality Assurance Report (QAR).

Event - A departure from approved procedures, formulas, standards, or parameters that has been determined to have no potential impact to product quality, GMP regulated systems, or regulatory filings. These are typically documented in a Notice of Events (NOE).

This document provides guidance on two approaches to assess the risks associated with identifying deviations vs. events.

The first approach is the generic systems assessment approach where the site completes a risk assessment of the most common types of issues and determines in advance which are deviations and which are events. The second approach is the individual assessment approach where the site completes a questionnaire for each issue to determine if it is a deviation or an event.

Through application of a simple tool coupled with requisite background knowledge, it is expected that this assessment will serve as a model to a GMP site to standardize the evaluation of deviations vs. events. With either approach, a few basic questions will need to be answered to gather enough information to determine whether the issue is an event or a deviation.

Approaches to assessing risk
Approach 1
System assessment approach
The following factors should be evaluated through a series of risk questions:

- Regulatory requirements and cGMPs
- Direct impact system
- Direct product quality impact
- Risk to patient

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

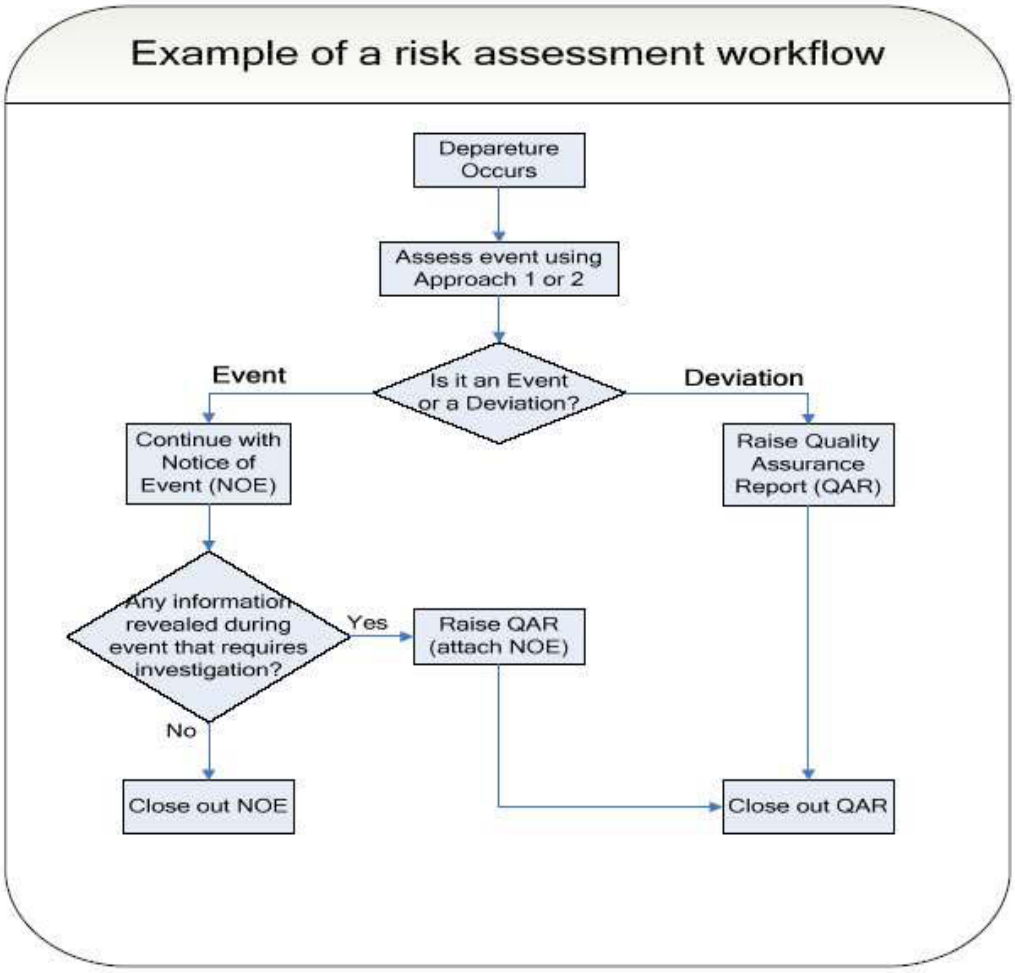
↑ **Increasing Probability**	5	5	15	25
	3	3	9	15
	1	1	3	5
		1	3	5

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.



* QAR: Quality Assurance Report or Deviation Report

