RISK MANAGEMENT EXAMPLE
Overview:

This example will take a risk that may be in the risk library and put it through the steps of the Risk Management Methodology.

The example provided below is for informational purposes only. Nothing in the example is intended to imply that the items below should or must be considered or managed in the way indicated in the examples. Each company is solely responsible for determining which risks should be considered, how they should be considered, and how to appropriately address any identified risks.

Risk: Storage Requirements not met for investigational product.

Critical Process and Data Identification

If deviating from Investigational Product (IP) storage requirements could affect the potency and/or purity of the IP then the proper storage of IP could be identified as a critical process given the potential impact to human subject protection. Based on stability data, this risk could also affect the reliability of trial results further supporting characterization of IP storage as a critical process.

Risk Identification

During the risk identification, we will define some of the specifics causes of this risk that may manifest during the process of IP shipment. This will allow us to have a better understanding of the nuances of this risk at further phases of the methodology. In this case we might divide the risk into the following more specific cases:

» Storage requirements not met during IP shipment
» Storage requirements not met during storage at the depot
» Storage requirements not met at the site

Risk Evaluation

Each of the above specific cases is assessed based on three characteristics: impact, likelihood of occurrence, and probability of detection. In this case, the impact, likelihood and detection may vary based on several specifics of the trial, some of these specifics which may be considered are listed below.

» Shipping complexity could increase the likelihood of an issue
» A temperature deviation at a depot could have a higher impact than a single dose deviation
» Impact could be lower for temperature excursions prior to study start up
» The impact may be greater or less for a given trial based on the characteristics of the investigational product
Differences among distributors, depots and sites may result in differences in scoring. For example, if based on our experience with the depot, it would be unlikely for them to fail to meet storage requirements, it is given a low occurrence score. The depot has also proven to be quite vigilant in detecting any storage requirement deviations, and therefore is also given a low detection risk score. In this example, the probability of occurrence will be highest during shipment and at the site, and so those two causes are given a high occurrence score. Due to monitoring strategies, failure to meet storage requirements will be more detectable at the site than during the shipment.

<table>
<thead>
<tr>
<th>Impact</th>
<th>Occurrence</th>
<th>Detection</th>
<th>Risk Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Storage requirements not met during CT shipment.</td>
<td>10</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Storage requirements not met during storage at the depot.</td>
<td>10</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Storage requirements not met at the site.</td>
<td>10</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>


**Risk Control**

After the risks have been scored, any risk that scores above the threshold requires mitigation. For this example, we will set a threshold of a risk priority number (RPN) of 160. Refer to section Risk Evaluation in “Risk Management Framework: Guidance for Successful Implementation in Clinical Development” to understand thresholds. Since the risk of “Storage requirements not met during storage at the depot” falls below our threshold, existing controls are deemed sufficient. This risk is accepted. The other two risks need to be either avoided or reduced.

In this case, based on experience with the distributor, we feel that the risk score is too high for “storage requirements not met during shipment”. It is too high based on the frequency that we have observed temperature deviations in the past, and in our confidence that temperature deviations are being detected prior to administration to the subject. For this risk, we will choose to lower the probability of occurrence by shipping the investigational product in insulated containers. Our expectation is that these insulated containers will reduce the occurrence to a score of 1.

We also see that the risk of “Storage requirements not met at the site” scores above our established threshold. This is also based on our experience with the sites involved, and past monitoring reports where possible. For this risk we could attempt to increase the probability of detection by increasing monitoring visits but lowering the likelihood of occurrence might be more effective by having strict requirements for site storage capabilities during site selection.
Risk Communication

Stakeholders should be identified, and a relevant communication plan should be developed. In our example, those functions directly involved in the handling of the IP material, sites and the study team will need to be aware of the risk controls. Those preparing the investigational product for shipment need to know the requirement for packaging of the material. The sites should be aware that those receiving the IP material should expect to receive insulated containers. The site should understand requirements for storage of the investigational product at the site.

The study team should make sure that these expectations are consistently reinforced to relevant personnel over the course of the trial (i.e., through monitoring visits), and the transition of responsibilities to new personnel is expected.

Quality unit personnel should also be aware of the controls that are in place and of risks which have been accepted.

Documenting the risks, causes, impact, likelihood, detectability and controls in a risk management plan supports communication to the various stakeholders and provides evidence that the risk management process was completed.

Periodic Risk Review

Any instance of storage requirements not being met would follow the issue management process. A serious quality issue may trigger a risk review.

In addition, periodic risk review should occur at predetermined timepoints. For our example the periodic review will need to answer the following questions:

» Have we effectively reduced the likelihood of occurrence of “storage requirements not met during shipping” by the use of insulated containers?

» Have we effectively reduced the likelihood of occurrence of “storage requirements not met at site” by selecting specific sites with proper storage capabilities?

If the answer is yes, then there may not be further action at this point. If the data supports the need for further action, we could at this point introduce additional risk controls, such as temp-tags if we are not comfortable with the probability of detection of temperature deviations during shipment and storage.

Risk Reporting

The risk report should contain a description of the quality management approach for the trial and a summary of important deviations from the predefined quality tolerance limits and remedial actions taken.