Case Study Title:	**Packaging Line GMP Optimization**	**Case No.**	**RMWG-05**
GMP System Impacted:	**Packaging**		
Introduction / Background	Packaging represents a critical manufacturing operation requiring strong Good Manufacturing Practices (GMPs) and quality oversight to ensure sustained and robust compliance. Historically, inadequate packaging practices have been a meaningful ongoing contributor to product recall actions industry-wide. A strong understanding of the compliance risks associated with product packaging is a necessary and important component of a good quality system. In this case study, the authoring firm has enjoyed satisfactory compliance performance across their international packaging operations. None-the-less, recognizing the criticality that packaging plays in ongoing quality assurance, the firm engaged in a risk assessment of a number of established packaging lines at several key packaging sites worldwide. The goal of the assessment was to further enhance the quality assurance of existing packaging operations and practices.		
Defining the Risk Question	The risk question developed for the subject case study is: ***What processes, procedures, and/or events during the packaging of a product create an unacceptable risk, real or perceived, to the quality of that product as received by our customers?***		
Selecting a Risk Assessment Method	The project team assigned to this initiative sought to find a method that was inductive, systematic, and comprehensive, with the understanding that the risk factors for this application were generally well-defined and quantitative. The risk tool selected was: **Functional Failures and Effects Analysis (FFEA)** This tool represents a hybrid of FMEA and used a Risk Matrix instead of a Risk Priority Number (RPN). FFEA is a systematic, function-based method for examining the effects of functional failures on system performance. The analysis was conducted by a team of subject matter experts who identified and assessed the effects on a system associated with individual functional failures. To apply risk-based, decision-making concepts to the FFEA, the team also identified the frequency of each functional failure and the severity of the potential effect (outcome) and compared each to predetermined risk acceptance criteria. The team suggested corrective actions when required by the risk acceptance criteria or when the team identified opportunities for improvement.		

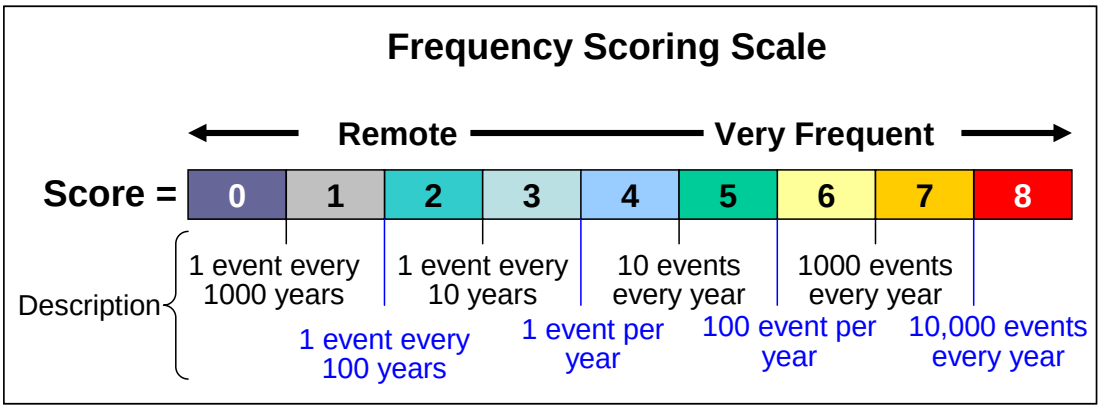
Risk Assessment (Risk Identification, Analysis and Evaluation)

This assessment effort first required that potential product defects from any given packaging operation be defined and graded for Severity, Frequency and on the ability of the operation and/or an operator to Detect the defect. Tables 1 and 2 below summarize the definitions and categories applied for Severity and Frequency respectively. Defect detection was categorized and graded on a scale from 0 to 4 to reflect a detection capability of "none" (unable to detect) to "always" detect.

Table 1 Example Severity Categories

Category	Severity Description
1	**Effect is not noticeable** No quality impact, production or financial impact insignificant
2	**Minor effect** No impact of license or NDA, possible quality problem (e.g., scuff label) and possible production problem (e.g., excessive rejects)
3	**Moderate effect** Quality concern (e.g., exceed internal metrics, customer complaint), impacts production for short period of time (days)
4	**Major effect** Quality impact, exceeds license or NDA limits (e.g., miscount, missing label/circular), impacts production for extended period of time (week or longer) (e.g., long equipment downtime, rework)
5	**Critical effect** Quality problem with potential impact to patient safety, (e.g. mislabeled product mix, resulting in a market action) and or significant production problem (e.g. atypical event which causes a major loss of production and/or potential impact to product supply).

Table 2 Example Frequency Categories



[Note: While frequency per year was a suitable metric for purposes of this case study where the packaging lines analyzed were generally consistent in total output, an alternative approach would be to assess frequency based on opportunity for the event to occur. In other words, defects per number of potential occurrences (or chances) may provide a better comparison for other risk analysis and resulting prioritization of response activities.]

A team of packaging subject matter experts, and local site packaging engineers familiar with the subject packaging lines under assessment, worked to collect relevant data about the packaging line. All operations involved with the line function (equipment, procedures, etc.) were listed and all corresponding potential failures were then listed. For each potential failure, the team worked to

understand its potential impact on packaging operations and then worked to assign a severity category. Following severity classification, the team worked to review all dominant causes relevant to the defined potential failure and then assigned a frequency category.

For each potential failure, all safeguards (e.g. detection capabilities) were reviewed and a detection capability was assigned. For Severity Frequency and Detection determination, all relevant data was taken into consideration, to include maintenance and operation logs, batch records, deviation investigations, customer complaint records, etc.

In the FFEA model, the calculated Frequency (F) is combined with the ability to Detect (D) and than plotted against Severity (S) as follows:

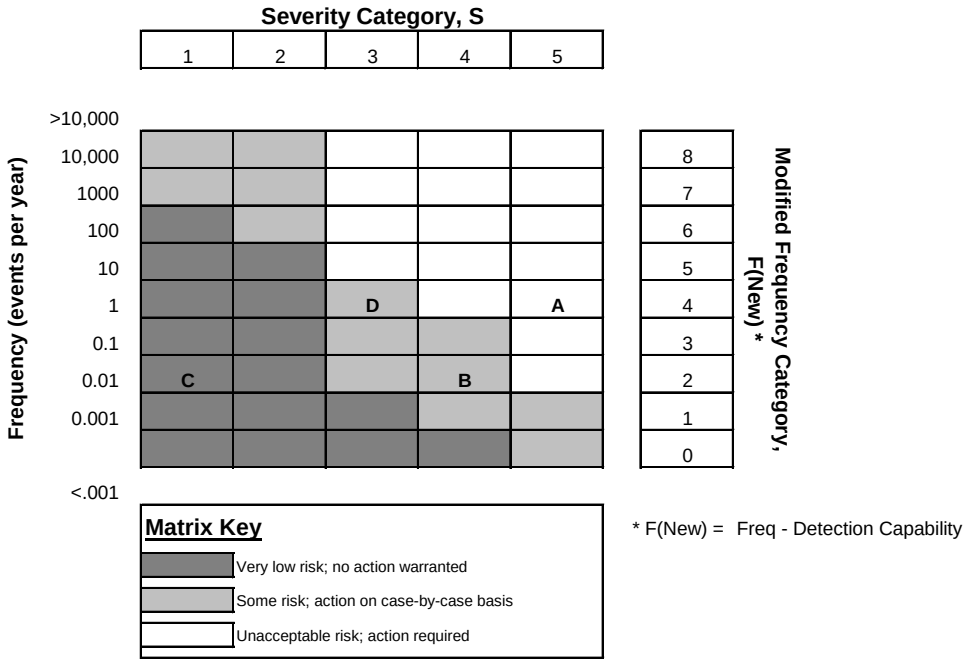
F- D = F(new)
S vs. F(new)

The resulting work output from this assessment was recorded in tabular form – *see Table 3 below as an excerpt of the resulting work product.*

Item No.	Potential Failure	Dominant Causes	Severity Category	Frequency		Safeguards	Safeguard Type and Category (Detection)	Eliminate or Mitigate Risk
				Events/Year Initiating Event after Safeguards	*Frequency* Category			
A	Incorrect expiry date printed on-line	Incorrect set-up	5	1 – 10	4	Engineering / Administrative Controls	D = 0	Yes
B	Overfill	Feeder failure (pin breaks, dropping excessive tablets) Flood feeder (no precise control) Static and dust build-up in the filler tubes	4	100-1000	6	Vision system with reject verification Flap detection for overfill	D = 4	Evaluate options and implement where appropriate
C	Wrong shrink wrap	-	1	0.01-0.1	2	-	-	None
D	Cleaning residue (left from cleaning agents)	Cleaning concentration is high Human error (improper cleaning, rinsing, and/or inspection)	3	1 – 10 1 – 10	4 4	Line cleaning inspection (extended time allocated for cleaning and inspecting due to equipment design)	D = 0	Evaluate options and implement where appropriate

Using the collected tabular information, a risk matrix can then be assembled – see Figure 1 (in this example, items A through D from Table 3 are noted to reflect their calculated frequency). The risk matrix helps to visually prioritize the results from the risk analysis.

Figure 1 – Risk Matrix



In this example, item "A" would get immediate action to eliminate or reduce the risk. Items "B" and "D" would be evaluated and actions would be taken if practical and appropriate to reduce or eliminate risk. No actions would be required for item "C".

Risk Control

In this case study, risk is reduced through the introduction of a structured and standardized approach to understand and determine the potential likelihood of system or operator failures and the probability of any resulting defect impacting the final product and end-user. Potential risks which are above a predefined threshold, taking into account severity and frequency of occurrence (the later of which is modified to account for the probability of on-line detection), are considered for elimination or mitigation.

Risk Documentation and Communication

The risk analysis for the subject case was reviewed by an oversight committee to confirm findings and support risk mitigation activities. Learnings from the assessment were shared with the firm's other operations that used similar packaging equipment and/or packaging practices. In addition, learnings from the full set of packaging line risk assessments were captured for consideration in future packaging line design and equipment procurement efforts.

Risk Review

As part of the firm's auditing activities, the corporate group responsible for periodic site audits received copies of the risk conclusions and action plans to confirm corrective actions were deployed and were effective.

In addition, the risk assessment summaries were maintained at the local site packaging departments for use in future troubleshooting exercises involving deviation investigations or product complaint evaluations.