



Case Study Title:	Process Deviation – Empty Product Capsules	Case No.	RMWG-08
GMP System Impacted:	Quality, Production		
Introduction / Background	<p>A drug product site produces PainFree® capsules, which are indicated as an anti-epileptic and for treatment of neuropathic pain. Multiple customer complaints of empty capsules were received. Lot ABC was fully distributed in the US and no product remains within company control. There is no evidence of tampering.</p> <p>Batch record review indicated that during processing, a loose dosator was replaced on the encapsulation equipment. Following replacement and prior to resuming encapsulation, acceptance testing of capsules produced required by Standard Operating Procedure was performed and product met requirements.</p> <p>Further investigation revealed that the loose dosator caused empty capsules to be produced. The encapsulation system utilized a vacuum system to remove empty capsules. This empty capsule removal system includes a reservoir for holding empty capsules rejected during the manufacturing process. As a result of the loose dosator, an atypically high number of reject empty/low fill capsules were produced during the encapsulation operation, causing the reservoir to be filled and eventually overflow. The reservoir was physically located over the acceptable capsule flow. Therefore, it was determined during the investigation that if the empty capsule chamber overflowed, there was potential for rejected capsules fall back into the acceptable capsule exit chute and be reintroduced to the lot.</p> <p>Sealed bottles were obtained from remaining inventory of the lot. Of 30,661 capsules examined, 151 empty and 5 low fill weight capsules were found. The inventory evaluation, one to five empty capsules were found in 46% of the bottles evaluated.</p> <p>In the current case study, the manufacturer decides to use quality risk management to evaluate the potential impact of the deviation.</p>		
Defining the Risk Question	<p>The risk question developed for the subject case study is:</p> <p><b><i>Do a small number of potential low fill or empty capsules in a single batch of PainFree® capsules pose an unacceptable risk to patients, and secondarily, to the company?</i></b></p>		
Selecting a Risk Assessment Method	<p>In this case study related to process failure, the risk factors are more qualitative than quantitative. FMEA is specifically designed to systematically study processes for possible failure modes and then to develop actions to mitigate these failure modes. An element that requires consideration in this case study is detectability of the defect. Is it possible for the pharmacist or the patient to readily detect empty capsules? Again, the FMEA technique is an optimal tool for this application as the standard methodology includes all three risk components (i.e. probability, severity and detectability).</p>		

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The risk methodology selected for the subject case study is:  
**Failure Mode and Effects Analysis (FMEA)**

**Risk Assessment  
(Risk  
Identification,  
Analysis and  
Evaluation)**

Risk Identification -

The process used intends to identify potential risks that could result from empty capsules in the market and the possible consequences of each risk. It is understood that sufficient data may not always be available to reach conclusions, and identification of risks should be based on best available information/data, scientific knowledge and historical experience. The rationale used to identify risks should be documented.

Examples of potential risks include; patients may receive empty capsules, patients may not have availability of medically necessary product, the company could receive an audit observation either from an internal auditor or external regulatory agency, etc.

Risk Analysis and Evaluation -

Numerical ratings for the FEMA analysis are based on the following criteria:

- Severity of the failure
- Frequency of the failure
- Ability to Detect the parameter

A numerical ranking of 1 – 3 is applied to each evaluated hazard, as demonstrated in the example FMEA Risk Score Ranking table with three point ranking scale presented in Table 1.

Numerical Ranking	Severity	Frequency of Occurrences	Detectability	Max Risk Score
1	Potential minor patient injury, but not permanent. Minor regulatory compliance issue that can be corrected.	Isolated occurrences	High ability to identify the risk, and take action to avoid	1
2	Potential serious injury, but not permanent. Significant regulatory compliance issue	Moderate Likelihood of occurrence	Moderate	8
3	Potential death or permanent injury; Major regulatory compliance issue	Inevitable at some point.	Low ability to detect the risk, and take action to avoid	27

The rating applied to each of these categories for each failure is then multiplied to result in a Risk Score. The Risk Evaluation Score is calculated as follows:

***(Severity x Frequency of Occurrence x Detectability) = Risk Evaluation Score***

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In the FMEA analysis executed for this current case study, the firm determined that if there was potential for greater than a moderate Risk Evaluation Score, appropriate risk mitigating actions would be required to lower the risk to an acceptable level. Therefore, If the score for an evaluated hazard exceeds 9, corrective measures to the reduce risk of failure will be taken. If after attempting risk mitigation, the score could not be lowered below 9, the resulting risk would not be accepted. For those items with a score below the defined threshold, risks will be accepted. Conclusions are documented.

An example worksheet for calculating the Risk Evaluation Score for this analysis is presented in Table 2.

<b>Hazard</b>	<b>Risk Reduction Controls</b>	<b>Frequency</b>	<b>Severity</b>	<b>Detection</b>	<b>Risk Score</b>
Patient may receive empty capsules.	A medical opinion was requested: Given the anti-epileptic indication, there is the risk of status epilepticus, which may be life threatening; Since the capsules are opaque, patients will be unaware of the potential problem.	2 (Uncertainty)	3	3	18
Patient may not have medically necessary product available	Incident only impacted a single lot, so supply is not significantly impacted	1	1	1	1
Could receive an audit observation either internally and/or regulatory agency	Comply with requirements of deviation investigation and notification to Management Field Alert Issued to FDA; Complaint and Deviation GMP requirements met via compliance to SOPs.	2	2	2	8

**Risk Control**

In the current case study, Risk Reduction and Acceptance decisions centered on patient safety. Despite the apparently low number of empty/low fill capsules that may be present, there was no assurance that the numbers of empty capsules in the market was low. There was little ability for a pharmacist or patient to detect an empty or partially filled capsule. Most importantly, the potential medical consequence for some patients due to receiving and administering an empty or partially filled capsule was severe. As a result of the potentially high risk associated with some patients taking empty/low fill capsules, and the inability of the firm to implement appropriate risk mitigating actions to lower this risk (i.e. severity and ability to detect) to an acceptable level, the decision was taken to initiate a product recall.

**Risk Documentation and Communication**

Site procedures require preparation and Quality endorsement of a Deviation Report. The risk assessment output was incorporated into a number of existing work processes and their associated documentation. In order to prevent reintroduction of rejected product to the product, an automated sensor was incorporated into the empty capsule reject reservoir. When activated, this sensor automatically shuts down the encapsulation machine if rejected capsules in the reservoir reach the sensor level, preventing overflow. The overflow sensor with automated equipment shutdown was applied to all encapsulation machines at the firm. Additionally, the results of the FEMA analysis and recommendation for product recall were presented at an internal management notification process meeting and minutes of risk analysis and associated conclusions were documented. Affected regulatory agencies were formally notified of the recall decision.

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<b>Risk Review</b>	Evaluation of product complaints, adverse event reports and further examination of product received from the product recall may potentially be used to gain additional understanding of the extent of the defect that reached the market.
<b>Tools</b>	<b><u>Trainer on Failure Mode Effects Analysis:</u></b> <a href="#">[insert slide deck here]</a>