Simplify Process Events Documentation During the Manufacturing Process in a Pharmaceutical Industry

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Abstract *— For a pharmaceutical company to function better all events during manufacturing must be resolved in a promptly manner and documented properly. It is very important to have a simple yet effective process that helps to determine the best way to resolve events. The mayor problem in the Manufacturing Area of the company considered is that the current procedures do not establish the specific circumstances in which a process event needs to be documented. For this project the methodology of Six Sigma DMADV was used. Prior to the implementation of the Project all 25 lots evaluated had the form. After the implementation of the new process only 16 lots had an Occurrence Form. This means a reduction of 36%. As per the results and after the evaluation, it can be concluded that the new process was successfully implemented.*

Key Terms *— DAMDV, Documentation, Manufacturing, Process Events, Simplification.*

INTRODUCTION

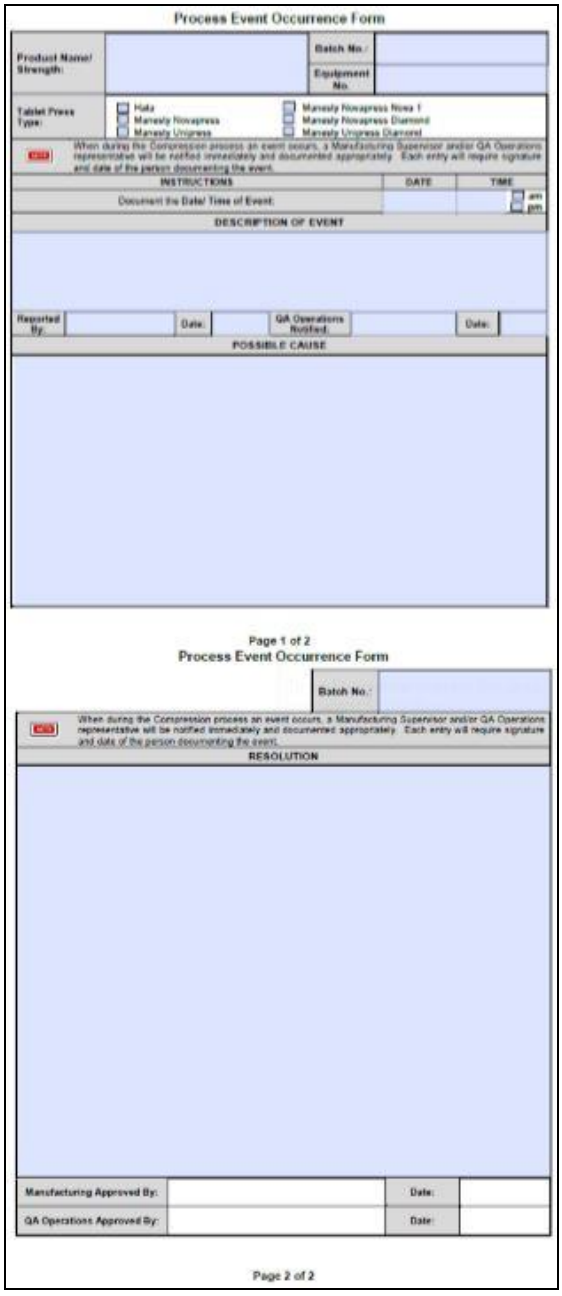
Every process has unplanned events, and the manufacturing process of pharmaceutical products is no different. All events during manufacturing must be resolved in a promptly manner and documented properly. If the events during a manufacturing process are not resolved and not properly documented, it may lead to some serious problems to the final product and/or the patient. Some of the problems may be additional waste, defects on the final product, rework and in some cases, it may even lead to recall of a product already in the market. All these problems may affect the quality of the product which in the case of pharmaceutical products, can also lead to adverse effects on the health of a patient.

Therefore, it is important to establish adequate corrective actions to resolve any process occurrence. It is also important to have robust yet simple processes that can help the employees follow the procedures and resolve any unplanned event during the process correctly.

The company in which the project was developed is a pharmaceutical company established in Puerto Rico for over 30 years. This company is dedicated to the manufacturing and packaging of generic medications and employs over 500 employees. The current procedures in the Manufacturing Area provide a form called Process Event Occurrence Form. In this form all the events that happen during the weighing, manufacturing and packaging of the product are documented. The situation identified is that each manufacturing stage has a different procedure with a different occurrence form. For example, the blending stage has an Occurrence Form in the blending procedure, while the compression procedure has another Occurrence Form. It was observed that the forms are similar, the only difference is that the list of equipment differ on each part. Refer to Figure 1.

The problem was discussed with the Manufacturing Management and it was emphasized that the mayor problem in the Manufacturing Area is that the current procedures do not establish the specific circumstances in which the form needs to be documented. The current practice is that a Process Event Occurrence Form is manually documented for every situation, including normal process situations like oil refill to a compressing machine. In addition, the situations are documented

in other electronical systems. This cause duplicity and delays in the manufacturing process.


Process Event Occurrence Form

Product Name/ Strength:

Batch No.:

Equipment No.:

Tablet Press Type:

Hata
Manesty Novapress
Manesty Unipress
Manesty Novapress Nova 1
Manesty Novapress Diamond
Manesty Unipress Diamond

When during the Compression process an event occurs, a Manufacturing Supervisor and/or QA Operations representative will be notified immediately and documented appropriately. Each entry will require signature and date of the person documenting the event.

INSTRUCTIONS | DATE | TIME

Document the Date/ Time of Event: am pm

DESCRIPTION OF EVENT

Reported By: Date: QA Operations Notified: Date:

POSSIBLE CAUSE

Page 1 of 2

Process Event Occurrence Form

Batch No.:

When during the Compression process an event occurs, a Manufacturing Supervisor and/or QA Operations representative will be notified immediately and documented appropriately. Each entry will require signature and date of the person documenting the event.

RESOLUTION

Manufacturing Approved By: Date:

QA Operations Approved By: Date:

Page 2 of 2

Figure 1
Current Process Event Occurrence Form

The purpose of this project is to resolve the duplicity of the process events documentation. In addition, it was decided to create a general procedure in which all the occurrence in the Manufacturing Area can be documented. The Manufacturing Management decided to start the project on the Compression Stage since this is the stage were Occurrence Form are documented most. After the implementation of the new occurrence procedure in Compression it will be decided to continue with the other stages.

The importance of the project is the results. A reduction in the duplicity and the delays in the Manufacturing Process due to Occurrence Form documentation is expected.

METHODOLOGY

The methodology used will be Six Sigma DMADV. The Six Sigma approach is a process to measure and improve quality [1]. This method has been proven to help standardize the processes and reduce the defects. The methodology of DMADV is the acronym for the five phases in which the methodology consists. DMADV consist of: Define, Measure, Analyze, Design and Verify (Figure 2).

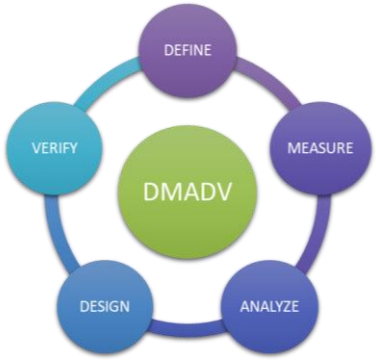


Figure 2
DMADV Diagram

DMADV is a data-driven quality strategy that differs from the traditional DMAIC (Define, Measure, Analyze, Improve and Control). The DMADV methodology is often used when implementing new processes based in data compared with the old process. Like DMAIC, DMADV is an integral part of the Six Sigma quality initiative [2].

RESULTS

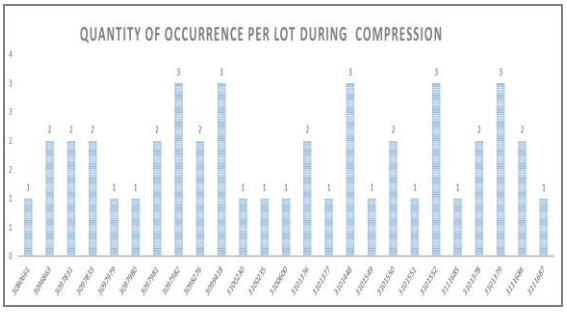
Define Phase

As part of the project it was identified that the documentation of Process Occurrence is not clearly

defined nor established. The Manufacturing Management decided to begin the project in the Compression Stage. They emphasized that the biggest difficulty in the Manufacturing Area is that the current procedures does not establishes the specific circumstances in which the form needs to be documented. Currently all situations must be documented and approved by the Quality Assurance Department (QA) prior the restart of the process. The average Process Occurrence Documentation is between 3 to 4 hours. In addition, the incidents are also required to be documented in other electronical systems like LIMS, which also requires the QA approval. This causes duplicity and delays in the manufacturing process.

Measure Phase

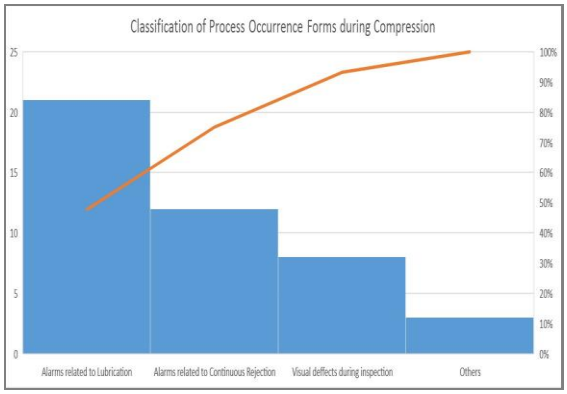
The second part of the project was to collect data and record specifications. A total of 25 batches manufactured were used to measure the quantity of Process Occurrence during the Compression Stage. Refer to Graph 1. All the batch gathered had a Process Occurrence form on the Compression Stage. The Average was two (2) Process Occurrence Forms per Lot.



Graph 1
Quantity of Occurrence Documented per Lot During Compression

Analyze Phase

The result from gathered data showed that all the lots manufactured had an event during the manufacturing process. Furthermore, in some cases, one batch had up to three (3) Process Occurrence Forms for different reasons. The largest amount of cases was due to alarms during the compression. A Root Cause Analysis (RCA) was used to determine the reason of the alarms. After the evaluation it was determined that the major cause was due to the alarms related to Lubrication. Refer to Graph 2.



Graph 2
Classification of Process Occurrence Forms During Compression

This alarm is considered to be a normal process alarm and does not affect the quality of the product. The alarms due to Lubrication represent 47.7 % of the Process Occurrence Forms in the Compression Stage followed by Continuous Rejection. The alarms related to Continuous Rejection represent the 27.3 % of the Process Occurrences. These alarms are required to be documented on the form and also on LIMS System. This situation is what causes the duplicity of the incident documentation. Resolving these two major offenders is expected to improve the process by 75%.

Design Phase

As part of the steps to resolve the two major offenders identified in the previous phase, it was decided to revise the current Compressing Procedures and to create a new Standard Operating Procedure for the Process Events Occurrence. The Compressing Procedure was revised to include a table of the most common alarms. Table 1 contains the alarm summary and the action to be performed when the alarm is triggered.

Table 1

List of Common Alarms Summary and Action to Perform Included in the Compressing Procedure

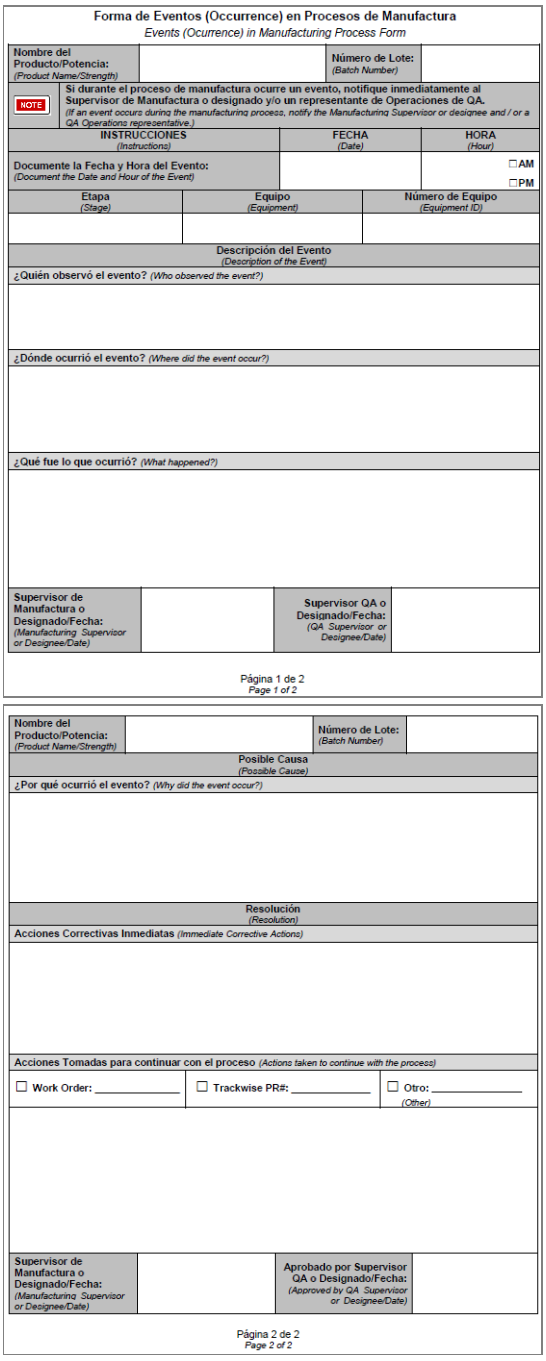
ALARM SUMMARY	ACTION
BACK LOWER GUARD OPENED	Close the Back Lower Door
BACK UPPER GUARD OPENED	Close the Back Upper Door
FRONT LOWER GUARD OPENED	Close the Front Lower Door
FRONT UPPER GUARD OPENED	Close the Front Upper Door
LEFT LOWER GUARD OPENED	Close the Left Lower Door
LEFT UPPER GUARD OPENED	Close the Left Upper Door
RIGHT LOWER GUARD OPENED	Close the Right Lower Door
RIGHT UPPER GUARD OPENED	Close the Right Upper Door
OVERLOAD TONAGE LOW WARNING	Contact the Supervisor or Designee to generate a Work Order. Document the Work Order Number on LIMS System
LUBE PUMP PRESSURE FAULT	Contact the Supervisor or Designee to generate a Work Order. Document the Work Order Number on LIMS System
LUBE PUMP OIL LEVEL LOW	Refill Lube Pump Oil. Document a comment on the LIMS System
TURRET MOTOR NOT RUNNING	Contact the Supervisor or Designee to generate a Work Order. Document the Work Order Number on LIMS System
FEEDER EMPTY DURING RUN	Contact the Supervisor or Designee and Quality Assurance Representative to start a LIMS Investigation
CONTINUOUS REJECTION	Contact the Supervisor or Designee and Quality Assurance Representative to start a LIMS Investigation
NUMBER OF STATION MISMATCH	Contact the Supervisor or Designee and Quality Assurance Representative to start a LIMS Investigation
MAXIMUM REJECTS PER SINGLE PUNCH	Contact the Supervisor or Designee to generate a Process Event Occurrence.
MAXIMUM REJECTS PER TURRET REVOLUTION	Contact the Supervisor or Designee to generate a Process Event Occurrence.
MAXIMUM CONSECUTIVE REJECTS	Contact the Supervisor or Designee to generate a Process Event Occurrence.
OVERLOAD TONAGE HIGH WARNING	Contact the Supervisor or Designee to generate a Process Event Occurrence.
OVERLOAD TONAGE HIGH FAULT	Contact the Supervisor or Designee to generate a Process Event Occurrence.
OVERLOAD TONAGE LOW FAULT	Contact the Supervisor or Designee to generate a Process Event Occurrence.
MAIN COMPRESSION OVERLOAD	Contact the Supervisor or Designee to generate a Process Event Occurrence.
HOPPER EMTPY FAULT	Contact the Supervisor or Designee to generate a Process Event Occurrence.
PUNCH PROX FAULT	Contact the Supervisor or Designee to generate a Process Event Occurrence.

This table was included in the Compressing Procedure as a guidance on what to do for the Manufacturing Operators. However, a note was added in the procedure indicating that if any other alarm not listed in Table 1 was triggered during the Compressing Process, the supervisor or designee must be informed for evaluation. The table and the Compressing Procedure include the specific instructions to determine when a Process Event Occurrence Form is necessary. In addition, the Process Event Occurrence Form of the Compressing Procedure (Figure 1) was removed. This form was replaced with a new procedure that specifies how to document the new Process Events Occurrence Form. In the Compressing Procedure all the reference to the old form were replaced with a reference to the new procedure.

The new procedure for the Process Events Occurrence was created to provide a specific instruction to the Manufacturing Supervisor and Designees on how to document the form. The procedure was created in Spanish with the purpose of a better understanding from the person responsible of performing the documentation. On the other hand, the form was created in dual language (Spanish and English) so that the person responsible for documenting the form can choose the language in which they feel most comfortable for better documentation results.

The other Compressing Procedures that included reference to the old Process Event Occurrence Form were revised to replace the reference to the new procedure. For this change a total of nine (9) Standard Operating Procedures were reviewed. Refer to Figure 3.

After the procedures were approved by the Manufacturing Management and the Department of Quality Assurance, the impacted personnel were trained. During this training the new procedure and the compression procedures that were revised were discussed. The questions of the Manufacturing Operators, Supervisors/ Designees and the Quality Assurance Representatives were clarified throughout the training. Then, as stablished in the current training procedure, the new Process Events Occurrence Procedure and the Compressing Procedures were made effective after all the personnel impacted with the changes were trained and informed of the changes. Refer to Figure 4.



Forma de Eventos (Occurrence) en Procesos de Manufactura
Events (Ocurrence) in Manufacturing Process Form

Nombre del Producto/Potencia: *(Product Name/Strength)*		Número de Lote: *(Batch Number)*	

NOTE **Si durante el proceso de manufactura ocurre un evento, notifique inmediatamente al Supervisor de Manufactura o designado y/o un representante de Operaciones de QA.** *(If an event occurs during the manufacturing process, notify the Manufacturing Supervisor or designee and / or a QA Operations representative.)*

INSTRUCCIONES *(Instructions)*	FECHA *(Date)*	HORA *(Hour)*
Documente la Fecha y Hora del Evento: *(Document the Date and Hour of the Event)*		☐AM ☐PM

Etapa *(Stage)*	Equipo *(Equipment)*	Número de Equipo *(Equipment ID)*

Descripción del Evento *(Description of the Event)*

¿Quién observó el evento? *(Who observed the event?)*

¿Dónde ocurrió el evento? *(Where did the event occur?)*

¿Qué fue lo que ocurrió? *(What happened?)*

Supervisor de Manufactura o Designado/Fecha: *(Manufacturing Supervisor or Designee/Date)*		Supervisor QA o Designado/Fecha: *(QA Supervisor or Designee/Date)*	

Página 1 de 2
Page 1 of 2

Nombre del Producto/Potencia: *(Product Name/Strength)*		Número de Lote: *(Batch Number)*	

Posible Causa *(Possible Cause)*

¿Por qué ocurrió el evento? *(Why did the event occur?)*

Resolución *(Resolution)*

Acciones Correctivas Inmediatas *(Immediate Corrective Actions)*

Acciones Tomadas para continuar con el proceso *(Actions taken to continue with the process)*

☐ Work Order: _____	☐ Trackwise PR#: _____	☐ Otro: _____ *(Other)*

Supervisor de Manufactura o Designado/Fecha: *(Manufacturing Supervisor or Designee/Date)*		Aprobado por Supervisor QA o Designado/Fecha: *(Approved by QA Supervisor or Designee/Date)*	

Página 2 de 2
Page 2 of 2

Figure 3
New Process Events Occurrence Form

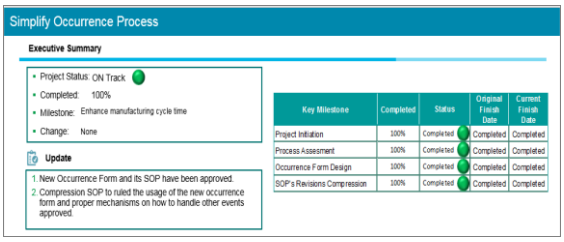
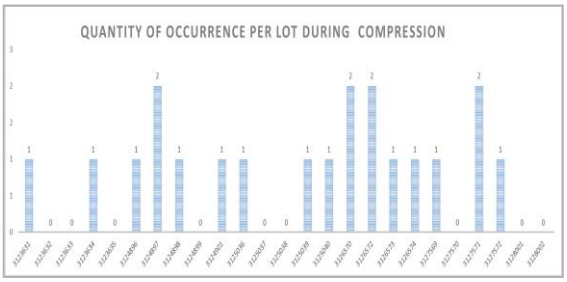


Figure 4
Simplify Occurrence Project Summary

Verify Phase

Once the new procedure was ongoing the effectiveness of the implementation was verified. Metrics are further developed to keep track of ongoing customer feedback on the product or service. For these purpose another 25 lots were gathered to evaluate the Compression Stage and to determine if further changes were required. Due to shortage of time the lots evaluated were chosen in campaigns (several batches of the same product).

As seen on Graph 3 a total of 25 lots were evaluated. From the lots evaluated, nine (9) lots did not have any Process Event Occurrence Form on the Compression Stage.



Graph 3
Quantity of Occurrence per Lot During Compression After Implementation

Prior to the implementation of the project all 25 lots had the form. This means a reduction of 36%. On the other hand, of the 16 lots with Occurrence Form, 20 Process Event Occurrence Forms were found. These 20 forms were also evaluated, and the mayor contributors were problems with the hopper and the feeder. These alarms and/or situations were part of the alarms listed on Table 1, which complies with the process established.

Another aspect evaluated was the reaction from the Manufacturing Personnel. Feedback of the new process was requested in the shift change. Most of the personnel were satisfied with the changes. They considered that the new form was easier to follow, and also, they preferred to document the events occurrence in Spanish.

CONCLUSION

In summary, this project was created to simplify the Process Occurrence documentation and to determine the instances in which the form needed to be documented. Accordingly, the project was implemented. The table with the alarms listed was created and placed in the Compacting Procedure. A new Standard Operating Procedure was created with the instruction of how to document the new form. After implementation the verification of the process was executed. As per the results it can be considered that the new process was successfully implemented.

RECOMMENDATIONS

The scope of this project was to create a general procedure for the documentation of the process events during the manufacturing. Further evaluation is recommended to include other alarms with the action to perform in the alarm list. Since this project was also applied to Compression Stage it is recommended to extend the project to all manufacturing stages.

REFERENCES

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