Improving the SOP of Managing Controlled CII Substances in the Laboratory from Receiving to Discarding

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Abstract *— As a contract manufacturing operation, the needs of our clients are our priorities. The inclusion of controlled substance schedule II to our list of products has been a challenge that we are still trying to overcome. Regulations and requirements for the management of controlled substances schedule II are very rigorous. They must be monitored from the time they arrive to the time they are disposed. A standard operating procedure (SOP) is established in order to meet regulations and have a clear and consistent procedure to manage CII substances as required. Nevertheless, flaws and gaps are found in the current SOP and it is mandatory to improve the procedure to meet regulations. The DMAIC tool was used to identify the deficiencies in the process. An improved process was suggested after analysis phase. The SOP was revised, and the improved process was placed as a new revision after giving training to the corresponding personnel.*

Key Terms *— Controlled Substances CII, DMAIC, Six Sigma, SOP.*

PROBLEM STATEMENT

The pharmaceutical industry must be aligned to the controlled substances' regulations. An operating standard procedure (SOP) is established to delineate such process.

It has been a concern that gaps and flaws are found in our processes (SOP). It is important to fill the gaps and identify the flaws to improve them and meet regulations and clients' needs.

The project pretends to delineate the flow of the Controlled II substances from the time they arrive to the laboratory to the time they leave the laboratory for disposition to improve the SOP M700-160.

Contributions

SOP M700-160 (Handling of Controlled Substances CII for the QC Labs-Chemistry, Microbiology and Stability) is audited by the Drug Enforcement Administration (DEA) and any found deficiency or non-compliance during audit will have a negative impact to the company. Improving the SOP will benefit the company to avoid deficiencies and non-compliance.

LITERATURE REVISION

Six Sigma Tool: DMAIC

Define phase: The problem is identified and well defined. Measure phase: The performance/output of the problem is measured, and the current state is well identified and presented. Analyze phase: The cause of the problem is identified. Improve phase: A solution to the problem is found and placed to test. Control phase: The proposed solution is being monitored to assure that the problem is solved [1].

Controlled Substances

Controlled substances are regulated by the DEA and the Puerto Rico Health Department (law #4 June 23, 1971) because of its potential for abuse and addiction. Following the Code of Federal Regulations (CFR 21 Part 1308), they are placed in different schedules (I to V) based on its medical use, potential of abuse, addiction and safety, being schedule I the more addictive. Controlled substances schedule II has a high potential for abuse but unless schedule I, they have medical uses. One big problem of controlled substances is that even if they have medical uses, the abuse may lead to psychological or physical dependence. Schedule II includes stimulants, narcotics,

barbiturates, opiates, depressants, hallucinogenic substances and immediate precursors. In addition, it includes the salts, isomers, isomer salts, esters and others if they are chemically possible to exist [2] [3] [4].

Define Phase

To define the problem, two meetings were held to discuss the problem statement. In the meetings, a Stand Alone Corrective Action Preventive Action (SACAPA) was discussed to include those corrective action in the SOP revision. The SACAPA points out some deficiencies of the SOP. Such deficiencies were:

1. Reconciliation for the sample when received between sample label and quantity received (first weight).
2. Include in SOP how to handle samples spill, how to discard and how to reconcile the spilled sample.
3. Correct section I step 12; it refers to a section and step that is not in the SOP.

Other deficiencies were discuss giving emphasis to the lack of information in the discarding process and the flow of the CII substance through the laboratory. All discussed deficiencies were attended, and it is expected to find more during the Analyze Phase.

Measure Phase

The measure phase includes the entire current process, from receiving to discarding, of the current SOP. The process was read and compared to the current practices to see if there was discrepancy between them. Discrepancies were found after comparison and deficiencies were detected which will be analyzed and explained in the next phase.

Analyze Phase

The current receiving process of the SOP has several deficiencies. It has misguided, incorrect and missing information. For that reason, there is discrepancy between the SOP and current practices. For example, it does not clarify how to coordinate the receiving process, which is important to be prepared. It does not clarify when to perform the initial inventory, which is performed once per substance, when the substance is received for the first time on site and it is performed by the laboratory. When the weighting process is performed, no document is signed and just the bulk samples are compared against a label weight while the SOP states that it is performed for all samples. Commercial, stability or micro samples are not compared with any weight. The reason is that bulk samples are brought by incoming, in a crystal bottle without any seal while commercial and stability samples are brought by packaging area in finish product packing which are sealed.

Stability samples have a form that is signed before entering the stability chamber and it is not clear where do the samples are received and weight. The SOP states that stability samples are first received in room Q-5A but they are received in room Q-29 and stored there in stability chambers except T-0 samples. The SOP suggests that samples are directly transferred to the Q-5A room after pull (pull is to remove samples from stability chambers). Turns out that stability samples are weighted (receiving process) after pull and then transferred to room Q-5A. It was not clear which process to follow after sample pull. Also, it was not clear how and when does samples T-0 are received. T-0 samples are received like the other samples (following the weighting process) and then stored in room Q-5A. Step indicating to follow SOP M700-118 and section 7.5.14 is misguided because the format of SOP M700-118 was changed and section 7.5.14 does not exist.

The step 9 of the receiving process indicates “to log standards on form M7050-060” and that form and process is for samples, not standards. The samples are stored in the safe box, but the SOP does not specify how. Instructions of how to organize the samples should be added to maintain order because one of the problems is the difficulty of finding samples after storage. DEA auditors want to find samples as fast as possible when they are requested for audit. Instructions of labeling the

samples' bag with the logbook and page should be also included.

In the use and reconciliation process it was not indicated to compare the weight before use with the receiving weight and it is very important to compare those weights before continuing. To generalize that instruction, it should be indicated to compare the weight of the bottle with the previous weight. Problems with reconciliation have occurred that could be avoided by comparing weights. The percentage of reconciliation could be reconsidered for a higher value because problems with moisture absorption have led to reconciliation fail or better temperature and humidity controls should be place. It was found that current humidity and temperature parameters are above USP acceptance criteria for dry place. The DEA 41 form is no longer used; instead form C850-133 is being used. DEA 41 form must be removed from the entire SOP and instead, the new form number must be added.

The discarding process is very vague. The discarding process as well as the receiving process has lack of information, misguided information and incorrect information. It refers to a step which does not exist (step 11 of section M does not exist in the SOP). It does not state how to coordinate the discarding process. It does not point out the important steps to follow previous the discarding process. It does not point out which forms to fill. It does not clearly indicate which procedure to follow; it just has some general statements. Not all listed SOPs are relevant, SOP M700-020 is for sample receiving, storage, handling and disposal of non-controlled samples; it is not relevant for discarding controlled substances. SOP M700-23 is for receive, storage, handling and disposal of non-controlled reagents; it is not relevant either. SOP M600-086 is used for controlled substances disposal but after the substance leave the laboratory; it is not relevant for the laboratory but relevant for the warehouse personnel. Those three SOPs should be eliminated from the list.

The discarding process should not be stopped once it is started. Steps indicating the important aspect to consider before starting the discarding process should be added to make sure that the discarding process can be completed. Instructions of how to handle generated residue during analysis should be added to have an idea of how to handle that residue, no matter if it is generated by the analysis or by spilling. Key instructions should be suggested if the spill is generated before or after being reconciled to give an idea of how to handle the situation. Finally, instructions on when to fill the form C850-133 step by step should be added to help the scientists during the discarding process.

Improve Phase

Suggested processes:

Receiving process for Stability Program, Finish Product, Raw Material and Microbiology Laboratory

1. Coordinate the receiving process with incoming or packaging personnel and notify the person in charge of the receiving process.
   a. Controlled samples must not be delivered to the laboratory after 2 pm if the receiving process must be performed the same day.
   b. The supervisor proceeds to notify the person in charge of the receiving process.
   c. One scientist per area (finish product, raw material, analytical service, microbiology and stability) must be dedicated to the task and he/she must have at least one person to back them up in case the person is not present or available.
2. Perform an initial inventory of the samples the same day that the samples are received for the first time.
   a. Fill the form C850-008 "Reporte del Inventario de Sustancias Controladas / Químicos Listados" to document this process.
3. Verify that the case where the controlled samples are transported is closed and in good conditions.

4. Receive the stability samples after pull and T-0 stability samples.
    a. Document the form M750-450 if no discrepancy is observed. Receive the samples as established in SOP M700-020 to verify that the information of the received sample is correct.
5. Receive samples as indicated in SOP M700-020 “Receiving, Storage, Handling, Testing and Disposal of Samples in the QC Analytical Laboratory” to verify that the information of the received sample is correct.
6. Weight or count (as required) each sample container including the cap; this is the quantity received weight or count.
7. Verify the gross weight or count with the information stated in the container label and/or in the receiving documents if apply.
    a. Report any discrepancy immediately to the QC Supervisor. Log each sample (lot and drum) individually in form M750-060 after being received. Document a full description of the material including dosage and if additional bottle is received from the same material. Attach the balance strip if samples were weight.
        - *Each sample lot arrives with 4 main bottles and 2 more if they require microbiology tests. Verify if this quantity of bottles is necessary or if the amount can be decreased to save space in the safe box. This way the safe box’s space is maximized, and samples can be better organized. Also, the reconciliation process is facilitated and less logbooks will be used at a time given that 1 page per bottle is used.*
8. Log each sample container individually in form M750-060 after being received.
    a. Document a full description of the material including dosage and if additional bottle were received from the same material.
    b. Attach the balance strip if sample was weighted.
9. Store the controlled substance CII in the safe box when the receiving process is completed if the samples will not be used at the time.
    a. Store the material in an organize way.
    b. Label sample’s bag including logbook and page.
        - *The samples should be grouped by logbooks.*
        - *Each safe box division could be assigned to a specific logbook to make the searching process easily. Refer to figure 1 for a proposed layout.*
        - *One shelf could be dedicated to samples to be discarded (identified with a label).*
        - *The samples are stored in bags and a label identifying the logbook and page where the samples are documented is attached to the bag.*

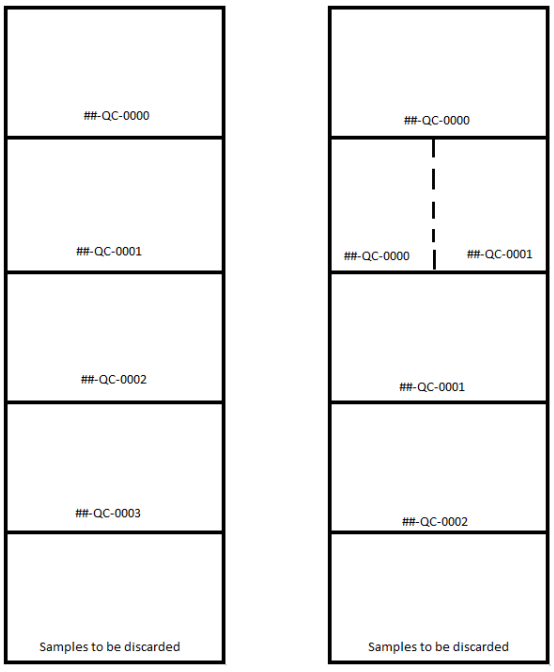

Figure 1
Proposed Layout for the Safe Box

Receiving Process for Substances CII under the Stability Program

1. Manufacturing and Packaging area notify in advance the date and time when the samples of the controlled substances CII will be delivered.
2. Coordinate with security and laboratory personnel before the receiving of the controlled substances CII.
3. The samples are received and stored in the corresponding stability chamber, which could be located on the Vindon Walking Chamber or room Q-29.
4. The quantity and documentation of the samples will be verified against the stability protocol.
5. Samples are segregated per quantities and conditions established in the stability protocol.
6. Form M750-450 is fill out by the stability personnel.
7. Samples are stored per each condition established in the protocol in the stability chambers.
8. Samples for the T-0 analysis are received by scientist following section E.
9. Follow SOP M700-118 "SQL LIMS Operational Procedure for SQL Stability Module", for the pull of the samples.
   a. Notify security in advanced to perform the pull of samples with the different conditions.
   b. Verify the samples pull with the stability protocol.
   c. The samples are received by a scientist following section E.

Use and Reconciliation Process

1. For reference standards:
   a. Ensure that the bottle tamper proof seal and the cap flip off have been removed (as applicable).
   b. Document in Form M750-339 the first weight of each bottle as Quantity Received.
2. For samples:
   a. Weight the container including the cap.
   b. Do not remove the seal, make a hole and make sure the seal does not rip off.
   c. Document in form M750-060 the weight obtained as Container Weight before Use.
3. Compare the weight before use with the previous weight.
   a. If discrepancy occurs, notify supervisors immediately.
4. Weight the amount of Controlled Substance CII to be used for the test.
   a. Document the weight obtained as Material Weight.
   b. Verify the difference with previous transaction and document the result in the reconciliation logbook.
   c. If a difference is observed, notify the QC supervisor or QC manager.
5. Weight the container including the cap.
   a. Document the weight obtained as Container Weight after Use.
6. Perform the reconciliation process after all samples has been weighted.
7. Determine the amount used as follows:

   Amount Used = (Container Weight before Use) – (Container Weight after Use) (1)

8. Reconcile the amount used after each transaction using the following formula:

   $$\text{Individual Reconciliation (\%)} = \left|\frac{\text{Amount Used} - \text{Material Weight}}{\text{Quantity Received}}\right| \times 100 \quad (2)$$

9. A second authorized person reviews this transaction.
10. After the sample has been approved:
    a. Determine the Final Amount Used once the material as follows:
    b. Final Amount Used = (Quantity Received) – (Total Amount Used)
    c. Total Amount Used = $\sum \text{Amount Used (all individual transactions)}$ (3)
11. Reconcile the final amount used using the following formula:

a. Final Reconciliation (%) = $\left|\frac{\text{Final Amount Used} - \text{Last Container Weight After Use}}{\text{Quantity Received}}\right| \times 100$ (4)

b. If a discrepancy is found during the reconciliation process, notify the QC supervisor.
   - *A person must be assigned to the final reconciliation task and another person must be assigned to the review. At least one backup must be assigned in case the dedicated person is not present or available.*
   - *The percent of reconciliation (0.1%) must be reconsidered for an increase (i.e. 0.2% or so). The DEA does not require a 0.1% of reconciliation.*
   - *Some products are known to be hygroscopic; extreme care must be taken when handling such samples given that water absorption could lead to reconciliation fail.*
   - *The laboratory has an acceptance criterion of 20 to 75% of humidity and 59 to 86° F; it is important to verify product storage recommendation to assure compliance.*
   - *"USP Controlled room temperature: The temperature maintained thermostatically that encompasses the usual and customary working environment of 20°–25° (68°–77° F). The following conditions also apply. Mean kinetic temperature not to exceed 25°. Excursions between 15° and 30° (59° and 86° F) that are experienced in pharmacies, hospitals, and warehouses, and during shipping are allowed. Provided the mean kinetic temperature does not exceed 25°, transient spikes up to 40° are permitted as long as they do not exceed 24 h. Spikes above 40° may be permitted only if the manufacturer so instructs" [5].*
   - *"USP Dry place: A place that does not exceed 40% average relative humidity at 20° (68° F) or the equivalent water vapor pressure at other temperatures. The determination may be made by direct measurement at the place. Determination is based on NLT 12 equally spaced measurements that encompass either a season, a year, or, where recorded data demonstrate, the storage period of the article. There may be values of up to 45% relative humidity provided that the average value does not exceed 40% relative humidity. Storage in a Container validated to protect the article from moisture vapor, including storage in bulk, is considered a Dry place"* [5].
   - *Humidity controls are vital to assure integrity of the samples. This type of material could be considered for a higher reconciliation percent or more strict controls for humidity must be placed.*
   - *Another recommendation is to weight those materials in a room where temperature and humidity are more controlled than the rest of the laboratory. For example, more strict parameters (i.e. humidity levels not exceeding 60%) and a balance could be place in the Q-5A room. All controlled samples can be weighted on that balance or at least the one with humidity problems.*
   - *The final reconciliation must be performed within 7 working days after the data is fully audited and no observation or DR is generated.*
   - *It was found that some sample bottles were overfilled. That practice leads to sample loss. Bottles for controlled*

samples must not be filled over the neck of the bottle to help avoid sample lost.

12. A second authorized person reviews this transaction.
13. When the samples or standards are ready to be discarded move the material to the shelf inside the safe box identified as "samples to be discarded".
    a. Do not remove the material from the safe until the final disposal.
    b. Refer to discard process section L.

Discarding Process

1. If a residue is generated as part of the analysis process, dissolve it and place it in the waste can (halogenated, non-halogenated, acid, base as applicable).
2. If a spill occurs:
    a. Notify the QC supervisor and QA Representative in Charge of Controlled Substances.
    b. Document the material loss in the reconciliation sheet with a sound/robust comment.
    c. The QC supervisor evaluates the event as per SOP C800-041 "Notificación de evento / Notification of Event".
        - *Spilled material during handling after the bottle has been weight and reconciled will be notify to the QC supervisor. Dissolve the material and place it in the water can. The sample will be weighted again, and a comment will be included explaining the situation and the reason to re-weight the sample.*
        - *Spills that occur before the bottle is weight; the QC supervisor will also be notified and will decide the process to follow. It is recommended to reconcile the bottle up to the previous test and request for a new sample to continue with the remaining tests.*
3. Before starting the final disposal process:
    a. Request to Manufacturing area for a tared container.
    b. Ensure that all samples to be discarded are reconcile.
    c. Coordinate with warehouse personnel to weight and receive the container.
    d. Coordinate with security personnel for escorting.
4. Follow SOP C800-011 "Manejo de Desperdicios y Sustancias Controladas y Químicos Listados".
5. Record in Form M750-153 the discarding process.
6. Assign a control number to each container following form C850-041 "Registro Emisión de "ID Envase" para el Envase de Sustancias Controladas y Químicos Listados para Destrucción".
7. Start filling the form C850-133 "Inventory Register Controlled Substances and Listed Chemicals for Destruction".
8. After all samples have been discarded, close the container and lock it.
    a. Document lock's number in form C850-133.
9. The container is transported escorted by a security guard and weighted in the warehouse or approved area.
    a. Include container weight in form C850-133.
10. The container is transferred to the warehouse's safe box.
11. Complete the form C850-133 and obtain a copy of the documents to keep record of the controlled substance waste.

Control Phase

Implementation of SOP M700-160 R.3

The SOP M700-160 R.2 was revised for improvement. The Improvement phase has the receiving, use and discarding process but the SOP was improved in other areas as well. Bullet points

written in italic are recommendations that could not be included in the revision because they need further evaluation but could be considered for future revisions.

Sections of the SOP were eliminated because they were not relevant to controlled II (CII) substances or were redundant. For example, section "Keys for the Room temperature-controlled substances wall cabinet" was eliminated because neither keys nor wall cabinet are used for controlled II substances. The section "Controlled Substances CII Storage was eliminated because appendix 3 and section "refrigerator and reach-in-stability chambers" already have the information.

The microbiology samples' receiving process was eliminated because even though it was written differently the receiving process is exactly as the other samples; therefore, one process was described for all samples. Other redundant and unnecessary information was eliminated, steps were re-arranged, and necessary information was added to improve SOP and comply with regulations. Refer to SOP M700-160 R.2 and R.3 attached to compare previous and current revision.

To make the SOP friendlier, paragraphs were changed to bullet points (in this case letters) or divided into steps. It is easier to read and understand instructions if they are written in bullets and multiple steps rather than paragraphs. People tend to avoid reading long boring paragraphs and the objective of the SOP is to be read by the person executing the task [6].

Training was given to the scientists. Important changes of the SOP were highlighted for their convenience. A quiz was given to all corresponding personnel before the implementation of the new revision. After obtaining more than 80% of personnel trained, the SOP was implemented on September 6, 2019.

CONCLUSION

The objective of the project was met given that the SOP was considerably improved. The process of substances CII from arriving to leaving the laboratory was well defined and explained. Key instructions and steps were added to indicate how to manage the samples and forms all the way.

The DMAIC tool helped the process of improving the SOP. The Analyze phase was the key to compare the current state of the process (current practices) with the current SOP and identify the gaps in it. There were steps that were being performed but were not included in the SOP, so they were included in the new revision because they were part of the process.

Additional recommendations were included in order to attend a problem regarding samples' reconciliation. Given that this revision was implemented with a SACAPA due date, there was a time limitation. For that reason, those recommendations will be evaluated for future revision given that some of them require change controls or more time to discuss it with the corresponding personnel.

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