# *Decommissioning of Retain Samples and GMP Documentation at a Manufacturing Site*

*Alex T. Higuera Santiesteban*
*Master in Manufacturing Competitiveness*
*Rafael Nieves, Pharm. D.*
*Industrial Engineering Department*
*Polytechnic University of Puerto Rico*

***Abstract*** *— During the past couple of years Elkay Corporation has been pushing to consolidate the product supply of its Hallo™ brands on a global scale. Elkay's Skin Care business which operates one of its plants in Puerto Rico, Elkay Corp., has decided to permanently seize operations of the Puerto Rico site effective June 2016. As a result of this business decision, the Elkay Corp. site has set a Decommissioning Plan which includes documentation and production sample transition to the production receiving site of San Diego, CA. This project will focus on the decommissioning of Retain Samples and GMP documentation, complying with Food and Drug Administration (FDA) and corporate guidelines. A focus on the DMADV (Define, Measure, Analyze, Design and Verify) tool for organizing and executing the project has been adopted. At the later stages of the project emphasis on results and next steps will provide a clear outlook on the remaining milestones not covered in the scope of this report.*

***Key Terms*** *— DMADV, FDA, GMP Documentation, Retain Samples.*

## PROBLEM STATEMENT

The current plan is to stop producing Hallo™ by November 2015, which will be carried over to the San Diego, CA site thru transfer validation commencing in August 2015 and culminating by October 2015.

As a result of this business decision, the Elkay Corp. site has set a Decommissioning Plan with includes documentation and production samples transition to the production receiving site of San Diego, CA.

In 2012 Elkay Corp. decided to invest in its Quality Assurance (QA) department therefore expanding its overall (QA) resources considerably. During this process, dedicated resources were assigned to exclusively manage the document center, an area thru which all filings passed thru before being stored in one of two documents retention rooms. In 2014 the decision to reduce operating cost drove all plant departments to consolidate roles and transition some positions into a forced separation from the company. QA's Information Management Team had then established a centralized inventory system for all document filing but was unable to make substantial headway. By the end of 2014 all departments and systems had gone back to their individual "tracking" systems that fit their needs.

In January 2015, news of plant closing was shared at a plant wide meeting. Beginning in June the Quality Assurance Department decided to start designing a plan to decommission and transfer all GMP documentation and retain samples to the production receiving site. Initial effort was placed on obtaining a general idea of what QA had stored in its retention system rooms throughout the site. This turned out to be everything from the first patent inscriptions and validations to employee records.

## RESEARCH DESCRIPTION

The project focuses on the implementation of DMADV to organize and execute the design of the decommissioning process. This involves defining steps, tasks and tracking progress to meet set goals while maintaining compliance.

The scope is contained in the period from June to September 2015 in which all of the planning has taken place and the bulk of the actual execution has been completed.

## RESEARCH OBJECTIVE

The following describe the objectives of this research work:

- Understand the scope of work;
- Define target dates that meet deadlines;
- Establish responsibilities and scheduling of resources;
- Revise procedures for compliance;
- Conclude with results that justify correct initial decisions.

## RESEARCH CONTRIBUTIONS

The success of delivering effective planning during this project will eliminate the need for third party support in handling samples and documentation. It will also establish a benchmark for future decommissioning processes at other sites and will help evaluate other in place retain sample and documentation systems from cost and resource avoidance if need be. This project may serve as a guide for the corporation in establishing structured decommissioning.

## LITERATURE REVIEW

CFR 211.170 specifies the reserve sample identification, quantity, and retention period based on manufacturing date and active ingredients in the formulation. The following information has been derived from 21 CFR 211.170 [1]. It states that samples need to be properly identified and "representative of each shipment". Differing to be more specific the term "shipment" may be considered ambiguous, and for this reason we will treat this statement as referring to "all batches", including raw materials, bulk production (intermediate) and finished product. The reserve sample needs to contain no less than twice the quantity needed to perform all tests that would determine compliance with specifications.

For the purpose of reader understating the different retention guidelines have been quoted from 21 CFR 211.170:

"For an active ingredient in a drug product other than those described in the reserve sample shall be retained for one year after the expiration date of the last lot of the drug product containing the active ingredient. For an active ingredient in a radioactive drug product, except for nonradioactive reagent kits, the reserve sample shall be retained for: Three months after the expiration date of the last lot of the drug product containing the active ingredient if the expiration dating period of the drug product is 30 days or less; or six months after the expiration date of the last lot of the drug product containing the active ingredient if the expiration dating period of the drug product is more than 30 days. For an active ingredient in an OTC drug product that is exempt from bearing an expiration date under 21 CFR 211.137 [1], the reserve sample shall be retained for 3 years after distribution of the last lot of the drug product containing the active ingredient.

An appropriately identified reserve sample that is representative of each lot or batch of drug product shall be retained and stored under conditions consistent with product labeling. The reserve sample shall be stored in the same immediate container-closure system in which the drug product is marketed or in one that has essentially the same characteristics. The reserve sample consists of at least twice the quantity necessary to perform all the required tests, except those for sterility and pyrogens. Reserve samples from representative sample lots or batches selected by acceptable statistical procedures shall be examined visually at least once a year for evidence of deterioration unless visual examination would affect the integrity of the reserve sample. Any evidence of reserve sample deterioration shall be investigated in accordance with 21 CFR 211.192 [1].

The results of the examination shall be recorded and maintained with other stability data on the drug product.

The retention time is as follows: For a drug product samples shall be retained for 1 year after the expiration date of the drug product." [1]

Current company policy on handling documentation covers both GMP regulated and those non regulated document as established in CFR 21 Section 211. Corporate document retention guides are referenced as to provide clearer understanding and in some cases a more strict retention period that those established in CRF 21.

The purpose of our procedure is to properly identify resources, classify documents and define retention periods and retain these until their destruction.

In order to standardize the system a series of forms were used to log all documents being filed on a daily basis which may include but is not limited to:

- Logbook for all temporary documents in the retention system.
- Logbook for all permanent documents in the retention system.
- Labeling formats and instructions for the above mentioned types of documents and their files.
- Retention period guide for all types of documents.
- Nomenclature to codify each sequenced box.

Once production and other GMP documents are delivered to the Information Management designee, Quality Assurance takes over the control of all documentation until their rendering which is coordinated by technical systems and overseen by a Qualified QA representative.

## METHODOLOGY

In choosing the correct methodology that would help us organize the various steps to a successful project, we evaluated Lean Six Sigma's tools and decided to compare the traditional DMAIC with DMADV. The first step of these two methods is the same "Define" and from this point forward they deviate. Below Table 1 has been included which simplifies the understanding of the methods.

**Table 1**
**DMADV vs. DMAIC Comparison [2]**

| | ***DMADV*** | ***DMAIC*** |
|---|---|---|
| *Define* | *Define project goals and outputs* | |
| *Measure* | *Measure to determine system needs* | *Measure current process performance* |
| *Analyze* | *Analyze to determine options in achieving systems goals* | *Analyze to determine root cause of performance issues* |
| ***Design*** | *Design the process to be used to meet the needs* | *N/A* |
| *Improve* | *N/A* | *Improve the system by eliminating defects* |
| ***Verify*** | *Verify the design performance and outputs to achieve the goal* | *N/A* |
| *Control* | *N/A* | *Control system performance* |

The table above shows that the DMADV methodology should be used when a new process or system development has to be implemented to meet a specific requirement. DMAIC is only to be used when an existing system or process is not performing up to its full potential and improvements need to be found.

DMADV will enable us to define and check the project and its systems thru its progress while verifying if the correct actions are being taken. Ideally once the "Analyze and Design" steps are completed there should be no readjusting, but some changes needed to occur to maintain the projected progress and even exceed the expectations.

**Define** - Most if not all projects start at this stage and this is no exception. The only way to have a successful outcome was to define what needed to be accomplished from day one. This means deciding how to manage all the information in to be generated for the existing retain samples and the documentation, both of which need to be organized in a manner that was easy to understand

by the initial resources at the site but also at the receiving site and under a possible FDA inspection.

**Measure** - Our measures are based on compliance with the defined methods and also with established dates given that phases and completion needed to happen with no exceptions. Measuring systems had to be in place to track progress and be able to move resources to support other areas that would collectively focus on the same goal.

**Analyze** - When looking at the various systems that had direct impact from the new methodology of the project, the first thing that came to mid was "procedures". In this and many industries SOP's are king. There is no other way to maintain consistency in the daily tasks or a way to prove that there is a standard that everyone follows. A total of three SOP's where identified to need a new revision that would mirror what the project would see as actual procedures.

**Design** - With a few constraints to contend with after the initial define phase, a new challenge arose. One would think that with all the technology available the process of obtaining all the data would be simple and quick, but no. The SAP reports were of little or no use when handling the retain sample inventory, and the historic document tracking found was in multiple files that made it difficult to transfer the data needed to new tracking systems.

**Verify** - Verifying the proper use of tools and progress became a daily task with this project. Thankfully the correct methods and tools were in place from the beginning and the constant verification was only a secondary and avoidance decision to what we had planned.

## RESULTS AND DISCUSSION

In this section the Planning and Design of the study are presented.

### Teams

Given the scope of the project, in this section we will discuss the structure design implemented to maximize resources. Upon initial assessment the magnitude of what needed to be achieved was not very clear. In the area of samples a crude but compliant inventory system had been in place for years and a good understanding of work load was rapidly available. On the other hand GMP documentation and documents in general had been archived with no reliable system to decommission these on a regular basis, while maintaining the inventory fresh and current.

Teams had to be created to delegate and maintain accountability for thru progress and completion of the phases. Below we will outline the various systems defined in the scope and how teams were created to maintain constant progress for delivering results. In total we assigned ten department teams and subcategorized into twenty one subsystems. Of the twenty one subsystems twenty were strictly dedicated to GMP documentation with one remaining to process decommission and transfer of retention samples.

On logical ground, and as expected by any regulated industry operation the vast majority of the responsibility lied on Quality Assurance. The only subsystems that were delegated to resources outside of the QA organization where Engineering Documents, Human Resources and Warehouse (Shipping and Receiving).

### Scheduling

Given the limitations of the current operation model and staffing requirements, it is expected not to be able to assign all resources to the decommission project. Initial efforts to avoid micro managing the proved unreliable and a series of schedules were designed to deploy personnel from several QA areas and discussion was incorporated during all morning meeting ensuring scheduling was being followed.

Due to the 4000 + stored boxes of retain samples, priority was given to this system. Therefore the schedule was designed to include from two to three people per shift. First shift ranged from 8am to 12pm and second shift from 1230pm to 430pm. Most of the resources assigned to the retain sample system where "offline" or non-operations direct reports that had the flexibility to

comply with this program. On occasion a third person was assigned to either catch up on previous days limitations or to exceed weekly goals of 10 pallets or 420 boxes.

**Table 2**

**Department and Subsystem**

| Department | Subsystem |
|---|---|
| Human Resources | Analytical Laboratory |
| Information Technology | Annual Product Reviews |
| Logistics | Change Control Management |
| Making Operations | Cleaning and Sanitization Records |
| Packing Operations | Engineering Documents |
| Quality Assurance | FDA Audit Files |
| Quality Control | Human Resources |
| Technical Systems | Improvement Program Files |
| Utilities | Microbiology Laboratory |
| Warehouse | Mock Retrievals |
| | Non-Conforming |
| | Operations (Utilities, Making, Packing, PM, Calibrations, AM) |
| | Operations Logbooks |
| | Product Stability Record |
| | QA Compliance |
| | Release records for bulk and finished products |
| | Retain Samples (Bulk, Raw Material, Finished Products |
| | SOP Standard Operating Procedures |
| | Training Records |
| | Validation Files |
| | Warehouse Documents |

## Define

- **Box Codes (Before and after)**

To find solutions to the issue with current labeling and the business need a new labeling system had to be devised.

- **Documentation**

Labeling of all documentation boxes at a site level was preceded by the same alpha nomenclature and only the following four digits differed from the rest. For example, when visiting document retention areas one noticed that all box codes were "QA-XXXX" (QA=Quality Assurance, X=#) without discriminating from one or another department or subsystem.

The main concern with this method is that for one the receiving site will be receiving thousands of boxes full of different types of documents and quick distinction of system would be impossible.

The solution consensus was to re-label all documentation boxes with codes that made more sense and avoided confusion for us during the inventory process and for the receiving site. In addition with a quick glance one could easily determine the system contents and sequence each box followed.

Given that all departments were divided into twenty one subsystems, the same amount of label types where designed. With this not only each subsystem had unique labels and sequence but also a color coding variable was added to further assist in rapid identification.

## Measure

In this section we will discuss the tracking system designed to gather all the information needed for a proper retain sample and GMP documentation inventory system.

As mentioned earlier during the team discussion a series of twenty one subsystems had been categorized in order to organize the scope per department. As a result of this a single prototype excel tracker was designed with the capacity to handle all the possible variables considering all possible combinations of documents and samples to be inventoried. After sharing this master tracker to all the department leaders and including their feedback we went ahead to duplicate this excel sheet into the subsystems. This allowed all departments to assign a single resource to their applicable subsystem and work in parallel with the other twenty subsystem trackers in the data entry task. At the end we had thousands of data entries scattered thru all the excel trackers that were processing information at the same time.

## Analyze

Because both the retain sample system and document retention guidelines are referenced in various SOPs, it was necessary to determine how the current procedure fit into the business need. Three main SOPs were identified as those in needs of a revision in order to establish the new procedures that serve as enablers. These changes created a backbone for process uniformity and compliance in having written procedures as established in Sec. 211.100 Written procedures; deviations.

- **013 Retain Samples**

This Standard Operating Procedure (SOP) outlined the requirements for retaining Raw Materials, Bulks and Finished Products. This SOP is not only designed to assure compliance with corporate requirements but also with applicable current Good Manufacturing Practices (cGMPs) as described above.

- **60 Document Retention Periods**

The greatest procedure impacts where seen in the SOP for handling documentation. This SOP defines the process to follow for the retention of all documentation in or site as established by CFR Title 21, Section 211 of the Current Good Manufacturing Practices (cGMP's) and corporate requirements. This procedure covers the retention of all documents until their destruction.

- **90 Laboratory Samples**

Although all samples originate from the operation being it, Sampling Area for Raw Materials, Making for bulk product or Packing for the finished product sample, it is the Analytical Laboratory who prepares these to the Sample Retention System.

This SOP instructs on the procedure to receive and test raw materials, in-process and finished product samples for the site thru the Analytical Laboratory in compliance with the Current Good Manufacturing Practices (cGMP) established in the 21CFR section 210 & 211. [1]

## Design

During the initial retain system assessment for decommissioning, the possibility of using data entered in SAP (Systems, Applications & Products in Data Processing) was considered to be the fastest method. For each type of sample (Raw Material, Bulk and Finished Product) and their batch number a series of inspections or files area created in SAP. Two particular entries of interest are that of "Box #" and "Retain Samples Amount" which the Analytical Technician testing the product enters results values. When looking at the parameters set for retain samples amount, there was no issue, being that two digits in the actual result entry would be consistent with the specification in that characteristic. The next result need, "Box #", was not obtainable in a report form. Unfortunately the only way to assure accuracy in our inventory and provide transfer lists to the receiving site was to manually open each box and enter data in a excel file.

## Verify

This section discusses the importance of proper project planning to obtain the proposed results. Since we did not have a benchmark reference to use in order to design this project the safest manner to achieve our goals was to work in phases that could quickly build up the capability and enable the decommissioning team with problem solving opportunity. During the "Planning and Setup" phase key steps were identified to build a robust work system which eliminated the end of month syndrome. First on the list was to discuss and design what needed to be achieved, who were the resources and set goals to have all sample and document backlog transferred before November 23rd, 2015. Then a series of tasks from relocating people to preparing layouts and network connections in designated workstations needed to be in place before any work could begin, some of which required change control approval. Almost in parallel a tracking phase was initiated, and soon after a progress measure phase which complied

with the set goals of transferring our samples and documents.

## CONCLUSION

Quality Assurance managed the retain sample decommissioning project with a 37% decrease in personnel, and the results showed commitment. Retain Samples inventory included more than 3,300 boxes that had to be manually documented before October 31st, 2015; these where completed 6 weeks ahead of schedule during the week of September 8th. As seen during the month of July the goal set for this month was not reached. Considering this as a ramp up period subsequent periods exceeded all set goals almost 200%. Retain Sample wave fulfillments are based on number of pallets per shipping container. To reduce the possibility of crushing or damaging the samples, no double stacking of pallets was allowed during transport. A 40 foot container holds a total of 22 pallets with approximately 930 boxes of retain samples. A total of 3.6 containers worth of retain samples were ready for shipping by September 8th.

Documentation progress was slower given that system owners were scheduled to work on the retention sample effort before being able to dedicate full time to their own documents. As of the second week of September all schedules were being managed by the individual department leaders and to date documents are also on track.

## REFERENCES


[1] FDA. (2015, April). *Title 21* (Version 4) [Online]. Available: http://www.accessdata.fda.gov/ scripts/ cdrh/ cfdocs/ cfcfr/ CFRSearch.cfm?fr=211

[2] I Six Sigma. (2015). *DMAIC versus DMADV* [Online]. Available: http://www.isixsigma.com/new-to-six-sigma/ design-for-six-sigma-dfss/dmaic-versus-dmadv/.