Evaluation of Reagents Used in Solution Preparation to Reduce Reworks in Research and Development Laboratories

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Abstract — *Research and development laboratories are working with improvements and discovery of new drugs. As part of their activities, they need solutions such as Buffers and Mobile Phases for analytical testing. It was found that a main reason that increase rework in solutions preparations is the unavailability of reagents. Looking for reagents for solution preparation with the correct purity grade and specifications is the main goal they face. Evaluating reagents, purchasing and establishing a tool for reagent reorder will reduce significantly rework and waste generated due to incorrect reagent used.*

Key Words — *Purity Grade, Reagent Inventory, Solution Preparation, Waste Reduction.*

INTRODUCTION

The pharmaceutical industry consists of Manufacturing areas, Quality Control laboratories and Research and Development laboratories. Manufacturing areas are focused on the execution of procedures regulated by the Food and Drug Administration (FDA) for manufacture of pharmaceutical drugs or medical devices.

Quality control areas aims for lot release before those pharmaceutical drugs are delivered to the markets. This includes the execution of procedures to analyze samples and determine whether they meet the acceptance criteria

On the other part, there are the Research and Development laboratories focused on process improvements with execution of analytical testing. This research is specified on this kind of laboratories.

Research and development can be considered a less risk environment because they are not involved in the manufacturing of a drug or releasing lots, but they are key in any improvement suggested for the manufacturing.

Pharmaceutical industries are regulated by 21 CFR Part 210 and 21 CFR Part 211 which focuses on quality.

PROBLEM STATEMENT

Research and development laboratories in the pharmaceutical industry are looking for improvements in drug manufacturing. As part of these laboratories, a preparation area is committed to the preparation of solutions such as Mobile Phases and Buffers for different testing. A main goal they face is the unavailability of reagents used in the preparation of solutions. Sometimes they need to use a specific reagent for each preparation and the reagent available do not meet the requirements needed by the procedure. The availability of each reagent is difficult if there is no way to track which reagent is needed versus which reagent is available. It is time consuming to investigate and look which equivalent reagent can be used in substitution of unavailable reagent. Sometimes there is no equivalent reagent and the user needs to purchase the reagent and wait for arrival in order to complete a request.

Research Description

This project is intended to evaluate the available and unavailable reagents used for Mobile Phases and Buffer preparations, to purchase and establish a system that help identify when a needed reagent is missing or need to be reordered. Looking for equivalent reagents can be time consuming because the user needs to evaluate certificate of analysis of each reagent and confirm with the end user if the

reagent can be used in the specific preparation. A wrong reagent can be selected for preparation after evaluating as possible equivalent and this led to a reworked prepared solution or failure in testing if used.

Research Objectives

For this project, there are four main objectives:
- Identification of most used reagents for solution preparation to add to main inventory if possible
- Purchase of identified missing reagents
- Look for storage for purchased reagents
- Evaluate a tool for miscellaneous reagent reorder to avoid unavailability.

Research Contributions

With this project Preparation area in Research and Development laboratories will be able to increase productivity of the employees in the work scenario while reducing waste generated due to the reworked prepared solutions.

LITERATURE REVIEW

Research and Development Laboratories may have electronic systems to keep traceability of purchased reagents, in terms of original quantity and expiration date but not necessarily take in consideration reagent reorder. Reorder is only included for those reagents in the main inventory, but miscellaneous regents needs to be purchased prior to use or when identified missing.

A rework means a solution preparation that failed a criterion from the procedure. There are some sources or error that could led to a rework including weighing, documentation, glassware or reagent which is the focus of this investigation.

Reworked solution preparation due to the use of incorrect reagent (incorrect purity grade) increase the waste generated on the facilities in terms of reagent consumption (large quantity of reagent or solution to dispose). Analyzing those possible miscellaneous reagents to be used and purchased them before preparation request while working with an assessment of frequency of use will help with the

reduction of waste generated due to expiration or incorrect preparation. The cost of an unnecessary, unused inventory is not only the purchase price of the reagent, it is also the cost of looking for necessary storage space, a cost which itself is not limited to purchase cost [1]. The available storage is an important part to take in consideration when evaluating reagents to be purchased. If the laboratories do not have enough available storage for reagents, miscellaneous materials cannot be purchased and stored.

Reagents are specified to have different purity grades. There are international standards for purity such as ACS Grade (American Chemical Society), USP Grade, (United States Pharmacopeia), Laboratory Grade among others. Each standard specifies the purity of each reagent in terms of assays performed looking for impurities. In the laboratories it is important to have available reagents with the purity grade intended for each experiment or assay. The designation of a substance as experimental material ("research grade") makes it clear that it differs from material intended for human use ("pharmaceutical grade") [2].

Inventory management systems provide the tracking of purchased reagents from receiving to consumption. Inventory systems do not include the 100% of reagents used in the Research and Development laboratories and this represents a risk in terms of workload because unavailability of reagent can lead to stop one or more processes (this can be hazardous for the operations).

METHODOLOGY

Various business management strategies have been developed to improve the performance of organizations by improving the processes by which they carry out their work [3]. Those strategies include Lean and Six Sigma for process improvements with a set of principles and practices to obtain high efficiency and reduce waste.

Six Sigma is a data driven statistical approach, embedded in managerial philosophies, that focus on reducing the process variations and improving the

bottom line of the process [4]. The first applications of Six Sigma were projects based on the manufacturing sector; later on it was diversified to other sectors and other objectives.

One Six Sigma methodology is the DMAIC model. DMAIC is a linear scheme of quality improvement summarized in five phases: Define, Measure, Analyze, Improve, and Control. The DMAIC model plan to improve, optimize, or stabilize an existing process with the detection and removal of defects or inefficiencies in the process [4].

Define: A problem is identified and needs to be attended for the improvement in the process.

Measure: This phase, includes the understanding of situations over the problem specified in the Define phase and actual processes are measured to identify how they can be improved.

Analyze: During this phase, the measurement and data collected in the previous phase is analyzed and used to determine the root cause of the problem stated.

Improve: Action is taken to solve the problem for the process improvement

Control: This phase is focused on keeping traceability that the problem is solved, and preventive actions are taken to avoid repeatability of the issue.

RESULTS AND DISCUSSION

For the executed assessment and the DMAIC model performed these are the results found:

Define Phase

Analyzed data have shown different factors that resulted in rework for solutions preparations. Those factors include Weighing, Documentation, Glassware and Reagents. These four factors are considered as human or technical errors. Figure 1 shows a fishbone that help determine that the main contributor for reworks in solution preparation is the reagents due to different reasons. That's why this project is focus on evaluation of available and unavailable reagents.

The evaluation of available or unavailable reagents contribute to the analysis of waste generated by reworked solution preparation. A complete analysis of solutions prepared, and reagents used on preparations was performed, capturing large quantity of waste generated due to the use of incorrect reagent in terms of purity grade. Another factor that impact the quantity of reworks is the unavailability of reagents as needed.
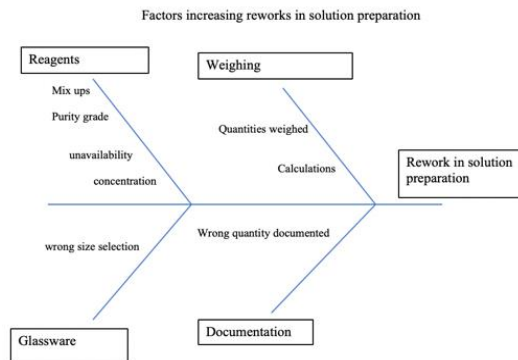
Figure 1
Fishbone of Factors that Increase Rework

Measure Phase

Actual processes include the use of available reagent for each preparation after search over the laboratories. Most consumed reagents have been evaluated and determine whether they need to be part of an inventory with reorder program. From a list of 35 evaluated reagents, only 8 reagents can be added to the main inventory due to the high use. The other 27 reagents need to be purchased by the user and look for storage and label them.

Figure 2
USP Grade Reagent [5]

Figure 3
ACS Grade Reagent [6]

Figure 2 shows a Sodium Phosphate Monobasic reagent that meets USP grade specifications, while in Figure 3 it can be seen Sodium Phosphate monobasic that meets ACS grade specifications. If those two reagents were available, the one specified by the procedure is the one that will be used. But if the only reagent available is the one that meets USP grade specification and it was used, it is probable that it results in a reworked preparation because both reagents presented here are not equivalents in terms of purity and in terms of composition.

Analyze Phase

The 100% of reworked preparations was due to the use of wrong reagent. As shown in Figure 4, a 29% percent of rework was due to the use of incorrect reagent purchased by the end user (similar name but different concentration), and 71% was reworked due to use of incorrect purity grade. Some reagents found on the inventory with a specific purity grade are less used than reagents with a better purity grade.
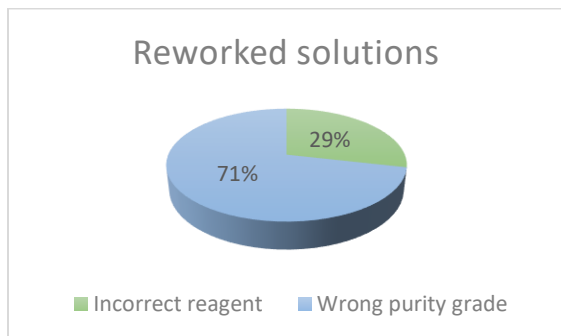
Figure 4
Reworked Solutions over a Period of Two Months

Improve Phase

Reagents were evaluated over two laboratories to analyze the most used and identify which of them can be added to the reagent inventory. It was found that commonly used reagents on current month are not necessarily the reagents needed on the next month. That's why those miscellaneous reagents cannot be added to the current inventory as mentioned in the Measure Phase. Those reagents need to be purchased by the end user or purchased by the people that prepare the solutions.

For those miscellaneous reagents not commonly used the form showed in Figure 5 which contains the data needed for the purchase of reagents and will be used for evaluation of use to keep visual record with a label similar to that shown in Figure 6.

Figure 5
Form used to keep Traceability of Miscellaneous Reagents

Figure 6
Label for Purchased Reagents

Control Phase

Miscellaneous reagents were purchased and physically located in the laboratory of preparation, labelled and segregated according to the available space for storage. A tool for track these miscellaneous reagents to avoid unavailability, includes a Spreadsheet with the main information of each reagent, physical location and the execution of an internal audit monthly for determination of reorder. This part of the process is not implemented because it requires user orientation and determination of how the task is going to be executed between the locations. Special attention is needed to those miscellaneous reagent consumptions to

evaluate if the basis of the internal audit needs to be changed.
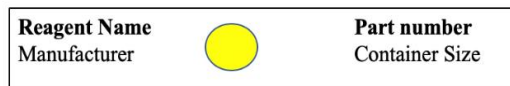
Figure 7
Label with Visual Aid for Miscellaneous Reagents

Figure 7 shows the proposed label for those miscellaneous reagents. This kind of label will include a yellow dot in the middle or at any side to help visual identification of those reagents that would be part of the internal audit for reorder evaluation. The proposed checklist for the monthly internal audit can be seen in Figure 8.

Date & Time	Auditor List	Auditee List
Checklist points	Observations	Status
1. Is reagent in the corresponding location?		
2. The container have a good physical appearance?		
3. The container seems heavy?		
4. Reagent needs to be reordered?		
Auditor Signature:	Auditee Signature:	

Figure 8
Proposed Checklist for the Internal Audit

CONCLUSION

Reagents identified as miscellaneous cannot be part of the main inventory due to the low frequency of use. Evaluating those miscellaneous reagents with the tool presented over this assessment can reduce or eliminate the reworked solution preparation, reduce the waste generated in the areas and higher up the productivity of those preparing the solutions. For the pharmaceutical industry area, implementation of a tool requires full evaluation of different departments. As proposed on this project it will be given for evaluation in order to improve the productivity in the specified area. It was hard work to get implementation of this assessment because there are few variables that need to be evaluated individually in order to improve the actual process in the Research and Development laboratories.

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