Risk Prevention in Syringe Filling Line in a Pharmaceutical Manufacturing Plant

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Abstract *— Risk prevention in syringe filling line can be achieved through the implementation of "Defense in Depth" concepts. Defense in Depth is based on the integration of 3-layers of operational controls which are Equipment, Procedure, and Well-Trained Staff. This project will be conducted through all stages of a syringe filling process area in a pharmaceutical company. The objective of this project is to mitigate critical errors and threat to operations through the establishment of the Defense in Depth and thus avoiding costly errors. This project has three main contributions which include evaluating the current state of control of Critical Process Parameters, providing an assessment of the current operational states, and lastly setting the expectation that all future modification to equipment, procedures or staff qualification should consult the methodology to ensure continuous improvement. Through Defense in Depth, this company was able to identify and strengthen vulnerable and high risk areas in a syringe filling line.*

Key Terms *— CAP Analysis, Defense in Depth, FMEA, Risk Assessment.*

INTRODUCTION

To fully apply Defense in Depth on all three layers of operational controls, several (3) methodologies were applied to the separate layers. This allows the evaluation to be focused primarily on the impact that equipment, method design, and staff performance have on product and process attributes.

Risk Assessment Methodology

The Risk Assessment Methodology will identify risks to process and product, identify controls to mitigate or monitor the risks, verify the adequacy and accuracy of those controls and identify gaps or unacceptable risks that need to be mitigated. Additionally, the methodology provides for opportunities to identify potential improvement recommendations to controls used to address risks.

Risk is an event that, if it occurs, adversely affects the ability of an engineering system project to achieve its outcome objectives [1]. The Risk

Assessment Methodology consists of four phases: establishing the requirements; evaluating the equipment and procedures and identifying its risks; determining and verifying controls that address risks; and a gap assessment.

The process sequentially addresses four major phases in the evaluation (Figure 1).

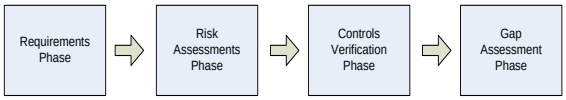

Figure 1
Four major phases of Risk Assessment Methodology

The output of the process is a list of controls consisting of Machine, Method or Manpower that are used to manage/mitigate risks to the process and critical quality attributes of product. Throughout the process it is also expected that gaps or opportunities will be identified to enhance/improve a control to better manage a risk. It is expected that the equipment and procedure assessment process will be cyclic in the three layers of DiD as Machine controls may require Method improvements that may drive Manpower changes that may drive machine improvements and so on as the process is refined.

The diagram below shows in greater detail, the activities and linkages for each of the four phases of the Risk Assessment Methodology (Figure 2).

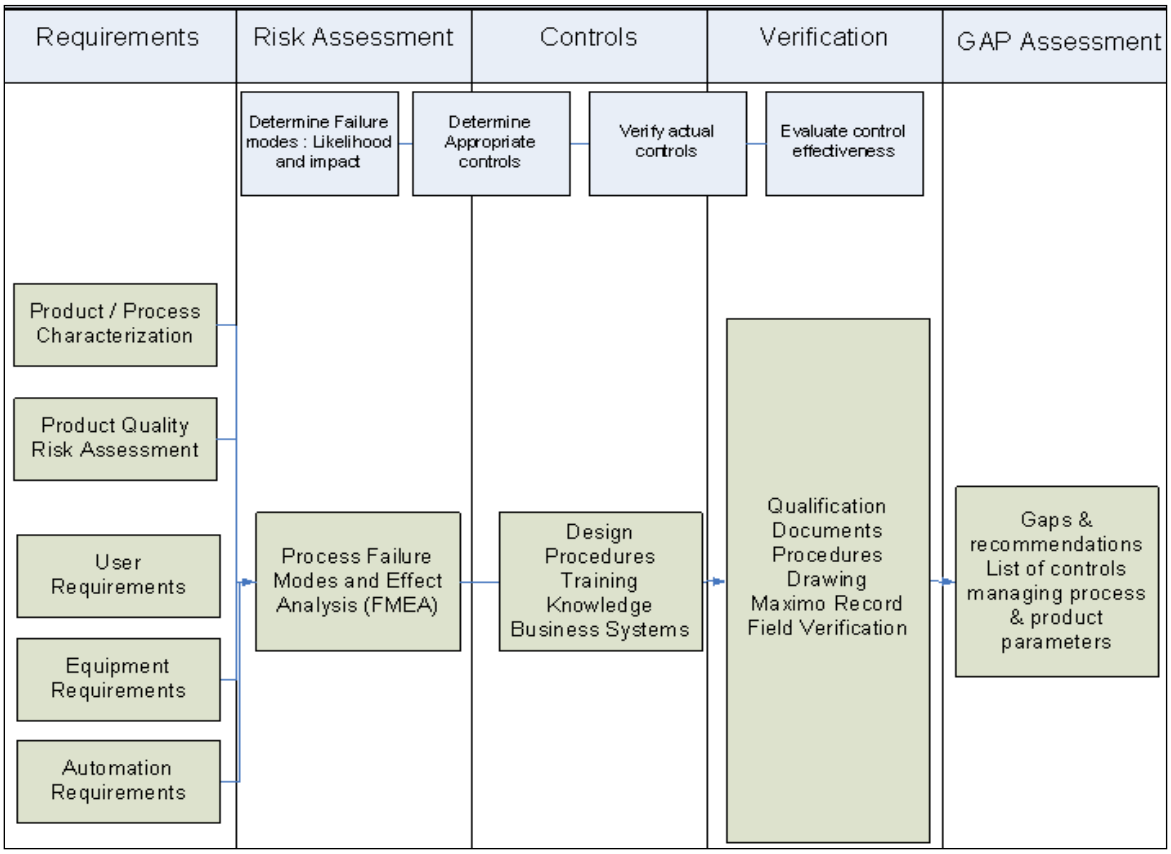

Figure 2
Equipment Evaluation Process for Proof of Concept

The scope of the Requirement Phase is to identify the requirements for the equipment, the staff and the product it processes. The deliverable is a document that compiles and defines the requirements flowing from the Product Quality Risk Assessment.

The purpose of the document is to provide the requirements for a given piece of equipment or procedure to the team. This way, the level of risk can be determined from a failure mode analysis. It should identify what is key to ensure patient safety, followed by potential business risk.

When compiling the list of requirements the team must be aware that the sources of requirements are varied and plentiful. These sources include the product and procedure, the equipment, the automation and instrumentation, the quality or regulatory, and the user and its health as well as any Environmental Health and Safety (EHS) requirements. The requirements for the product and the procedure are considered the most important because these directly affect the end product and can cause critical losses.

The primary focus of the Risk Assessment Phase is to understand the risks to product quality attributes that could result from equipment performance and its operation. This will occur through an integrated evaluation of Machine, Methods and Manpower. Therefore the primary risk evaluation step is to perform an assessment to identify risks to achieving the process/product requirements. This will be performed using the Process Failure Modes and Effects Analysis (pFMEA).

The controls verification phase is an activity performed by the varying disciplines associated with the risk assessment or pFMEA. The pFMEA identifies the controls as Machine, Method or

Manpower. The controls verification confirms those controls through review of Objective Quality Evidence (OQE) to include SOPs, Maximo, Automation, etc. The scope of this phase is to identify existing controls that address the risks identified in the Risk Assessment phase. During the Control and Verification phase the actual controls identified established to either mitigate or eliminate the risks are reviewed

The purpose of the control and verification phase is to ensure the control measures identified by the site or facilities to address the risks from the Risk Assessment are in place.

The combined output of the Requirements Phase, Risk Assessment Phase and Controls Verification Phase is a Gap Assessment document in the form of a pFMEA. It is important to understand that the overall risk score for a single unit operation/sub-system may be high or severe but the overall risk of the process or integrated unit operations is moderate or low as a result of a subsequent verification or control step.

Standard Operating Procedure (SOP) Development

Standard Operating Procedures (SOPs) provide detailed instructions for properly executing tasks. In order to set operators up for success, procedures must be simple and well written with a focus on required steps of execution.

SOP development is a staged process that is expected to evolve with experience. The procedure workstream is one that overlaps both other workstreams while following its staged process as is evident in Figure 3.

The output of this layer is a simple, operator friendly set of execution steps that can be performed as written without workarounds. This effort is centered on understanding the current state of procedures as they relate to task execution.

There are three main elements to consider in defining which SOPs are impacted for DiD revision. The first is any SOP that is identified as requiring update to close a gap identified for a critical control. Secondly, SOPs that were identified to contain critical controls as already in place where those instructions need to be controlled so as to not be removed. Thirdly, any SOP that is required to be updated for inclusion of alarm response instructions.

The instruction set needs to be developed in context of criticality to process and risk of failure. It is important to consider the need for current controls in order to determine the level of instruction that is needed for a given step in the operation. Instructions should include proceduralizing the response to failure risks identified in the equipment evaluation.

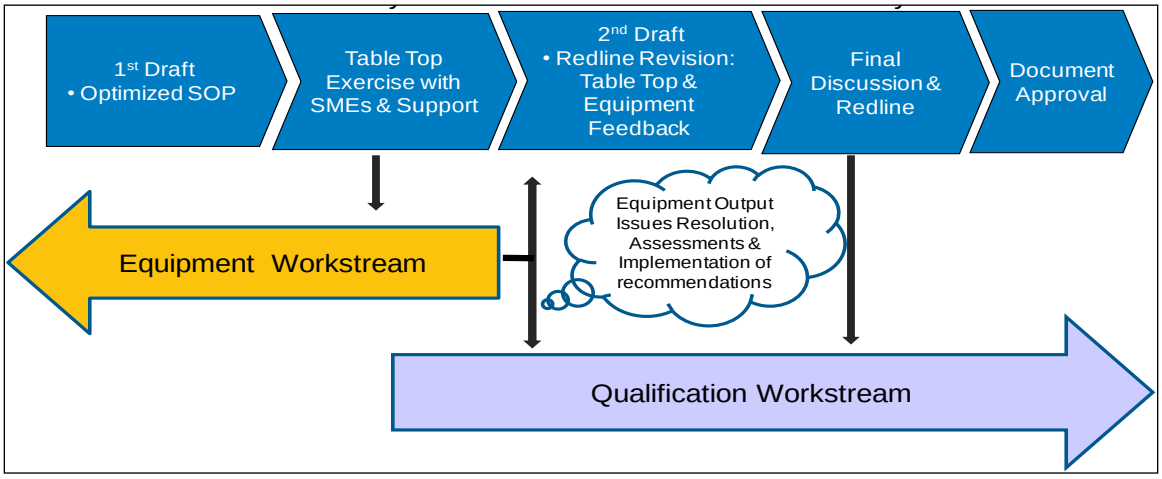

Figure 3
Procedures Workstream

Well Trained High-Performing Staff

A systematic approach to training named ADDIE was implemented in the third layer of DiD. Each successive initial represents the steps of analysis, design, development, implementation, and evaluation. Rigorous adherence to the principles underlying these five steps is an effective one common model path for developing instruction in any context [2].

A Pre-project phase for the ADDIE methodology typically begins with the perception that training may be needed for one or more staff members. There are several triggers to this perception, including:

- New equipment, product, or process;
- SOP revisions;
- Risk Assessments Analyses;
- Staffing or job changes.

Activities in the Analysis phase produce a Training Needs Assessment, which should identify:

- The desired outcome and scope of the qualification model;
- Defining between skill, rule or knowledge based performance;
- Critical task identification;
- Understanding of process flow and vulnerabilities;
- Responses to normal and abnormal conditions to incorporate in qualification process.

The Design Phase produces the learning architecture for the training materials that will subsequently be built. In this phase, the task requirements are transformed into learning objectives. Then a decision is made on the optimum way of testing for learning objective mastery, either live or simulated and these may be performed, written or oral.

The Development phase of the approach creates the learning materials, any associated examination materials, evaluation materials. It includes the review of all materials by SMEs and approval of materials by a Line Management owner. It also includes the piloting of materials prior to publishing.

For Critical Tasks, it is important to have an objective evaluation of learning objective attainment by the most experienced group of job incumbents. Designated trainers will be involved in the qualification of trainees as well as the proficiency checks and requalification activities associated with critical tasks. The Evaluator then conducts an objective performance and knowledge evaluation without coaching the trainee. Evaluators are individuals who should be considered to be task experts and proficient in its performance. After the trainees perform the live or simulated tasks the evaluators compare that to the objectives, provide feedback and recommend the best course of action.

The sustainment of a well-trained and ready workforce is dependent upon careful application of two elements, proficiency and requalification.

Proficiency is a measure of task fluency and expertise; records should be kept on logs. Full requalification will be necessary, using the same process as required for initial qualification, prior to expiration. An internal log is important to notify staff members of approaching expiration of past qualifications.

Managers should include periodic checks of training proficiency on the floor. At a minimum, this should include observation of tasks being performed. Periodic questioning of knowledge components may also be done, but should not pose a distraction to the individual performing the task.

METHODOLOGY

By applying three separate methodologies on the several layers of DiD various different tasks must be performed. These tasks are not completely separate as they work together as a system being directed by each other.

Requirements Phase

First, the team will confirm the standard or known requirements that are applicable for the type of equipment and/or procedure and the product

processed e.g. temperature, UV degradation, shear sensitivity, particulates and time. The team will ensure that they identify the requirements for each item.

Next, the team will identify the types of requirements and potential sources for these requirements. In all cases, one would start with any existing User Requirements Specification documents (URS). Product specific requirements may exist in characterization or other process development documents. The intent in this phase is for an evaluation team to extract the requirements from many sources and compile and categorize them in a single document.

Risk Assessments Phase

The Risk Owner and the Risk Assessment Facilitator shall work with Subject Matter Experts (SMEs) to understand and identify potential failure modes and pre-populate the pFMEA worksheet. In order to achieve this, the team shall follow the outlined steps:

1. The Risk Assessment Owner shall coordinate the risk assessment meeting to describe the purpose and process.
2. The team should visit the equipment/system and witness its operation
3. The team shall then review the draft pFMEA worksheet and work to develop the sheet until it contains all the potential failure modes the team can identify.
4. Using the process flow diagram, for each step in the process flow, identify potential failure modes. A cause-and-effect diagram would be helpful in making sure all potential failure modes related to machine, method, man, material, etc. are identified for each process step.
5. After all effects are identified and captured, the team can, for each effect under a failure mode, assign severity scores based on the definitions.
6. Determine and capture the causes of the potential failure modes. When there are several causes of failure for a failure mode, capture each cause separately.
7. Use available equipment reliability data, data from Computerized Maintenance Management Systems (CMMS) or supplier meantime between failures (MTBF) and/or process SME expertise/experience to estimate the occurrence rating for the potential failure mode or cause of the failure mode.
8. Rate failure detection based on the likelihood that the current controls will detect the cause/mechanism of failure or the failure mode itself using the detection rating scale.
9. Using the rating evaluation criteria determine the risk level of the identified potential failure mode. During the risk assessment it is an opportunistic time to capture potential recommendations to mitigate high and medium risks

Control Verification Phase

The primary focus of the legacy equipment evaluation is to understand the controls identified and instituted to address risks to process and product. The verification performed will confirm that the identified controls are actually in place. There are many controls available to a site or facility including instruments, equipment procedures, alarms and indications, operator actions and business systems. There are several means to verify the controls identified and include reviewing qualification documents, procedures (SOPs and MPs), review of drawings (GA, P&IDs, schematics) and automation systems (PCS, PLC, BMS) looking for alarms and interlocks as well as reporting and archiving features, actual field verification as well as review of the company's business systems.

Gap Assessment Phase

These documents will be used to re-evaluate the risk scores identified in the Risk Assessment Phase with possible recommendations for improvements to mitigate or reduce the current risk scores. Reviewing and reporting of risk assessment and tracking of risk mitigations will be done consistent with the plant's SOPs.

Standard Operating Procedures Methodology

SOPs should focus on 'what' to do to perform a step in the operation. Instructions that describe 'why' to perform and action are better suited to be included in training documentation rather than the SOP. Instructions that describe 'how' to do something need to be evaluated to determine if there is a training opportunity, an engineering improvement opportunity or if the 'how' is a necessary part of the instruction.

Well Trained High Performing Staff

The methodology for staff training which will be followed is the ADDIE Methodology as stated in the literature review chapter. In the Pre-project phase we identify what triggered the need for training. In the Analysis phase we identify the critical tasks and the desired outcome, keeping in mind that normal and abnormal process must be pointed out. In the Design phase the task requirements are transformed into learning objectives, these include the performance and the knowledge of the task. During this phase the optimum way to train and test are selected. The Development phase creates the learning materials, any associated examination/evaluation materials; and it also reviews all the material produced by the SMEs. In the Implementation phase Trainers are responsible for the conduct of the trainees that are preparing for qualification. In the Evaluation phase the Evaluator is responsible for objectively assessing the trainee's mastery of the learning objectives. In the last phase which is the Sustainment phase, proficiency and requalification are kept by the continuous use of proficiency checks and periodic questioning of knowledge; this information must be kept on records.

RESULTS AND DISCUSSION

For each of the three different areas of the Defense in Depth, a project charter was made defining the members of each workstream. These three workstreams were Equipment, SOP, and Qualifications.

Equipment Assessment (ERA/FMEA)

While going through the four phases of the Risk Assessment Methodology (Requirements, Risk Assessment, Control Verification, and Gap Assessment) the output obtained was a list of controls consisting of Machine, Method, and Manpower (Table 1). Through the use of this list, risks were identified to manage or mitigate critical processes. The output from the analysis of the equipment workstream, was used as an input for the other two workstreams that compose the three layers of DiD.

SOP Workstream

Based on the results of the ERA (Table 1), five (5) SOP procedures were changed or created to incorporate recommendations. These SOPs include equipment procedures such as Filler Machine and the Stopper Placement Unit (SPU). Also, procedures for setup, material, process flow, in-process check, and equipment assembly were impacted by these changes.

Qualification Workstream

A task analysis was performed to define the critical tasks in which the operator was trained and under which training method. In order to make this task analysis, an evaluation matrix was created to determine the criticality of each task. Refer to the following table (Table 2) for an example of task criticality for the SPU Machine.

Task Criticality Analysis refers to how critical is the task to the effectiveness of the process examined. It's assessed in regards to the impact of errors and/or associated risks to the process. A task is critical when any of the following conditions applies:

- Error has potentially severe impact to staff or product safety.
- Error could result in or lead to a failure that creates high damage, significant reprocessing, or irrecoverable act.
- Task has been identified as critical via a risk assessment (FMEA, SPoF, PHA, etc.)

Table 1
Critical Process Risks

Recommendation	Risk level	Recommendation Classification	Responsibility
Add/Improve instructions for alignment verification of the nozzle during setup process.	H	**Method - SOP**	Procedures Team
Improve associates and mechanics qualification material per the actions above.	H	**Manpower**	Qualifications Team
Verify stack up tolerance report and provide any applicable inputs to procedure and qualifications teams.	H	**Method - SOP & Job Plans**	Procedures Team
Add/Improve instructions for alignment verification of the nozzle during setup process.	H	**Method - SOP**	Procedures Team
Improve associates and mechanics qualification material per the actions above.	H	**Manpower**	Qualifications Team
Management to evaluate the use of redundant filters during filling operations, or acceptance of risk.	M	**Machinery**	Qualifications Team
Implementation of aseptic connectors	H	**Machinery**	Engineering Team
Add guide inspection from wear and damage	M	**Method - Job Plans**	Procedures Team
Job Plan modified to increase frequency of replacing seals on a monthly basis	M	**Method - Job Plans**	Engineering Team

Table 2
Task Criticality

Function	Task	Subtask	Error has severe safety impact	Error results in failure and creates irrecoverable act	Task identified critical via risk assessment	Critical or non-critical
SPU	**Operation**	Equipment set up				NC
		Operation				NC
		HMI Alarms		x		C
		Air Gap Measurements		x		C
		Segregation				NC
		Disassembly				NC

After identifying the critical and non-critical tasks, a level of training effort matrix was developed. Level of Training Effort is the grade, intensity or amount of on the job training (OJT) elements required to achieve performance qualification for a certain task or subtasks. The level of training effort (L, M, H) is based in difficulty, frequency and criticality to the process. For the level of training effort refer to the following table (Table 3).

Frequency is defined as the number of times (within a period) that a typical qualified staff member performs a task. These are graded as high if performed daily, medium if performed one every week of month, and low if performed in less than a month.

Difficulty is assigned by the amount of the following criteria that may apply to the task:

- Requires high degree of technical skills.
- Requires multiple simultaneous subtasks with different levels of difficulty.

Table 3
Level of Training Effort
Criteria for Training Effort and OJT and Proficiency Requirements

Criticality	Difficulty	Frequency	Level of Training Effort	OJT and Proficiency Requirements
C	H	H	H	In-depth knowledge review, knowledge check, KYT, Practice on the floor or simulated, documented practice Knowledge Challenge (TE or TQ or both), Performance Challenge in TQ, fluency standard prior and post TQ proficiency check. Exception: for difficulty high and frequency low= Job Aid
C	H	M	H	
C	H	L	H	
C	M	H	M	In-depth knowledge review, knowledge check, Practice on the floor or simulated, Knowledge Challenge (TE or TQ), Performance Challenge in TQ.
C	M	M	M	
C	M	L	M	
C	L	H	L	Basic knowledge review, knowledge check, Practice on the floor or simulated, Performance Challenge in TQ or knowledge challenge in TE or TQ
C	L	M	L	
C	L	L	L	
NC	H	H	L	Basic knowledge review, knowledge check, knowledge challenge in TE or TQ
NC	H	M	L	
NC	H	L	L	
NC	M	H	L	
NC	M	M	L	
NC	M	L	L	
NC	L	H	L	
NC	L	M	L	
NC	L	L	L	

- Requires direct oversight from other to perform.
- Requires critical decision making.
- Requires that abnormal situations be identified and addressed.

If two or more of these criteria are met, then the difficulty would be high. If one criterion is met then the level to apply would be medium and low if no criterion is met.

With the criticality and level of rigor outlined, the task analysis was properly constructed. The following table (Table 4) shows, according to each task, the best training method and qualification techniques.

Performance is categorized in two different ways. Skill based performance applies to the execution of a task during operations, per the SOP. Setting up a machine for routine operations, and identifying a defect you have been trained to detect, are examples of skill-based performance.

Rule based performances require recognition of an atypical or infrequent condition outside of normal operations and knowledge of the proper response (IF-THEN rule). IF-THEN rules in SOPs prevent untrained staff members from trying to fall back on expert-knowledge based performance when faced with a problem or condition they have not encountered. Responding to a defect you have not been training to detect requires rule-based performance.

Table 4
Task Analysis

Function	Task	Subtask	Skill- or Rule-based performance	Level of Training Rigor required	Knowledge Review (basic; In Depth)	Knowledge Check	Knowledge Challenge Either or Both
SPU	Assembly, Operation & Cleaning	Equipment set up	Skill -based	H	B	X	E
		Operation	Skill- based	L	B	X	E
		HMI Alarms	Rule- based	H	ID (sensors)	X	BT
		Air Gap Measurements	Skill- based	L	B	X	E
		Segregation	Skill- based	L	B	X	E
		Disassembly	Skill- based	M	B	X	E

After the rigorous implementation of training, the staff is tested on the task with greater attention placed on critical processes. The tables below (Table 5 and Table 6) show the increasing knowledge of the staff after general concepts training and the passing rate after new task qualifications.

Table 5
Staff Knowledge Gain

QUALIFICATIONS	PRE TEST	POST TEST	GAIN (%)
Equipment Concepts Filler Process	77	86	9

Table 6
Staff Task Qualification Pass Percentage

QUALIFICATIONS	TOTAL AUDIENCE	PASS %	
Syringe Filling: Peristaltic Bomb	28	**28**	**100%**
Syringe Filling: Robot Alarms	28	**26**	**93%**
Tubing Drainage & Syringe Line	28	**27**	**96%**
Pendant Use on Filling Lines	16	**16**	**100%**
Mechanic Interventions	7	**7**	**100%**

CONCLUSIONS

Through the Defense in Depth methodology this pharmaceutical manufacturing plant was able to identify and strengthen vulnerable and high risk areas for the pharmaceutical company in the syringe filling line. The Defense in Depth principle has been a major driver in the development of such protection concepts as:

- Containment systems capable of containing major accidents.
- Very conservative design basis accidents.
- The single failure criteria: i.e., the requirement that a plant be able to withstand the failure of any single component without product damage [3].

In the first phase which is the equipment workstream, we identified and addressed more than 30 critical areas as a result of FMEA. These critical areas were channeled through all three different workstreams of DiD.

Through the SOP workstream we strengthened five (5) procedures. By doing this, we gave the operator clear and more detailed instructions to respond/manage critical tasks.

A lot of effort was put into the third workstream which was Qualifications. During this

workstream, the data from the previous equipment and SOP workstreams were used as an input for the task analysis and the new training qualifications. From this workstream the staff was provided general concept training showing an increase of knowledge of 9%, and also they were qualified on five new task qualifications. All certified staff demonstrated proficiency on the task evaluated.

It is important to mention, that after the implementation of the Defense in Depth methodology on the syringe filling line, it is expected that any major change to the process needs to go through all three layers of DiD. Also the changes on SOPs are not expected to happen in a period of six months to a year after the implementation of the project to demonstrate stability. Finally, staff proficiency checks will be done every year to make sure that staff is still proficient on the critical tasks performed.

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