Validation Exercise for a Vial Secondary Serialization Packaging Line Upgrade

Carlos M. Fargas Landrau
Master of Engineering in Manufacturing Engineering
Carlos González, Ph.D.
Department of Industrial Engineering and Systems
Polytechnic University of Puerto Rico

Abstract *— Serialization has been the focus during the past years due to the new worldwide regulation related to the track and trace of pharmaceutical products. Companies dedicated all their efforts incorporating new technology to their actual packaging lines. Some has to update their serialization systems versions to improve their process. For this update a complete validation strategy and exercise was developed: from Commissioning and Qualification to Packaging Line Integration. Ten (10) protocols were executed, documents were updated and reports were generated to assure the system was satisfactorily upgraded. From 202 steps executed, 73.80% passed and 53 steps failed generating discrepancies and re-test exercises related to protocol errors, error in reference documents and equipment failures. It was concluded that main culprits were lack of information, human error, wrong information found on vendor's documents and configuration errors. A closing meeting was held to identify lessons learned and improvement's opportunities for upcoming packaging line upgrades.*

Key Terms *— Packaging, Serialization, Upgrade, Validation.*

INTRODUCTION

For many years, the manufacture of products has faced serious problems of counterfeit, adulteration and misbranding that results in damages to both consumers and manufacturers.

"The World Health Organization (WHO) estimates that as much as 30% of the medicines sold in parts of Asia, Africa, and Latin America are counterfeit. In 2011, 64% of antimalarial drugs in Nigeria were found to be counterfeit. Worldwide, an estimated 10% of all medicines are counterfeit." [1]

"The problem of counterfeit drugs and drug adulteration has been a worldwide issue for decades. An estimated 80 percent of counterfeit drugs come from overseas with most of them manufactured in India and China." [2]

One of the areas that has boomed in these days is the interest in "tracking and tracing" those products that are directly used at health level like controlled drugs, over-the-counter (OTC) medicines, and medical device products. The goal of developing regulations focuses on the most vulnerable points at the supply chain. Countries like China, Brazil, Turkey and United States have developed their own laws and regulations.

Serialization: The Solution

Serialization has been adopted with the purpose of controlling and reducing the vulnerability to counterfeiting by assigning a unique number to each product and monitoring its passage through the supply chain until it reaches the end user. Identification of the product begins with the most single unit that can be marked (e.g. each unit in a blister, a bottle with tablets, a syringe, a vial) and ends with the identification of the highest packaging level: the pallet as shown in Figure 1. Some of the information required for serialized products includes date, batch number, human readable markings, number of containers per transaction, among other details.

Finally, individual units are separated and their distribution is monitored until they arrive to the consumer. Figure 2 shows how units moves in the supply chain. All information regarding the creation and movement is collected in a central database. This exercise requires a complete commitment from all the units.

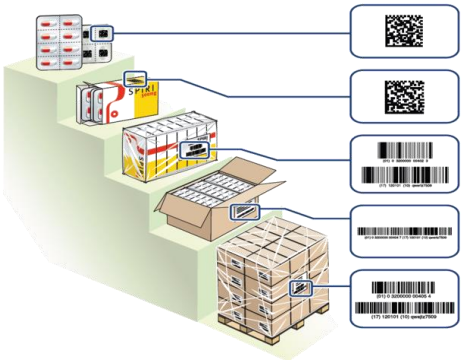

Figure 1
Relationship between Packaging Stages and its Unique Identification [3]

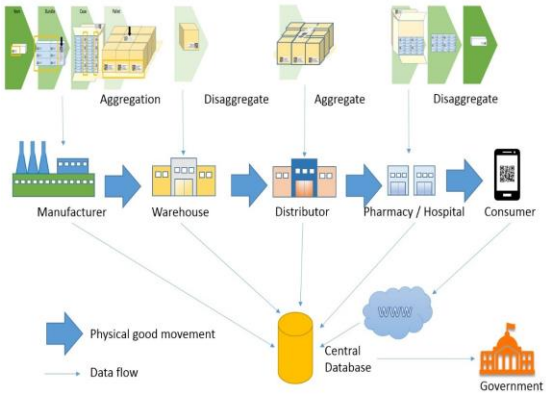

Figure 2
Example of a Serialized Product Movement through the Supply Chain Units [4]

Serialization's Impact in Existing Lines

Serialization introduces noticeable modifications to existing production and packaging lines. The implementation of serialization requires an individual assessment inside the industries to determine if they can integrate new technologies that allow them to comply with law requirements. A closer integration between different plant's areas such as automation, manufacturing and packaging is required to successfully incorporate serialization to the process. Activities like re-design has been necessary and the whole exercise includes huge capital investments, develop specialized training to mechanics, operators, Information Technology and Automation personnel, and the installation of new technologies (e.g. vision systems, printers, sensors, check weighers) to improve and complement existing operations.

Serialization in the United States

In the United States of America, the Drug Quality Security Act (DQSA) was established to meet the worldwide track and trace requirement. Title II, known as the Drug Supply Chain Security Act (DSCSA), contains in its Part 582 the requirements for the identification and tracking of the products. The law requires pharmaceutical industries to establish electronic tracking systems for their products. The regulation became effective on January 2015 and by November 2023 the system must be fully operative. The database created will allow the Food and Drug Administration (FDA) to determine the legitimacy of a product in the market.

Serialization Programs

There are several serialization systems in the market that can be integrated into existing packaging lines like Antares, Optel, Cognex, and Systech. All of them are designed with a common structure, which is adjusted according to the needs of each. For serialization in packaging lines, the Systech general arrangement of the structure can be seen in the following diagram (Figure 3):

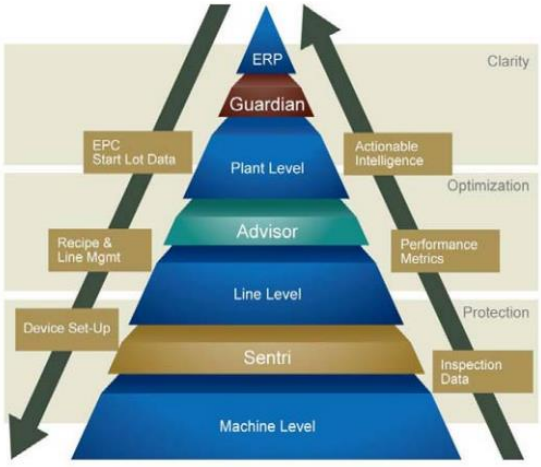

Figure 3
Systech's Serialization System Structure [5]

This structure is aligned with the hierarchy of plant, line, and machine level. The whole structure provides the tools required to meet serialization requirements. The major components are the Guardian, the Advisor, and the Sentri. Another components can be included, such as: Remote

Workstation and Pallet Handheld. Each of them is associated with an equipment in the line.

Serialization and Validation

As it is known, serialization is a compliance issue and, like all compliance topics, it is subject to evaluation by the regulatory agencies like the FDA. Here is where validation comes, because serialization programs are required to be verified against its specifications. The benefits from validation provides the company the chance of evaluating its process [6].

Validation not only takes place at the beginning of a process, but also when the system suffers any type of modification. Revalidation assures that the system that suffers a change in its status maintains its integrity. Because an upgrade of the serialization program impacts the current state of the packaging line, it is subject to revalidation.

PROJECT DESCRIPTION

This research project focused on an existing packaging line that will be converted in a serialized packaging line. The product serialization system is the company's response to the markets' request to assure product authenticity and avoid counterfeit product in the marketplace. The packaging line upgrade will use "2D Data Matrix" code to uniquely identify cartons of vials and carton trays. Case and pallets labels will be printed and verified with 2D data matrix and barcode serialization. A site level infrastructure in combination with SAP application will manage the serial number generation as well as the tracking of the item to case to pallet aggregation. Due to this a full validation for the program is required. This project wants to present the complete validation exercise for the packaging line. The results from the upgrade will show the gained experience and the lessons learned.

PROJECT OBJECTIVE

Because the serialization project is an emerging topic for the industries, there are not many available studies and reports regarding the packaging line upgrade exercise. It is expected to present the complete development of a validation of a serialization upgrade to a packaging line. The objectives for this project are to:

- Research available information regarding serialization validation to apply to current upgrade exercise;
- Develop a general mapping on serialization upgrade validation;
- Perform a full validation to the existing packaging line that will be converted in a serialized packaging line.

RESEARCH CONTRIBUTIONS

This serialization project will expose the current process of upgrading at one biopharmaceutical company in Puerto Rico. The intent of this project is to contribute by: Providing a guide by presenting the knowledge acquired through this validation upgrade exercise; Serve as a reference and act as a framework for those companies that have not yet performed a serialization program upgrade.

LITERATURE REVIEW

The importance of performing verifications and validations for systems and equipment is not only for purposes of compliance with the laws and regulations established by local and global government. Systems and equipment need to be evaluated to ensure that they work properly, that are able to reproduce consistently, and that meet the specifications under which they were created.

At the global level, practical guides have also been developed focused on the different systems, such as the Good Automated Manufacturing Practice (GAMP) in 1991 with the aim of meeting the requirements of the European agencies. The GAMP guide has been adopted by the United States

as part of the harmonization process. [7]. A combination of the guidelines and practices along with the Regulations is key to a successfuls validation when introducing a new system or program or when updating an existing one.

The evaluation of the pharmaceutical facilities and their systems begins with an engineering exercise called Commissioning and Qualification (C & Q). Its purpose is to ensure that the design requirements not only meet the expectations for which they were designed but also seeks to evaluate the quality aspect related to the manufacture of the product. This requires the application of what is known as Good Engineering Practices (GEP). The relationship between the documents that are developed and / or updated as part of the commissioning stage and the type of test performed to ensure that they are correct can be seen in Figure 4.

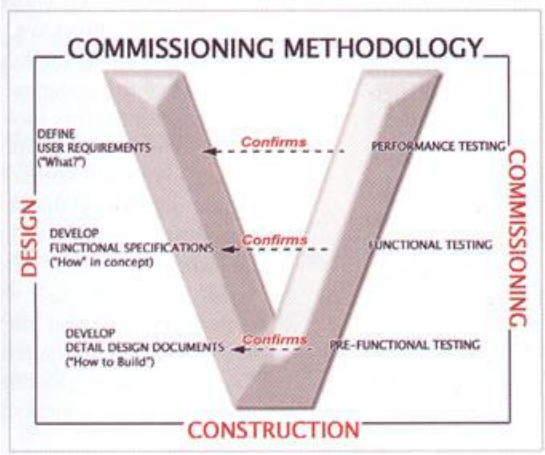

Figure 4
Relationship between C & Q Documents and Testing [8]

Once C & Q is completed, the validation stage takes place by performing another set of document evaluation, testings, and final reports generation. Those testing are summarized in Figure 5 [9].

Due to the presence of technology in the processes, the systems and equipment undergo constant updates. In order to comply with the regulations, it is necessary to keep them up to date. This exercise is a dynamic one and still involves both the physical and the hardware part.

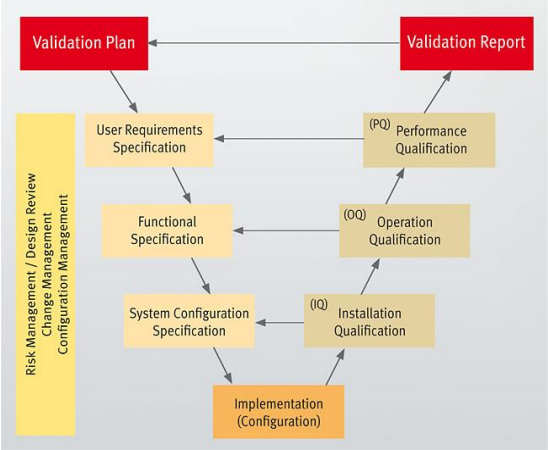

Figure 5
Validation V-model [9]

Understanding Serialization

Serialization is being introduced recently worldwide, the requirements lend themselves to multiple interpretations, which is also a challenge. [10] Due to this, it is necessary to pay more attention to details at the moment of implementing the program and when validating it. Although product serialization was developed in order to solve mainly the problems of counterfeit in the market, there are additional benefits that comes along with this practice. Information obtained from the data base is real-time, more precise data. With this, it is easier to track units, supporting in this way the current inventory management.

Serialization and its Impact at Line Level

Serialization in the production and packaging line needs to be considered in detail since it triggers additional changes in the process. A detailed evaluation must be done to assure compliance while lowering the impact to actual production performance: each company has its particular needs and adding serialization adds complexity to the process. On the other hand, sometimes it is necessary to buy new equipment and decommission current one.

Serialization is an Inter-Departmental Matter

Serialization systems are not stand-alone. This means that to keep the system working it is required that different company's departments work together

not only during validation stage but also as part of daily operations.

When talking about testing, under normal conditions, computer system validations and upgrades are performed by the Automation area in coordination with the Information Technology (IT) area as the program is associated with a device within a production or packaging line. Manufacturing personnel must also be included because they can provide information regarding line improvements that can be done due to the introduction or upgrade of serialization. Incorporating the operators will help them understand better the usage and importance of the system. The validation team must lead the validation exercise and Quality Assurance (QA) participation is a requirement since it guarantee compliance.

Importance of Keeping Updated Serialization Systems: Why Upgrade?

Serialization systems are also dynamic and require to be upgraded. Prior to the upgrade, it is critical to evaluate carefully the changes and their impact on the systems to which they are tied. They must also be validated in alignment with the original systems since normally, they directly impact the manufacturing processes. The same strategy used for the original validation can be implemented for the validation of the upgrade. Figure 6 shows the traditional model used during software validation.

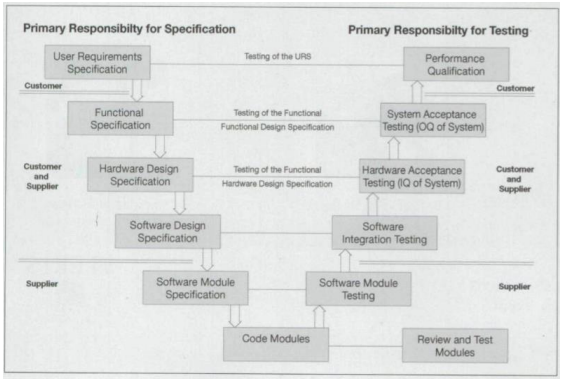

Figure 6
Validation V-model for Software [7]

Validation Upgrade Approach at a Biopharmaceutical Industry

The design of software used in some plants makes the validation process a complex one. Because serialization programs are new to industry, they require improvements to continue complying with the law. Also, updates are necessary to correct programming errors (gaps) that could make the system vulnerable at some point in its use. In addition, some modifications are needed for the program to communicate with other system programs (ERP, MES) to feed data, store data, or transmit data. Validation upgrades for systems and software follow the same basic models for C&Q and validation. Two main strategies are used; the "onsite/offline testing" and the "Front End Loading" (FEL). Jordon and Pirrea explain in their article the benefits of using this kind of strategy [11].

Another strategy used in industries when upgrading in the area of automation is the Front-End Loading (FEL). Sigmon describes this strategy in his article. [12]

Normally, FEL is performed by an external provider to avoid compromising plant staff that is dedicated to run business. The analysis is provided to the plant to develop the final upgrade plan. Once the initial upgrade strategy is defined, another option available is the use of leverage. The benefit of doing it is to avoid repeating the same testing multiple times. Careful evaluation must be done because not all tests can be leveraged. It is important to understand that the leverage strategy must be discussed with Quality Assurance (QA) and they must approve it prior to its implementation.

Validation Exercise for a Vial Secondary Serialization Packaging Line Upgrade

This project will focus in the development and execution of the validation upgrade for an existing packaging line that will be converted in a serialized packaging line at a biopharmaceutical industry in Puerto Rico. As part of the strategy, the core testing related to SAT will take place at a Vial

Packaging Line. Leverage to common test will also be performed.

METHODOLOGY

This exercise was defined by management as a full Computer System Validation (CSV). Each of the elements that compose the Systech Vision Systems, Advisor, Sentri and others packaging equipment will be validated independently. After their validation, an integration exercise will take place at packaging line to assure there is no impact in their production activities.

Scenario

At the selected biopharmaceutical company, there is an existing packaging line for vials. This vial packaging line was selected to perform the serialization packaging line upgrade validation. Because available time at lines is limited, the Front-End Loading (FEL) strategy will be used to perform the validation exercise. For the FEL strategy, the vial serialized packaging line installed at a biopharmaceutical industry in Puerto Rico will be used to perform all testing related to Site Acceptance Tests (SATs) Systech Vision Systems, Advisor, Sentri and others packaging equipment. Leverage to common test will also be performed if required.

Initial Assessment and Project Scope

A Change Control will be achieved by reviewing, approving, and documenting all changes made to the validated serialization system. The validation exercise will be documented as part of the Commissioning and Qualification Plan. An authorization from Corporate Headquarters is required in order to initiate the upgrade validation. Once they approve the deployment of the program to the site, the Subject Matter Expert (SME) in Serialization will perform an assessment and will provide the recommendations on how to update documents and how to create the required protocols to comply with the validation required.

Project Team

Different external companies were contracted to perform the upgrade validation. The team will be composed of a Project Manager, a Commissioning and Qualification lead, two Validation Specialists, one Automation Technician, and one Serialization SME.

The team will receive support from the Validation team and from two Quality Assurance Specialists (one for the C&Q stage and another for the packaging line stage). Due to the aggressive dates, the team will distribute the activities in two shifts and will include weekends and holidays as required as part of the schedule to comply with the dates (although initial timeline do not include it).

Weekly meetings will be held with Sponsors to notify project progress and daily activities will take place led by the Serialization team to coordinate activities and monitor progress. Communication with the packaging management will be established from the beginning of the exercise to coordinate the packaging line activities. A table with the main activities were developed to assign Responsible, Accountable, Consulted and Informed roles.

Project Timeline Overview

This project has a timeframe of eight (8) months to complete the vial's packaging line validation. A general plan with all the required activities was developed in coordination with a Scheduler to assure the correct time distribution. A Gantt chart for the serialization packaging line upgrade validation activities will be developed. A master list of impact documents will be created to assure correct evaluation and update of each one. Deviations found during the execution of the testing will be documented in an official form and must be evaluated and approved by QA Specialist.

Pre-work Activities

Main activities include the generation of the Change Controls, one for the serialization packaging line upgrade validation activities. Also, the purchase order will be placed to buy new serialization packaging equipment (e.g. Sentri

Vison Systems, Advisor, hardware/software, IPCs, cameras, printers and others). Communication will be established with packaging line owners to share with them the proposed strategy for the validation and to request support for the different activities on schedule. Evaluation of the Product Configuration documents will be performed to preliminarily identify the products that can be run in the line during the Integration and End of Line activities.

Table 1

Test	Justification
Test Equipment Calibration / Certification Review	Record calibration/certification information.
Alarms and Interlocks Verification	Verify that alarms/interlocks are triggered by the corresponding conditions
Source Code Review	Verify that the equipment Source Code of the PLC is clear, correct and no dead codes are present
Control Panel Verification	Verify that the control panel devices operate as per manufacturer specifications
System Security Verification	Assure that the software security is adequate to avoid unauthorized access
Screen Navigation Verification	Assure each of the screens available from the equipment are configured, operates and displays the functions as required
Boundary Conditions Verification	Verify that the parameter values within the specified boundary conditions are accepted and those outside are denied
Backup and Restore Verification	Document that a procedure or steps for the back-up and restore of the program used in the equipment and PLCs is available, complete, and secure
Input/Output (I/O) Verification	Verify that equipment input and output devices (e.g. sensors, switches) are properly hardwired to the PLC I/O Cards and addresses were configured as per requirements
Setup Parameters Verification	Verify that the setup parameters for each presentation are documented and classified as critical or guide.
Efficiency Test Run	Verify that the equipment is capable of continuously and repeatedly processing products, counts and bottles at the specified production rates and efficiencies
Communication Test Failure Verification	Verify if the different components of the control system can register a communication loss with peripherals
Power Failure Verification	Verify that the equipment does not lose any relevant operational data during a power failure

Core Activities

Once the new released version is received by IS Director at corporate, it must be approved and released; then the plant can proceed to develop in detail the validation strategy. As a first step, it is required that the Serialization SME perform an evaluation of the program release notes to identify which are the changes and to determine if the changes impact current serialization requirements. If so, he/she must determine what kind of tests are required for the validation to cover the change. An update of actual requirements document (Serialization URS) might be necessary.

The following table summarizes the main activities identified as part of the Serialization Systech upgrade validation exercise:

Table 2

Type of activity	Sub-activities
Serialized Packaging Line Upgrade	• Install the new packaging equipment (e.g. Sentri Vison Systems, Advisor, hardware/software, IPCs, cameras, printers and others) to achieve the packaging serialization.
Packaging Line window coordination	• Coordinate with Packaging Planner to request a window to execute protocol at packaging line. • Coordinate with Packaging Line Supervisor the availability of resources to provide support to the protocol execution.
Documentation Update or Creation	• Verify if there are new versions of Systech manuals or new manuals to upload into the Document Management System (EDM). They will be referenced in Commissioning & Qualification and Validation protocols. • Update or create new Serialization Requirements in the corresponding documentation (e.g. Functional Specifications, Design Specifications). • Identify the tests that are going to be executed at serialized packaging line.
Create new or Update the build SOPs and the corresponding IQ/OQs	• Update existing or create new build Standard Operating Procedures for new packaging equipment • Perform dry run to challenge documents. • Create Installation Qualification and Operation Qualification protocols. • Wait until Change Control reach implementation status to proceed with the approval of documents.
Create the Matrix Report	• Generate initial report draft for the Matrix Report to identify what additional tests are required to include in the addendum.

Addendum	• Identify specific test that applies to packaging line. • Include any missing test that was not evaluate as part of the SATs and that was identified during the preliminary evaluation of the matrix report. • Upload Addendum and route for review. • Route document for approval.
Addendum execution	• Train operators. • Run Addendum at packaging line. • Manage any possible deviation (discrepancies). • Prepare Addendum binder. • Submit binders for review and approval. • Generate and Approve final reports. • Complete Matrix report. • Route for review and approval the Matrix Report.
Closure activities	• Close Change Control. • Release packaging line for packaging activities.

RESULTS AND DISCUSSION

As stated in the strategy, protocols were executed in the serialization packaging line upgrade. Table 3 presents a summary of the quantity of steps (individual activities) performed per protocol. The execution of them generate attribute (nominal) data: pass or fail. For the complete computer system validation exercise, a total of 202 steps were executed in a timeframe of 8 months, from which the 73.80% were satisfactory (passed) on the first attempt and the 26.20% generated a deviation from the step as established.

Table 3

Protocol	Steps Passed	Steps Failed	% Pass	% Fail
Systech Advisor System IOQ-001	19	8	70.30	29.70
Systech Sentri System at Labeler Machine IOQ-002	19	7	73.08	26.92
Systech Sentri System (PIM 110C) IOQ-003	16	11	59.22	40.78
Systech Sentri System (PIM 210C) IOQ-004	16	11	59.22	40.78
Cartopallet Machine IOQ Addendum (ADDM-005)	16	4	80.00	20.00
Central Control Unit IOQ-006	19	5	79.20	20.80
Shipper Label Printer Machine (IOQ 007)	24	1	96.00	4.00
Systech Sentri System Addendum (PIM 210C) ADDM-008	8	4	67.00	33.00
Cartopallet Machine IOQ Addendum (ADDM-009)	8	0	100.00	0.00
Installation and Performance Qualification Protocol for the Vial Line After the Serialization Integration Activities (IPQ-001)	4	2	67.00	33.00
Total	149	53	73.80	26.20
		Average	75.10	24.90

For those steps that failed, a deviation memorandum was generated in order to describe in detail the finding, identify the root cause, and to assign a correction and/or preventive action. Table 4 shows a compilation of the discrepancies. They were grouped in three main categories described by a legend. After an evaluation of the root cause, some of the tests were performed again (re-tested) to obtain or to confirm a final and official result.

Table 4

Protocol	No. of Disc.	Type			Re-test
		1	2	3	
Systech Advisor System IOQ-001	8	0	7	1	1EQ 1PE 1CE
Systech Sentri System at Labeler Machine IOQ-002	7	1	6	0	1PE
Systech Sentri System (PIM 110C) IOQ-003	11	4	5	2	2CE
Systech Sentri System (PIM 210C) IOQ-004	11	4	5	2	2CE
Cartopallet Machine IOQ Addendum (ADDM-005)	4	0	2	2	2CE
Central Control Unit IOQ-006	5	2	3	0	0
Shipper Label Printer Machine (IOQ 007)	1	1	0	0	0
Systech Sentri System Addendum (PIM 210C) ADDM-008	4	2	2	0	0
Cartopallet Machine IOQ Addendum (ADDM-009)	0	0	0	0	0

Installation and Performance Qualification Protocol for the Vial Line After the Serialization Integration Activities (IPQ-001)	2	1	1	0	0
	53	15	31	7	10
%Disc.	---	28.30	58.50	13.20	---

Legend:

Type 1 - Protocol Generation Error, Lack of Information for protocol redaction, Human Error

Type 2 – Wrong information found in protocol reference documents (SOPs, Manuals, Design Specification, Navigation Guides, Systech manuals error), incorrect images on Vendor's documents

Type 3 - Equipment failure or Configuration error

Re-test – Additional test performed due to Discrepancies

EQ – Equipment

PE – Protocol Error

CE – Configuration Error

Regarding impact in controlled documents, a total of 52 documents required creation or update. Table 5 summarizes the documentation exercise that took place during the whole validation.

Table 5

Documents created	Qty	Documents updated	Qty
Change Control (CC)	1	Functional and User Requirement Specification	3
Commissioning and Qualification Plan	1	Risk Assessment and Traceability Matrix	2
Functional and User Requirement Specification	3	System Design Specifications (SDS)	3
System Design Specifications (SDS)	4	Addendum of Installation and Operational Qualification	2
Installation and Operational Qualification (IOQ)	7	Addendums of Installation and Operational Qualification Report	2
IOQ Report	7	Build SOPs	6
Installation and Performance Qualification (IPQ)	1	Engineering drawing for Equipment	7
Build SOPs	1	[redacted]	
IPQ Report	1		
Commissioning and Qualification Report	1		
Total	27	**Total**	25

From a total of 53 discrepancies generated (Refer to Table 4), 27 were classified as protocol generation error, meaning a 28.30% of them. Errors in the protocol are due to the lack of information available for some of the tests. Although several dry runs were performed before starting the validation exercise, not enough time was dedicated to identify and analyze the main changes in the new serialization packaging line upgrade and its impact. Due to this, some details could not be captured on time within the protocols, generating discrepancies during the execution. The same thing happened with manuals and navigation guides, among other company's documents, that cannot be fully updated prior to the validation exercise.

The Serialization packaging equipment (e.g. Sentri Vison Systems, Advisor, hardware/software, IPCs, cameras, printers and others) manuals came with a Document Library folder that contains all required manuals related to programming, navigation, and functionality of each system. They were used to update all the documentation related to the validation exercise (e.g. SOPs, protocols, navigation guides). During the protocol's execution, it was found that some Serialization packaging equipment manuals used as references were not updated with photos or ranges of values for some of the variables, among others, and were the cause of 58.50% of the discrepancies (31 discrepancies generated). As a corrective action, it was requested to each equipment vendor to update and correct their manuals. All manuals were corrected and approved prior to finish the validation exercise.

Equipment failure and configuration errors cause 13.20% of the discrepancies (7 discrepancies generated). Errors in the system, like equipment and configuration errors, were a result of system gaps that included screens that froze and required to reinitiate the equipment (making the test fail), system malfunction, sequence operation errors, logical security errors, network connection errors, among others.

Also, some of the tests that were performed could not be completed in the serialized packaging

line, generating deviations because some systems were not ready yet or correctly installed.

For the biopharmaceutical industry, this upgrade validation exercise was considered a complete learning curve and will be used for future serialization packaging line upgrades. The lessons learned will help to improve planning for the other packaging lines to be serialized in the future. Other opportunities of improvement identified include topics like:

- Project design distribution - Project management techniques will be refined (e.g. better time distribution based on current experience since the first time they were estimated)
- In-depth analysis of Serialization packaging equipment manuals - These documents are key when beginning the generation of documentation. This information allows the Serialization SME to develop more accurately the tests that will be included in the validation protocol.
- Request close support from each Serialization packaging equipment expert - When upgrading from an existing packaging line to a new serialized packaging line, more support from Equipment representatives is required to understand changes in the system. Constant communication with them is necessary during the equipment integration and validation.

CONCLUSIONS

Since the regulation came effective on January 2015, most of the companies are focused on complying with the Law and incorporate serialization to their processes. Due to this, a few companies have focused in making upgrades of their packaging lines.

It can be concluded that the main objectives were satisfactorily attained. During the research part of this validation, it was found that although there was not enough public data available related to this topic, the information obtained helped in the development of the initial validation strategy. A general mapping of the main activities was initially developed and details were added during the validation exercise. A final project structure was developed and will be used for the next packaging lines upgrades. The complete validation exercise was successfully completed.

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