Design of a Cleaning Change Over Reduction Strategy for a High Volume Product in a Packaging Line

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***Abstract* —** *Currently packaging operations are trying to reduce the downtime and operational cost among others activities to enhance efficiency and overall process performance. Based on this objective, pharmaceutical packaging operations defined, proved and validated a process that allowed to use five released bulk lots be combined into one packaging lot. The strategy proved to be efficient for operational cost, unproductive time reduction and cross contamination. An identified disadvantage was that if a quality event was noticed in the release product, no bulk segregation could be done. Once each bulk lot is added into the filler machine or product bottle, it was mixed with previous bulk lots and it cannot be determined which tablet belongs to a specific bulk. Redesigned batch record includes a table to estimate the bulk traceability when it is packaged as Combolot. A project to develop a sub-lot numbering system was identified as future wok for this research.*

Key Terms *— Cleaning validation, campaign, change over, combined lots, packaging lots, process improvements.*

INTRODUCTION

Currently manufacturing and packaging operations are trying to reduce the downtime, operational cost, production waste among others activities that do not contribute to good performance. To achieve continuous productivity packaging operations have to become efficient, user friendly, offering flexibility, easy operation, robustness, intelligence and protection from interference. Globalization in the pharmaceutical industry is moving. To package small batch sizes, companies are evaluating if actual or new equipments should be used. If existing packaging equipment is used, the productivity will have a considered effect due to the long change overs. Therefore will require to evaluate the usage of new equipments since the change overs are flexible and consume less time.

This research is to evaluate and design a cleaning change over strategy to reduce the packaging process cycle time duration of a high volume product (Product X). The actual line clearance procedure requires a minor cleaning process between each packaging lot of the same drug product and strength and a major cleaning after packaging three (3) consecutive lots. Current packaging strategy is to assign a packaging lot number to every manufacturing lot. In the current packaging strategy one bulk or manufacturing lot is converted into one packaging lot.

The research proposal was based on combined lot strategy. This new strategy is based on reducing the cycle and change over time. With the implementation of combined lots or multiple bulk manufacturing lots into one packaging lot, the line cleaning process and the packaging line down time were reduced.

Research Objectives

The purpose of this research was to design a change over reduction strategy to demonstrate that after continuous operation, the bottle packaging process maintains its current validated and control status when packaging multiple manufacturing lots. Successful completion of this research provided assurance of the packaging process for larger packaging lots will reduce the cleaning process. This was showed consistency and reproducibility to meet the process control limits such as traceability,

product specification, active ingredient residuals (AI), detergent traces (DT) and microbial growth (ML).

METHODOLOGY

DMADV is a one of the methodology of the Six Sigma system. The DMADV is a helpful way to create a new product or a new process design. This methodology's goals are for its designs to be predictable, and defect free. There are five steps in the DMADV process, they include; Define, Measure, Analyze, Design and Verify the Design.

Define

The define step is where the problem, project goals and costumers needs are discussed. SIPOC diagram is a Six Sigma tool used to define a high level view of the process for an effective definition of the project and its boundaries.

The combined lots packaging process was defined using the SIPOC diagram. Combo-lot process begins with scheduling and planning activities for the packaging process. Once it is planned, the product bulk lots and the packaging materials are placed on the packaging line room. After completion of the packaging process, the cleaning process for the packaging room and change over parts begins.

Product selection for the design project, the forecast was evaluated. The product selected for this research was Product X and the forecast is 190 lots for 2010. The existing product campaign length was evaluated. Cleaning campaign length allows a continuous packaging of three (3) manufacturing lots into three (3) packaging lots of the same product and potency without performing a major cleaning. Therefore with this campaign a total of two (2) minor cleaning processes and one (1) major cleaning are needed. Since the strategy was to combine Product X lots together, the change over and cycle time were expected to be reduced. The baseline changeover average time was of is approximately seven (7) hours. The actual average packaging process cycle time for Product X is of thirty-seven (37) hours. The cycle time is the period of time for the complete packaging process. Figure 1 showed the packaging process time. Figure 2 showed the change over times.

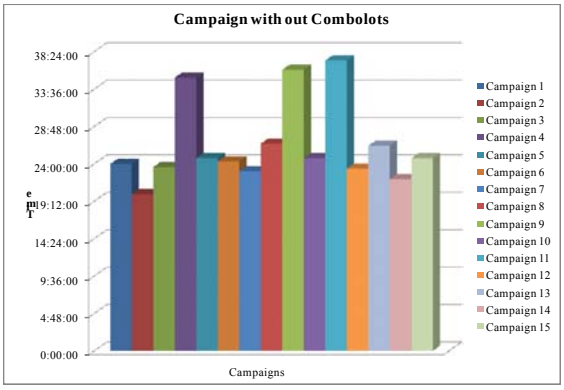

Figure 1
Regular Packaging Lots Process Time

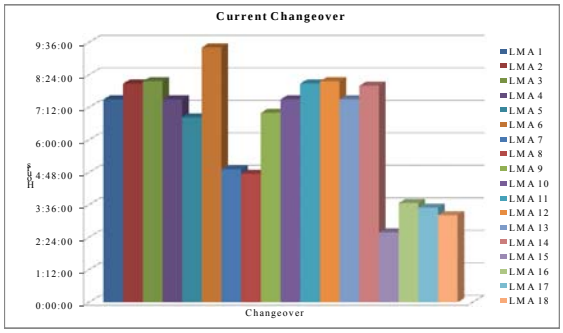

Figure 2
Regular Packaging Process Change Over Time

The proposed campaign was to combine five (5) bulk lots into one (1) packaging lot. This strategy was based in increase the lots size quantity by 51,750 bottles approximately. Actual lot size was 12,950 bottles approximately and after the combo lot implementation the new lot size would be 64,700 bottles approximately. With the new packaging strategy implementation the minor or interval and major cleaning was reduced as well the down time.

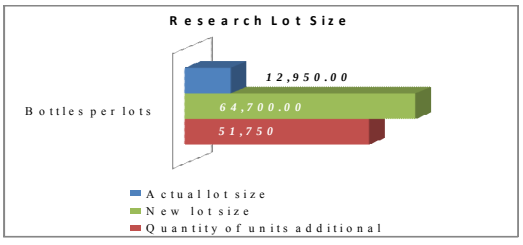

Figure 3
Research Lot Size

In terms of expiration date, it will be assigned using the oldest bulk expiration of the manufacturing lots packaged in the combo lots. In terms of traceability, the bottle/shippers will be properly identified with numbers or suffix to allow bracketing and fencing capability in the event of an investigation. The proposed campaign was detailed on Figure 4.

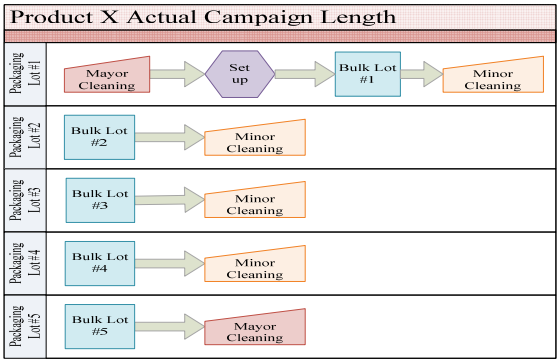

Figure 4
Combo-Lots Proposed Campaign

Measure

The purpose of the measure section is to establish the process baseline measure characteristics and process specifications. A trend for the current state of the changeover and a FMEA was developed. The current state of the changeover provided an insight of how the process behaves. [1] FMEA is used for analyzing potential reliability problems early in the development cycle where it is easier to take actions to overcome these issues, thereby enhancing reliability through design. [1] FMEA for this project was based in the risk of the possible recalls or complaints on a packaged lot. Refer to Table 1 for the FMEA.

Analyze

Since the packaging line is not dedicated to Product X only, the possible AI, DT and ML needed to be re-evaluated to prevent any cross contamination. Cleaning validation (CV) is the methodology used to assure that a cleaning process removes residues of the product manufactured active ingredients in a piece of equipment, the cleaning aids utilized in the cleaning process and the microbial attributes. [2]

CV includes determining the limit for AI and DT. Residual Acceptability Limit (RAL) is the calculations done to determine the acceptance criteria for the AI and DT. The detergent and active RAL was calculated using "Equation (1)", "Equation (2)", "Equation (3)", "Equation (4)" and "Equation (5)". [3]

To calculate the RAL for non therapeutic dosage, the acute oral LD (50), a safety factor (SF), maximum daily dosage (B_b), unit weight (C_b), smallest batch size (L_B) and product contact surface areas (E_W) were taken in consideration. NOEL is the no observed effect level for a person weighing 70 Kg, expressed as mg/day. The LD (50) is half of the lethal dosage for the detergent expressed as mg per Kg of the body weight. SF is the safety margin used when defining an acceptance limit for product carryover. It was applied during calculation to ensure that the level of product carryover is low and within safety threshold limits that there will not be a pharmacological effect due to any product carried over into the subsequent product. For the NOEL calculations a SF of 0.0005/day was used. Refer to "(1)". [3]

$$NOEL = \left(Acute \quad Oral \quad LD\left(50\right)\right)x\left(SF\right)x\left(70Kg\right) \quad (1)$$

Once the NOEL was calculated, the maximum allowable residue (MAR_N) was calculated. SF used in this step was 1/100 commonly used for oral products. [2] The equation for the MAR_N is detailed below. [3]

$$MAR_N = \frac{\left(NOEL\ \frac{mg}{day}\right)\left(1{,}000000\frac{mg_B}{Kg_B}\right)\left(SF\right)}{\left(B_b \quad units\right)\left(C_B \quad \frac{mg_B}{unit}\right)} = \frac{mg_A}{kg_B} = \frac{\mu g_A}{g_B} \quad (2)$$

Then the RAL_N was calculated for the non therapeutic material or DT. The previous calculated MAR_N was compared with the value of 10ppm. If the MAR_N was ≥10 ppm, the MAR_N value will be substituted in the equation with 10. If the calculated MAR_N was ≤10, the calculated MAR_N value will be used in the RAL_N formula. RAL_N formula is detailed below. [3]

Table 1
FMEA Combined Lots

Process Function / Requirements	Potential Failure Mode	Potential Effect(s) of Failure	Potential Cause(s) / Mechanism(s) of Failure	Current Process Controls	Recommended Action(s)
Prepare the packaging schedule	Lots are not available	Quality testing fails	Lots are not released to be packaged	SOP's are approved indicating the procedure	Verify that the bulk lots are approved
	Packaging materials not available	Incoming testing fails	Packaging materials are not released to be packaged	SOP's are approved indicating the procedure	Verify that the bulk lots are approved
		No availability at the warehouse	Information incorrectly entered to the MRP system	MRP system	Verify the safety stock values and update with the
Prepare change parts and tooling	Change parts are not cleaned	Change parts can not be used for the packaging	Tool room operators did not verify the cleaning checklist for	SOP establishes that CEHT is for six months	Retrain the operators in the SOP
	Change parts are broken	Change parts can not be used for the packaging process.	Tool room operators did not verify the status of the change parts	Tooling Kanban operators fills a inventory status card to reorder the broken tools.	Verify the last inventory card and reorder the broken parts
Assign packaging operators	Operators has lack of training	Packaging process can't be executed	Operators can not perform the packaging process	Operators needs to be trained in the SOP's	Perform an assessment of the operators that needs
Packaging line setup	Operators has lack of training	Incorrect line setup	Operators can not perform the packaging setup	Operators are trained in the set up procedures. Visual aids are placed at	Perform an assessment of the operators that needs training
	Change parts not available	Change parts can broken or dirty	Tool room operators did not verify the cleaning checklist for the change parts	Packaging schedule is given to the Kanban operator room to prepare	Verify the last inventory card and reorder the broken parts. Clean the
Packaging process	Operators packaged the first bulk lot and stop	Packaging line is stopped and the downtime	Operators are not trained in the new Packaging process and batch	Operators needs to be trained in the SOP's and	Retrain the operators in the SOP's and PBO's
	Operators stops the packaging process after the third lot to perform	Packaging line is stopped and the downtime increase.	Operators are not trained in the new Packaging process and batch record. Operators follows the	Operators needs to be trained in the SOP's and PBO's	Retrain the operators in the SOP's and PBO's
	Samples for retention, stability and other testing are not documented	Sampling required during the packaging process can not be completed.	Operators are not trained in the new Packaging process and batch record.	SOP and PBO indicates the sample quantity to be taken from the Combined lot.	Retrain the operators in the SOP's and PBO's. Generate a deviation report. Take the samples
	Operator did not document the start and end shipper for each bulk lot.	Bulk lots traceability can not be determined. During a an investigation, the whole Combolot is in	Operators are not trained in the new Packaging process and batch record.	SOP and PBO indicates the sample quantity to be taken from the Combined lot.	Retrain the operators in the SOP's and PBO's. Generate a deviation report. Take the samples

$$RAL_N = \frac{\left(MAR_N \quad \frac{mg_N}{Kg_B}\right)\left(L_B \quad kg_B\right)}{\left(E_w \quad in^2\right)} = \frac{mg_N}{in^2} \quad (3)$$

The RAL_T for therapeutic dosage, minimum therapeutic dosage (T_A), B_b, C_b, L_B, E_W and SF were used. To calculate the RAL_T, MAR_T for therapeutic material needs to be calculated using the "Equation (4)". [3] The B_b, C_b and SF are the same values used on the "Equation (2)". [3]

$$MAR_T = \frac{\left(T_A \quad mg_A\right)\left(1{,}000{,}000\ \frac{mg_B}{Kg_B}\right)\left(SF\right)}{\left(B_b \quad units\right)\left(C_B \quad \frac{mg_B}{unit}\right)} = \frac{mg_A}{kg_B} = \frac{\mu g_A}{g_B} \quad (4)$$

Once the MAR_T was calculated, the RAL_T will be calculated using the same variables used for non therapeutic material. "Equation (5) shows the RAL_T formula for the therapeutic material or AI residual acceptability limit". [3]

$$RAL_T = \frac{\left(MAR_T \quad \frac{mg_A}{Kg_B}\right)\left(L_B \quad kg_B\right)}{\left(E_w \quad in^2\right)} = \frac{mg_A}{in^2} \quad (5)$$

$RAL_N \leq 35.51\ \mu g/in^2$ and $RAL_T \leq 2.70\ \mu g/in^2$ were the calculated acceptance criteria for the research.

ML aspects of equipment cleaning were also considered for assuring cleaning procedures. Manufacturing and packaging process equipments routine lifecycle are particularly prone to challenge from microorganisms. Cleaning procedures needs to be designed to assure that routine cleaning do not allow ML proliferation. Table 2 establishes the acceptance criteria for ML.

Table 2
Acceptance Criteria for Microbial Load

Test	Monitoring Limits	Specification	Upper Control Limit
Bacteria Count	Max. 15 cfu/swab	Max. 100 cfu/swab	Max. 20 cfu/swab
Mold/Yeast Count	Max. 10 cfu/swab	Max. 20 cfu/swab	Max. 15 cfu/swab
Escherichia coli	None	None	None
Salmonella spp	None	None	None

Design

The design step covers all the activities needed to meet the objective of this project design. [2] Packaging batch record was re-designed to include a traceability section for the manufacturing lots used, cleaning SOPs were updated with new partial and major cleaning requirements based on study results, also maximum number of bulk lots packaged into a single packaging lot campaign. SOP's detailing the expiration period was updated to include the combined lots strategy.

The CV strategy for sampling was also redesigned to demonstrate that no ML is carried or added to the Product X lots before starts the experimental and validation packaging process. Product contact parts were sampled prior start the Combo/campaign lots packaging process. Product contact parts were sampled for microbial test, after completion the packaging process of each combo lot to provide evidence that no potential ML was added. After completion the packaging process, product contact parts were cleaned using the approved procedure and were sampled for microbial test, AI and DT. Experimental design was executed using one (1) run of five (5) bulk lots and repeated three (3) times for a total of three (3) packaging lots (containing 5 bulk lots each) with 2 partial cleans in between and a major clean at the beginning and end of the packaging process for a total of 15 bulk lots. Refer to Figure 5 for the sampling plan.

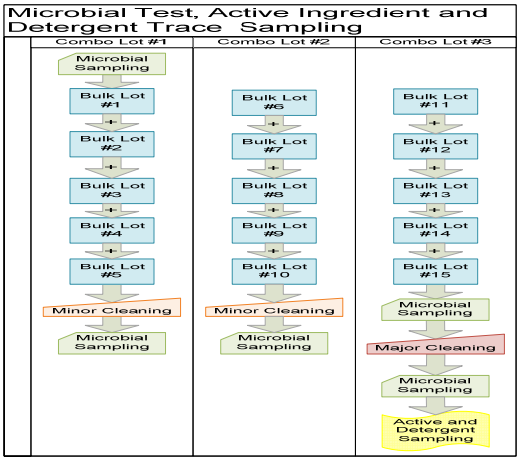

Figure 5
Combo-Lots Proposed Campaign

Verification

Once the design was analyzed and tested, it was verified. Verification usually occurs through experimental runs. Since the design was tested through the experimental run and executed in parallel without impacting production schedules, it can be ready for implementation. [4] Tools used in this phase were the SWOT Analysis, comparison between current and the new changeover down time. The comparison between these two scenarios showed the increase in the line performance. A total of three (3) runs of five (5) lots each one was observed to verify the implementation of this experiment.

DISCUSSION OF RESULTS

As part of the project implementation modification to current standard procedures and batch records were done. On the lot release SOP the worst case expiry dating will be performed by including an expiry period based on oldest lot in the combo-lots. In addition the bulk lots used in a combo-lot should have a manufacturing date within two months. No pending testing or results from the testing should be pending prior use this manufacturing lot into a combo-lot.

The batch record modifications done were to add a table to document the information related to the manufacturing batch number, sequence, when the manufacturing lot was added to the packaging filler machine and the approximated shipper number that contains the first bottle of each bulk lot.

Experimental and verification run of Product X combined lots were packaged following the instructions specified in the Packaging Batch Record (PBO). The purpose was to prove that all the control placed on the SOP's been suitable for the combo-lots activities. A total of 12,918,700 bottles of Product X were packaged.

The cycle time for the combo-lots is of twenty five (25) hours. Refer to Figure 6. The experimental and verification runs showed that approximately six (6) hours were reduced with the combo-lots if it is compared with the same lots packaged on a regular

campaign. Changeover time was ten (10) hours. The regular change over in a regular campaign length is of sixteen (16) hours approximately. Refer to Figure 7 for comb-lot change over time.

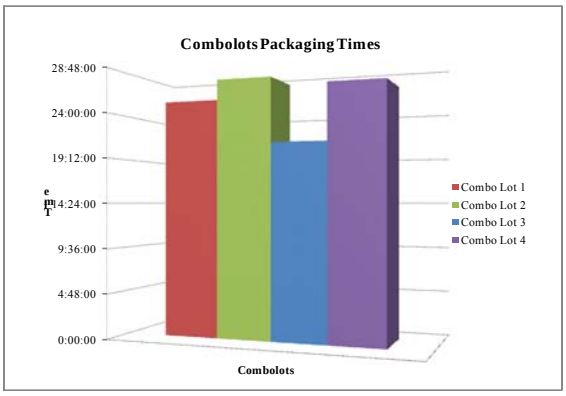

Figure 6
Regular Packaging Lots Process Time

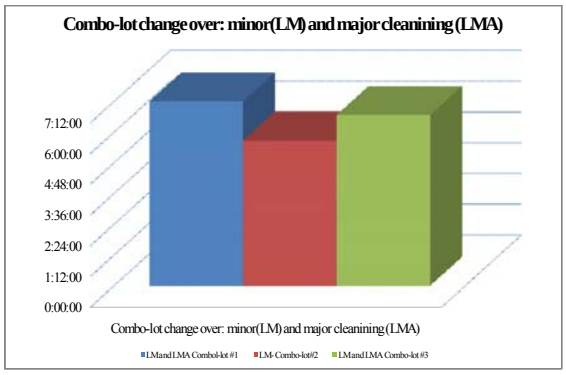

Figure 7
Combo-Lot Packaging Process Change Over Time

Combo-lots performance was of 100.2% which indicates that the performance was within the established parameters of 95.0% to 102.0%. This performance was calculated taking in consideration the total quantity of bottles packaged (E) versus the estimated material quantity (G) minus the material quantity returned to the stock (H). Refer to "(5)"

$$\frac{E}{(G-H)} x100\% \qquad (5)$$

Since the packaging line is not dedicated to Product X, AI, DT and ML were monitored to assure that no possible cross contamination occurred. ML, AI and DT sampling was performed on the product contact parts. Results obtained from these runs indicate that actual cleaning procedure is capable to reduce to acceptable limits any possible ML, AI and DT traces. Table 3, Table 4 and Table 5 details the obtained results for microbial, active ingredient and detergent traces.

Table 3
Results for Microbial Load

Equipment Part	Results			Results
	Bacteria Count	Pathogens	Mold/Yeast Count	
	Cfu/swab		Cfu/swab	
Swiftpack - non dedicated parts	< 5	None	< 5	Pass
Swiftpack – dedicated parts	< 5	None	< 5	Pass
Hopper – lateral walls	< 5	None	< 5	Pass
Hopper – lower interior corner	< 5	None	< 5	Pass
Hopper – vibrator plate	< 5	None	< 5	Pass
Scoop	< 5	None	< 5	Pass
Metal Trays (Parrilla)	< 5	None	< 5	Pass
Manifolds	< 5	None	< 5	Pass
Dividers	< 5	None	< 5	Pass
Slats	< 5	None	< 5	Pass
Brushes - small	< 5	None	< 5	Pass
Brushes - large	< 5	None	< 5	Pass

Table 4
Results for Active Ingredient Traces

Sampling Points	Active Ingredient Results (µg/in^2)	
	Sample	Pass / Fail
Main Hopper Lateral Walls	1	Pass
Main Hopper Lower Interior Corner	1	Pass
Main Hopper Vibrator Plate	ND	Pass
Swiftpack – hopper interior surface	ND	Pass
Swiftpack – exit hole interior	1	Pass
Swiftpack – vibrating feeding channel	1	Pass
Blank	ND	Pass

LOQ = Limit Quantification Limit = 0.03 µg/in^2
RAL_T = 2.70 µg/in^2

Table 5
Results for Detergent Traces

Equipment Part	Detergent Results (µg/in^2)	
	Sample	Pass / Fail
Swiftpack - non dedicated parts	< LOQ	Pass
Swiftpack – dedicated parts	ND	Pass
Hopper – lateral walls	ND	Pass
Hopper – lower interior corner	<LOQ	Pass
Hopper – vibrator plate	1	Pass
Scoop	ND	Pass
Metal Trays (Parrilla)	ND	Pass
Manifolds	<LOQ	Pass
Dividers	ND	Pass
Slats	<LOQ	Pass
Brushes - small	1	Pass
Brushes - large	1	Pass

LOQ = Limit Quantification Limit = 0.03 µg/in^2
RAL_N = 35.51 µg/in^2

Benefits and Disadvantages

The combo-lots implementation generates benefits to the packaging operations. The most important benefit is the packaging cycle time reduction due to the major and interval cleaning consolidation. The estimated savings are $210.00 in the changeover hours per Combo-lots. The operational cost for the combo-lots was of $4,026.00 approximately between direct and indirect labor.

With the implementation of this project the appropriate procedures are in place for batch

traceability to mitigate any potential impact due to investigations or complaints that could result in product recall. Therefore, from a risk-based approach, adequate controls and procedures have been implemented as part of the design project.

The possibility of an adverse quality event was evaluated and a traceability system was placed with future recommendations. Bulk lot traceability can be estimated with the new table included in the batch record. This table document the information related to the manufacturing batch number, sequence, when the manufacturing lot was added to the packaging filler machine and the approximated shipper number that contains the first bottle of each bulk lot. In the future an automated sub-numbering system is recommended for full and 100% traceability of bulk lots within each combined lot packaged. A SWOT analysis was generated for the combined lot project.

Strengths	Weaknesses
1. Reduce the downtime due to minor and major cleaning process. 2. Helps to release more lots for distribution. The release and lot review is simplified due to several lots are packaged together. 3. Line performance is been optimized. 4. Financially, more absorption is generated. 5. Retain and stability samples are less that a regular manufacturing lot packaging process.	1. The required manufacturing lots are no released for packaging into combined lots. 2. Human errors can be done when the manufacturing lot start and end is been indentified during the packaging process. When the new manufacturing lot is being added to the filler machine, the bottle that contains it can be difficult to identify. Therefore when a sampling is performed, no representative sampling from each manufacturing lot can be performed.
Opportunities	**Threats**
1. Extend the campaign length that allows packaging more combined lots continuously. 2. Use this methodology to package other high volume products. 3. Design a lot sub-numbering process for the each bottle packaged in the combo-lots. This sub-numbering process will provide traceability of the bulk lots used to package each bottle. The sub-numbering process can be created as a new or future project.	1. The required manufacturing lots are no available for packaging into combined lots. 2. The required BOM's are no available for packaging into combined lots. 3. Distribution can be affected if the lots are not approved.

Figure 8
SWOT Analysis

CONCLUSION AND FUTURE WORK

Manufacturing operations are constantly trying to find different ways to be more competitive. These initiatives include reducing the operational cost, downtime and processing cycle time in order to attractive without risking the product quality. The implementation of this project creates a more agile manufacturing reducing the downtime due to the cleaning process.

This project can be implemented in those products that are considered high and medium volume. The packaging line capacity can be organized in a certain way to dedicate packaging lines to these products and the combined lots activities.

Based in the obtained results it can be concluded that the research was fulfilled. The minor cleaning process and the campaign length was validated based on the acceptable results obtained for AI traces, DL traces and ML. the changeover time was reduced to approximately six (6) hours. Minor cleaning process was reduced from four to one when five bulk lots are packaged together. Major cleaning process was reduced from three (3) to one (1) after packaging fifteen (15) bulk lots continuously. SOP’s were updated to include the applicable modifications in order to document the combo-lot packaging process.

Bulk lot traceability can be estimated with the new table included in the batch record. In the future an automated sub-numbering system recommended for full traceability of bulk lots used or combined together as a combine lot.

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