Study of automated quality control system for sampling weighing of packaging materials in the Pharmaceutical Industry with recording and analysis of data.

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***Abstract*— Automation means standardizing a process through certain steps that must be followed to produce a desired result. Automation was reinterpreted through engineering and electrical engineering in the 20th century, as a field of mechanical science dealing with the control of processes and their maintenance in a defined state and is conceptually based on control theory and feedback mechanisms. Specialized high-powered computers, programmable logic controllers (PLCs), are used to synchronize the flow of input from physical sensors with the flow of commands to output devices. The present dissertation presents the study of an automated quality control system for sampling weighing of packaging materials in the Pharmaceutical Industry with recording and analysis of data. You do this by inputting weighing data from power cells and analyzing the results via a programmable logic controller (PLC). Operation is via SCADA. In addition, the equipment included in the parts of the mechanical and electronic system that will be needed for the implementation of the construction is described in detail. The master's thesis is completed by recording the comparative results of the construction.**

***Keywords*— Automation, Programmable Logic Controller (PLC), Load cell, Quality control, Pharmaceutical industry.**

I. INTRODUCTION

The primary purpose of this study is to increase the available production time in the packaging lines of the Pharmaceutical Industry while increasing the profit from reducing the time required to implement the process of recording the weighing data of packaging materials and calculating the weight limits of the final product. . The secondary purpose is to automate this process by eliminating the possibility of human error in calculating the balance limits of the final product, increasing the reliability of quality control systems.

II. PRESENTATION OF THE PROBLEM

In each packaging line of the Pharmaceutical Industry there is a dynamic balance where it ensures that the final package contains the right amount in the primary container as well as the secondary materials, based on the limits and regulations set by the legislative authorities for each product.

In addition, in some packaging lines there are dynamic scales where they ensure the filling weight in the primary container, immediately after it is filled by the filling machine, thus adding more profit to the total batch, as in case an underweight or overfilled piece is found, it will discarded before the secondary packaging thus avoiding the cost of the secondary packaging materials.

It is worth mentioning at this point that dynamic scales control 100% of the products produced in the packaging production lines, offering, with the appropriate software, a complete picture of the packaging data, such as measurement of the packaged products, total weight per batch, minimum, maximum product weight limits, desirable and disposable weights.

Adjusting the limits (minimum and maximum) of the weight controllers requires a procedure for recording the weights of all the primary and secondary packaging materials that will be used to package a product. Then, based on the limits of the primary container, the total limits to be set in the final weight controller are obtained. This procedure varies by type of packaged product (creams or ointments, liquids, suppositories, solids) and uses a different way of calculating the limits of the weight controllers of the packaging lines.

<u>The disadvantages of the existing procedure are:</u>

- Time consuming process.
- High cost of unproductive hours in man-hours. (Labor Hours)
- High cost of unproductive hours in Machine Hours.
- Reduced production of packaged products with each product change.
- Reduced productivity index (OEE - Overall Equipment Effectiveness).
- High risk of human error.
- Large number of discarded products due to incorrect limits.
- Possibility of skipping secondary packaging items due to incorrect limits.
- High risk of not ensuring quality standards.

III. NEEDS ANALYSIS – STUDY RESTRICTIONS

- Display of batch numbers from each packing material (Batch Number) as well as the order number (Process Order) in the final weight recording report.

- Automated recording of the weights of the primary and secondary packaging materials.
- All calculations will be done automatically via a programmable logic controller (PLC).
- Save copies of the weight report.

IV. REGULATORY AUTHORITIES – STANDARDS

In the Pharmaceutical Industry, a number of national and international regulations and industry standards provide guidance to ensure the safety and efficacy of products.
Due to the rapidly growing globalization of the pharmaceutical industry and markets, regulators are trying to harmonize regulations and facilitate faster and more efficient drug development and production processes.
A central document for the pharmaceutical industry is Pharmacopoeia which is a collection of published standards describing the requirements for testing chemical and biological drugs and dosage forms, as well as methods for drug analysis. These standards are set to ensure that medicinal products have the appropriate identity, as well as durability, quality, purity and consistency.

Certain regulations and standards, including GMPs, have been established to ensure accurate and consistent measurements. Some, such as the USP-NF, have set specific standards, while others set general principles. We will then refer to the standards and principles related to weighing procedures and provide guidance on how to ensure regulatory compliance.
Although there are differences in the wording of the different GMPs, the basic principles are similar. Therefore, reference is made to documents provided by the FDA (21 CFR), the EU (EudraLex) and the ICH (Quality Guidelines such as Q7: GMP for API). In addition, it is worth noting how USP and ISO standards and regulations affect the selection, installation, operation and maintenance of weighing instruments.

The regulations relating to weighing instruments and weighing procedures can be summarized as follows:
• The weighing equipment must be designed for its intended use, prevent contamination of the medicinal product and facilitate easy cleaning.
• The manufacturer must select the appropriate equipment with appropriate weighing ranges and accuracy to meet the specified process tolerance.
• Weighing equipment must be calibrated according to written procedures and set schedules.
• Weighing systems must be adequate and weighing procedures must be validated to document compliance with specified specifications.
• Advanced weighing systems based on computer hardware and software must comply with specific regulations for computerized systems.
Most countries have legislated that pharmaceutical manufacturers must follow GMP procedures and have developed their own version of GMP. However, two key players are driving the development of GMP with a strong global influence. These are the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

Summarized the regulatory authority and guidelines are:

- FDA - Food and Drug Administration

CFR - Title 21 - Food and Drugs

- EMA - European Medicines Agency

Eudralex, Volume 4: EU Guidelines to Good Manufacturing Practice.
ICH Q7A GMP Guidance for API.

- WHO - World Health Organization
- EOF - National Organization of Medicines

Summarized the standards are:

- ISO - International Organization for Standardization

ISO9001:2008 - Quality management systems — Requirements (Clause 7.6 Control of monitoring and measuring equipment)

- ISO 3951-1 - Sampling procedures for inspection by variables
- GMP - Good Manufacturing Practice
- URS - User Requirement Specification

[1][2][3][4][5][6][7][8][9]

V. QUALITY CONTROL

Quality control is that part of the Quality Assurance System which deals with the specification, sampling and testing of materials and products as well as with the organization, documentation and release procedures that ensure that the necessary tests and inspections have been carried out and that the materials will not be put to use, nor the products for sale or distribution, until their quality has been deemed satisfactory.

Key areas of Quality Control:

- Frequency of Checks
- Special Instructions and Exceptions
- Packaging Stages
- Form Structure / Template
- Categories / Levels of Controls
- Product content control
- Deviations, findings outside AQLs & product reprocessing
- Sampling plan
- Actions in cases of weight outside the limits
- Product filling weight control marked "e"

Checking the proper operation of checkweighers:

For each batch of product, a sample is created to check the correct operation of the balance (challenge sample), the weight of which is calculated if 0.5 g is deducted from the minimum adjustment limit of the balance, which is the uncertainty value (±) of the balance.
The challenge piece is easily made / achieved by removing 0.5g of product from the primary container.
Before the start of the packaging and then as part of the checks by the person in charge of the line and the IPC person,

a check is made to verify the correct operation of the checkweigher as follows:
• The samples used for the test (challenge samples) must be marked with the indication of the batch of the product and its weight and are always at the top of the balance in a special place throughout the packaging.
• In case a batch of a packing material is changed and the minimum limit is changed, the resulting lower limit is compared with the previous one and if necessary the sample is changed.
• When passing the sample through the yoke, the sample must be discarded immediately, via the line rejection system. Otherwise the packaging is stopped and the person in charge of the packaging is informed immediately.
• In the systems control form (AQAls List per line) of the corresponding form for each line, it must be indicated every time the correct operation of the balance is checked, the indication of the balance during the passing of the sample and the adjustment limits of the balance.
• Throughout the packaging, each challenge sample is kept in a specially marked box (located above each yoke) and after the completion of the packaging is destroyed by the responsible person according to the procedure. [10]

In the case of a packing line with a serialization system that cannot be implemented above, the creation of the sample to check the correct operation of the balance (challenge sample) as well as the control of the correct operation of the checkweigher is differentiated due to the addition of the system serialization. This system does not allow the same sample challenge piece to be used throughout the voucher package. In detail, not only 0.5g, which is the uncertainty value (±) of the balance, but also the average weights of the materials are deducted from the minimum adjustment limit of the balance. In this way the weight of a filled tube is calculated. This tube (and not the final product) is the challenge sample and replaces the filled tube in a piece of cardboard each time the correct operation of the balance is checked. This is because the box print control station precedes the balance station so it is essential that the box is not printed. After the completion of the test, only the tube - challenge sample is retrieved from the disposal station for use in the next tests. [10]

Requirements for the use of scales:

- Scale position

The accuracy and correctness of the scales' results are closely related to the position and balance of the balance. The stability of the balance position must be ensured. The bench that is installed must ensure that it is not affected by parallel work that can cause vibration. If there is a risk of instability, the balance should be equipped with a bubble check.

- Temperature

Weighing results are affected by ambient temperature. The room temperature should have a constant temperature which should not change at a rate higher than 5^{o}C per hour.

- Moisture

Humidity conditions at the time of weighing should be between 20-80% for Class II and III scales found in factory production and packaging.

- Light

Scales should be protected from direct sunlight (high temperatures).

- Air

The scales should not be placed near air flow (laf, ventilation, doors) as their function may be affected. [10]

Balance Calibration & Validation:

Balances are critical instruments and therefore their proper calibration and operation are prerequisites for accurate measurements. Each balance is used for weighing weights of a certain scale, which is determined by its technical functional characteristics and the requirements of its operating space.
A suitable label is affixed to each balance to indicate the weight scale for which the balance can be used. In general, the higher a scale can weigh, the less accurate it is. The proper operation of each balance in relation to the specified requirements for the weight scale for which it is used is checked by the use of appropriate station standards tested by an authorized person once a year. Appropriate standard weights are used to control the scales. The use of the standards is strictly done with the use of forceps up to 500mg and with gloves for the rest (located in the box of the standard weights) and the operator should wear gloves when doing the test. [10]

Weighing procedure:
The process concerns the packaging department of the Pharmaceutical Industry and in particular concerns the development of the application which results in the optimization and accuracy of calculation of existing procedures that contain manual arithmetic or logical calculations. The description of the process of calculating the rejection limits during the final weight control, and how to check the correct operation of the On-Line packing scales (Challenge Test). The scales (Checkweighers) on the packaging lines perform 100% control of all packages / products and are used to confirm, the packaged quantity of the product and / or existence of the primary container or some packaging material.
Note that the scales (Checkweighers) cannot confirm in any case that all secondary packaging materials are within the final packaging. This is because deviations in the weights of materials such as the box or glass vial as well as fluctuations in the filling weight as a whole are likely to cover the weight of one of the materials. The existence of materials, such as the instruction (Leaflet) in the secondary container, is confirmed by individual automated quality control systems installed at various points on the packaging lines during the process. One such system is the instruction photocells inside the box. [10]
Electronic online scales are affected by environmental factors and can adversely affect their accuracy, such factors are:

- humidity
- temperature changes
- air currents
- the vibrations of the floor or the packaging line
- electromagnetic noise and interference from electromagnetic fields

To these we will add some technical factors related to the physical condition of the mechanical parts of the balance such as:

- corrosion / wear of parts of the balance(eg belts & bearings).
- the mechanical stress of the power cells.

All these effects appear as instability in the weighing indicators. This practically means that the repeated weighing of a certain weight under the aforementioned - changing - conditions does not always give the same result.
This variation in the behavior of a balance is called uncertainty and should be taken into account when adjusting the weight limits.
The uncertainty of the measurement as a parameter characterizes the dispersion of the values that can be attributed to the result of a measurement. For example, when measuring the weight of a piece on a balance, if the balance is 100g and the uncertainty in that measurement is 0.5g, this means that the actual weight of the item is estimated to be between 99.5g and 100, 5g. Note that for all weighing scales the uncertainty value is (±) 0.5g.[10]

VI. Basic levels of packaging and packaging materials

There are three basic levels of packaging, primary, secondary and tertiary. It is important to understand that all levels of packaging serve specific purposes with specific requirements in order to get products to people safely, efficiently and consistently.

- The primary package is the one that immediately encloses and contains the medicine.
- The secondary packaging is the outer packaging of the main packaging which groups the packages and further protects or characterizes the medicinal product.
- Tertiary packaging is used for bulk handling, storage, and distribution.

Secondary packaging is important for a variety of reasons, including physical and barrier protection, secondary restraint, compliance, and patient safety. Although secondary packaging can take many forms, it will always contain a level of packaging within it. Usually, the level of packaging that a consumer will see first is secondary packaging. This makes the appearance of the secondary packaging very important.
Secondary packaging for clinical trials can take many forms, depending on the primary packaging. An example of a secondary packaging used in both clinical trials and commercial products is a box. The artwork can also be easily printed on boxes, making them a popular choice for almost all secondary packaging applications.

Secondary packaging plays a huge role in distribution. During distribution, the secondary packaging protects the primary packaging and the product. A glass vial if packaged directly in their transport cartons would have a high probability - certainty, of breaking during transport. The secondary packaging creates a safety net, protecting the primary packaging from each other.
Although a significant benefit of the secondary packaging is the transport, it plays a more direct role on a daily basis mainly in the protection of the product. Because secondary packaging often comes into contact with consumers, they must protect the product in the event that the consumer abuses the packaging as in the simplest case a customer accidentally drops and smashes a primary packaging, such as a glass vial. The geometric characteristics of the cartons allow the tertiary packaging to be properly and smoothly managed at all levels of the supply chain and can take full advantage of the dimensions of the means of transport (trucks, containers, etc.) so that the products do not shift during transport. Cartons are also easier to handle than primary packaging, so packaging or unpacking containers is smoother than a configuration without secondary packaging.

VII. Presentation of the Application

Adjusting the weight limits on the Checkweighers:

Limits are calculated separately for both the online scales of the filling machines (for all the packaging lines that support it) and for the final product control scales.
The following procedure also provides for cases where the product includes additional material (eg dosage spoon, implementor plug, comb, etc.) or only primary container (absence of leaflet and / or box). For each type of packaged product (creams or ointments, liquids, suppositories, solids, etc.) the following are followed.

The present application consists of ten weighing points where they record automatically through the Programmable Logic Controller (PLC) and the corresponding calculations are made in the weight recording fields. The following is a detailed description of the procedures followed to record the weights of the primary and secondary packaging materials.

TABLE 1. Weighing Process of the primary and secondary packaging materials.

STEP	DESCRIPTION
1	Collection of primary and secondary packaging materials.
2	Recording of batch numbers from each packaging material (Batch Number) as well as the order number (Process Order) through the Barcode Scanner.
3	Simultaneous placement in the weighing positions of the 10 pieces of each primary / secondary packaging material.
4	Automated simultaneous calculations: Maximum, minimum and average weight per category of secondary packaging material. Minimum and maximum filling weight of the primary container. Minimum and maximum weight limit of the final product. Weight of the Challenge Test. Automatic printing and saving of a copy of the weight recording report.
5	Adjusting the limits of the dynamic balance of the packaging line based on the calculations depending on the type of product.

VIII. CONCLUSIONS

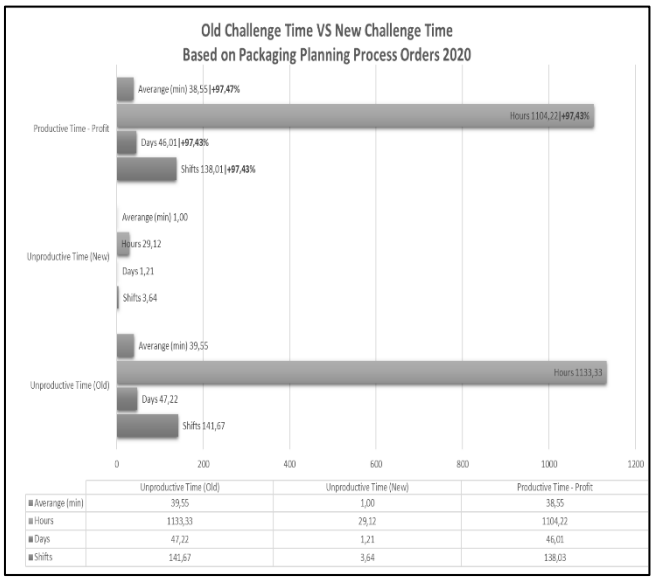
In the present study, the eleven (11) Packaging Line of the Pharmaceutical Industry was recorded and analyzed in the 1747 process Order assignments.
Initially, the PO's per packaging line are presented in detail with the average time required to implement the packaging material weight recording form and the issuance of the final results for the adjustment of the limits of the weight controller of the final product. The method to be followed should be stated as done with static balance and manual recording in the corresponding weight recording form of the corresponding packaging line, as well as the calculations required for the limits of the weight controller of the final product to be adjusted on the weighing lines of the packaging line.

The main advantages of the application are the following:

- Simultaneous weighing of 10 packaging materials per group of materials.
- Maximum implementation time is 1 min (4 clicks).
- Easy to use and easy graphical user interface.
- Create a database of weight recording forms per PO.
- Remote technical support.

In summary, the last graph presented shows the total time required for the implementation of the process of recording the weighing data, the two methods and the profit, mentioned above, clearly stating that the annual profit rate reaches at least 97.43%, which means that the time required for the existing method was spent 1133.33 productive hours while now 29.12 hours will be spent. The financial profit of a total of 1104.22 hours includes, the corresponding profit of the Pharmaceutical Industry, in the reduction of costs in man-hours (Labor Hours) and in machine hours (Machine Hours) and of course in the increase of the time of availability and utilization of the packaging lines.

Graph 1. Old Challenge vs New Challenge Time per Year



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