Portable Raman Spectroscopy: An Improvement in the Raw Material Quality Identification Testing Method

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Abstract *— An external contract laboratory performs the identification testing method of raw materials for a pharmaceutical company. Performing this current activity affects the product release timeframe and represents a high-cost process to expedite the release of the results. It's in the company's interest to improve the current process with a cost-effective analysis by avoiding the time waste associated with sample preparation, processing, and travel time. The portable Raman spectroscopy method testing for raw materials was proposed as a possible option to perform in-house analysis and as a rapid data acquisition tool. Three raw materials were analyzed using the current process and the Raman method to compare the cycle time of each activity. This research showed that using portable Raman spectroscopy is an effective way to perform the identification testing of raw materials by reducing cost, lowering cycle time, and improving process results in one day instead of one week.*

Key Terms *— Cycle Time, Raman Spectroscopy, Raw Material, Testing Improvement.*

PROBLEM STATEMENT

A pharmaceutical company in the north region of Puerto Rico is allocating its resources to finishing its Phase 3 clinical trial of the extended-release tablets and starts the manufacturing operations as soon as possible. It has been determined that the Quality Control Lab needs to improve its testing operation to a more competitive and lean sustainable process. It was observed that an identification test is required for each container of raw material received used in the manufacturing process of extended-release tablets, which now is an annually high-cost activity that requires the services of an external contractor company. To improve the identification testing, the portable Raman spectroscopy method would be an affordable option to reduce cost and cycle time. By implementing this method, the testing could be performed by the company's analysts, doesn't require an external contractor, and the process can be validated before the manufacturing operations for the extended-release tablets start.

Research Description

This research analyzes the differences in the cycle time and quality control of identification testing of raw materials performed by the current laboratory techniques against the new Raman technology at a pharmaceutical company. Evaluates the cost-effectiveness of improving the testing process so it can be performed by the internal staff and discontinue the necessity of external services.

Research Objectives

- To implement a cost-effective quality Raman spectroscopy method to improve the identification testing analysis of raw materials at the company's QC Lab for introduction of a new product of extended-release tablet.
- Reduce 60% of the annual cost for ID testing per container using the Raman Method with Truscan RM equipment by February 2022.

Research Contributions

The project implementation of Raman Spectroscopy will provide the following benefits:

- Incoming and QC Lab operations cost and cycle time reduction.
- Introduce Faster Forward culture of innovation, decision making at the right level, agility, and value creation at the Incoming area.
- Helps achieve On-Time Delivery Company goal.

- Help reduces adverse impact for the environment with the reduction of samples generated (less high-density polyethylene and chemicals for waste).
- Non-invasive testing, less personnel exposure to chemicals.
- Less risk of cross-contamination of materials.
- Less sample handling between deliveries to an external lab.
- Testing can be performed at the Company's Main Lab site.

LITERATURE REVIEW

The pharmaceutical industry strives to deliver the best quality product to "the consumers", which are the patients in need of their medications. These products must comply with the "Good Manufacturing Practices" or GMPs to assure the quality of the process under the guidelines established by the regulatory agencies. Nevertheless, maintaining a level of quality that could impose a benchmark in a very competitive industry comes with a substantial cost that affects the overall operation. To protect the safety and well-being of all patients, pharmaceutical companies invest a lot of effort in improving their operations without affecting the level of quality. In a Puerto Rico pharmaceutical company, the Quality Control Lab (QC Lab) was identified as a prime candidate to improve its raw material identity testing analysis for the introduction of a new product of extended-release tablets.

The scope of this research is to identify the cost-effective and quality control advantages of the adoption of a portable Raman spectroscopy method in exchange for the current identity methods of raw materials used in a pharmaceutical company. The current operation for raw material identity testing consists of different stages. The first stage of the process is the inspection and sampling of the raw material at the Incoming Area by two quality control inspectors. The quality control inspectors extract and prepare a representative composite sample to be sent to an external QC Lab for chemical analysis. The technologies and identification testing methods used at this external QC Lab are high-pressure liquid chromatography (HPLC) and near-infrared (NIR) spectroscopy. These testing methods have been identified as a high-cost activity taking several hours or days to acquire the results, during which time the material is unavailable for production [1]. Nevertheless, according to Green "In terms of analytical characteristics, Raman spectroscopy is particularly effective for identity testing because of its high degree of selectivity. Every chemical compound with covalent bonds produces its own characteristic pattern of Raman shifts, which can be used to chemically fingerprint and therefore identify the compound" [1].

As described by Heintz, "In Raman spectroscopy, an unknown sample of material is illuminated with monochromatic (single wavelength or single frequency) laser light, which can be absorbed, transmitted, reflected, or scattered by the sample. Light scattered from the sample is due to either elastic collisions of the light with the sample's molecules (Rayleigh scatter) or inelastic collisions (Raman scatter). Whereas Rayleigh scattered light has the same frequency (wavelength) of the incident laser light, Raman scattered light returns from the sample at different frequencies corresponding to the vibrational frequencies of the bonds of the molecules in the sample. Since the bonds for every molecule are different, the Raman scattering for every molecule is also different. Thus, a Raman spectral "fingerprint" can be generated by recording the intensity of light as a function of the frequency difference between the laser and Raman scattered light. In a typical powdered substance, the intensity Raman scattering is roughly 10 million times less than the intensity of Rayleigh scattered light, and therefore very sensitive instrumentation is needed for Raman spectroscopy." [2].

A handheld Raman spectrometer can quickly perform on-the-dock authentication of incoming raw materials, enabling a move toward 100% inspection while saving time and reducing handling [1]. As described by Dolitch, Developing Portable Raman Spectroscopy for Identification of Raw Materials

used in Pharmaceutical Development and Manufacturing, “The idea of testing the sample at its origin minimizes the number of samples taken, sampling error, labeling error, potential worker exposure, and so on, and allows for increased efficiency when testing multiple drums and batches. Unlike laboratory testing where standards are prepared and tested along with the sample, portable methods rely on stored reference standard spectra for sample identification, and evaluation of these libraries for sustainability and robustness is critical to the long-term success of material identification. For water solutions, Raman is an ideal measurement technique because water will not interfere with the Raman signal of the material of interest, unlike Fourier transform infrared (FT-IR) and near-infrared (NIR) spectroscopy where water produces a strong background and can in most cases interfere with the material of interest” [3].

Raman spectra can be acquired through transparent packaging materials such as the plastic bags commonly used to line drums containing incoming raw materials. This means of testing reduces the time between receipt and availability to the production line, minimizes handling and, for materials packaged in transparent media, eliminates the risk of contamination posed when the packaging seal is breached [1]. This ease of use enables nonexperts to positively verify the identity of materials at the point of receipt, increasing an organization’s throughput and cycle time. Moreover, it maintains a higher degree of quality control by the identification of foreign matter, especially with the introduction to the new product of extended-release tablets at the pharmaceutical company. As described by Lee “Raman can be used for identification of materials on a tablet confirming it was not counterfeit, and for identification of a black contaminant as charred organic and not metal or dirty oil from the processing equipment. In addition, spectra of different areas of the tablet can also identify the tablet materials to confirm the tablet’s legitimacy” [4].

METHODOLOGY

To meet the objectives of this research, a quantitative methodology was performed to examine the relationship between variables after careful understanding of the data and make changes accordingly. The first step was to establish a schedule between the Quality Control, Quality Assurance, and Supply Chain departments. The materials used for the study must not impact the manufacturing operation and can be used as an experimental sampling procedure. All the personnel from the Quality Control Lab were trained on the management of the portable Raman equipment and safety precautions. The next step was to identify the most sampled raw materials used in the manufacturing of the new product.

Once the raw materials were selected, the quality control inspectors follow their sampling procedures for the preparation of the samples that were going to be analyzed by the current lab equipment and the portable Raman equipment. To prepare the test samples to challenge the portable Raman method, samples of approximately 2 g of each raw material container were sealed in 2-m-thick polyethylene bags to emulate expected-use scenarios (measurement through plastic bags) for incoming material inspection. Before the analysis of the samples, the spectra virtual library of the portable Raman equipment was updated with the spectra of each raw material. The testing of the samples was performed at the Quality Control Lab with the same environmental conditions and material specifications for all the identification analysis equipment by the Quality Control Analyst. The data was analyzed through graphics and statistics which showed the numerical data of the difference in cycle time and cost per sample by the current identification testing method compared to the suggested portable Raman spectroscopy method.

RESULTS AND DISCUSSION

Every organization strives to become a benchmark in its field, to satisfy customer needs with high-quality standards, low costs, and low cycle

times. To achieve a quality lean performance of every process in a manufacturing operation, a pharmaceutical company in Puerto Rico has determined to explore the possibilities in improving the Quality Control Lab identification testing methods by using a portable Raman spectroscopy instrument. As part of the improvement process, a Voice of the Customer and a Critical to Quality diagram were designed for discerning customer needs, as presented in Figure 1.

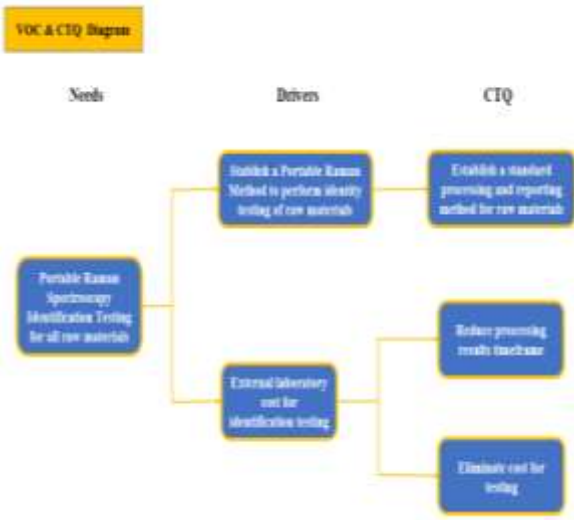

Figure 1
VOC & CTQ Diagram

The introduction of a portable Raman method for identification testing of all raw materials used to manufacture extended-release tablets was adopted to reduce and eliminate all possible costs associated with the external laboratory activities to provide the test results. Moreover, being able to perform the testing in its facilities and consolidate operations in a streamlined process is one of the company's goals.

To determine the areas of opportunities for improvement in the operation, a Process Flow Chart was developed to identify those activities that generate the most waste. The current state of the process consists of taking a sample from the raw material container to the external laboratory for identification testing, processing the satisfactory results, and performing a release disposition of the material, as represented in Figure 2.

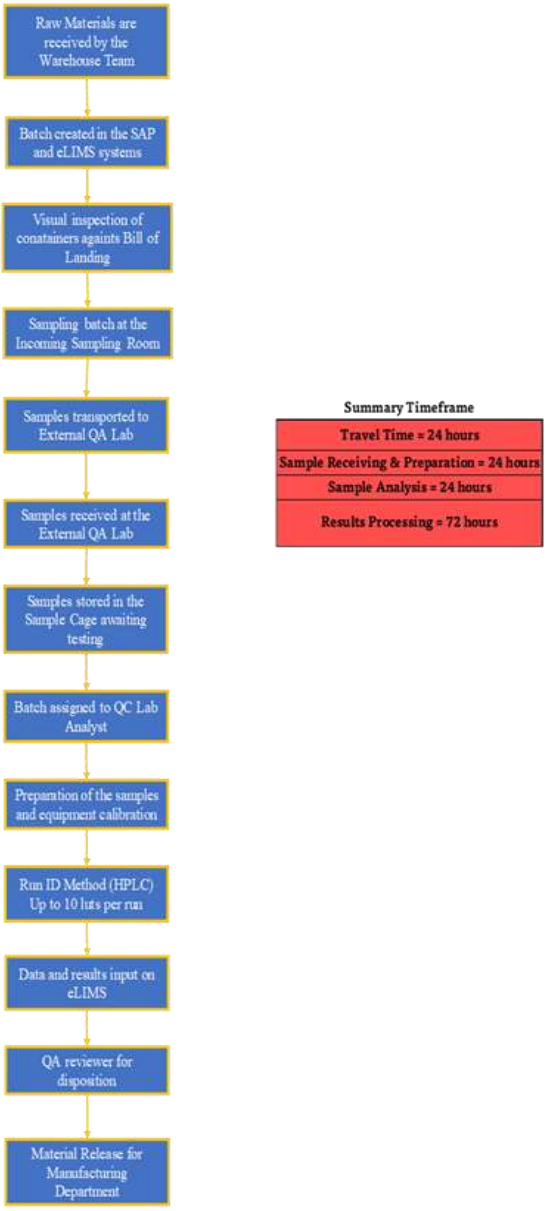

Figure 2
Current State Flow Chart Diagram

By analyzing the process flow, it was observed that the preparation and receiving of the sample, the sample analysis, and the travel time of the sample through the process are the critical steps that affect the cycle time. For the current state of the process, the total processing time is of 144 hours. The total timeframe for the current test method shows that it can't comply with the new company's need to have on-time lots releases for the introduction of new products. This usually leads the lot to be held for one week in the warehouse area, waiting for the results.

The new product bill of the material shows that the three raw materials needed the most in the manufacturing process are Croscarmellose Sodium, Opadry Yellow, and Magnesium Stearate. These raw materials are classified as excipients or inactive ingredients, which are added intentionally to the drug substance, and should not have pharmacological properties. Each lot of raw materials has 10 containers which a sample was prepared from each container to be analyzed by the current testing method and the proposed Raman method. The samples were prepared and sent to the External Lab, where the analysis timeframe for both testing methods was evaluated.

Figure 3 shows how many minutes the current process and the portable Raman method took to analyze ten samples of each raw material. The Raman method took considerably less testing time and an 87.5% reduction in cycle time for each raw material than the current method. This difference in testing time corresponds to the current process's sample processing and data management, which includes many methodologies and multiple operational steps.

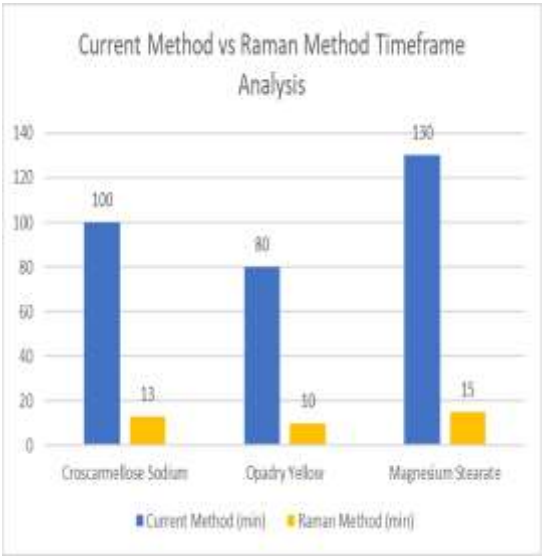

Figure 3
Current Method vs Raman Method Timeframe Analysis

The current practice for container ID sampling and testing is a high-cost activity, but by implementing the portable Raman method, a cycle time and cost reduction of the process is attainable. The current process was improved by performing the testing directly through the polyethylene bag of the material at the Incoming Area, reducing sample analysis, eliminating travel time between sites, and reducing results processing. For raw material identity verification, Raman spectroscopy —with its point-and-shoot operation and unambiguous results presentation—is an ideal tool for busy warehouse personnel, removing the need to collect samples and providing immediate results [5]. Performing all identification testing activities to the company's own facilities will cover the initial investment of $100,000 for the equipment and validation requirements. Refer to Figure 4 for the current process vs. the portable Raman method flowchart diagram.

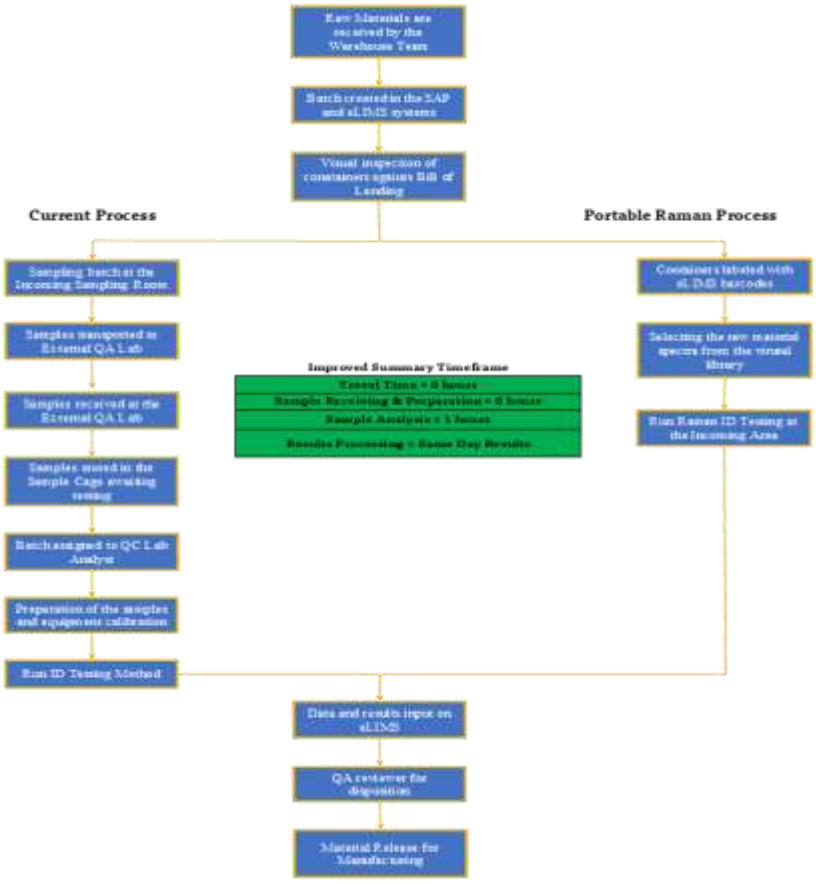

Figure 4
Current Process vs Portable Raman Process Flowchart Diagram

Currently the total cost is $48.59 per sample, as presented in Table 1. In 2020 the ID sampling and testing cost $383,356.50 approximately. For example, the company received a batch of Croscarmellose Sodium of 28 containers in 2020. The sampling and testing for ID per container total cost were $1,360.52 approximately and a cycle time of 4.89 min/sample. However, using the Portable Raman ID testing method for the same batch of 28 containers, the activity cost would be $368.20 approximately and a cycle time of 1.07 min/sample. For this lot, there is a cost reduction in testing activities of $992.32 and a reduction of 3.82 min/sample cycle time. The result of this exercise means that by adopting the portable Raman method, the cost per sample would be lower, from the current cost of $48.59 to $13.15. Performing all identification testing activities to the company's own facilities will cover the initial investment of $100,000 for the equipment and validation requirements within the first annual quarter.

Table 1
Total Cost per sample

Current Quality Control Activities	Cost (per sample)
Incoming Activity: 1. Container identification & sample preparation 2. Sample extraction per container 3. Systems batch processing (SAP, Logbooks & eLIMS)	$18.64
External Lab Testing Activity: 1. Sample and documentation receiving 2. Run ID Testing and result verification 3. Results processing (ELIMS)	$23.97
HDPE Containers & Labels	$1.48
Sample Delivery	$4.50
Total	$48.59

The Truscan RM equipment and the Raman spectroscopy method are beneficial in examining non-polar bonds, functional groups, and highly symmetrical vibrations. There was an equipment limitation in the capability of the equipment to differentiate between materials with similar molecular structures, distinguished by polar bonds and materials that may exhibit fluorescence. As described by Dotlich, "Failures classified as false negatives or positives are directly related to the variability captured in the library standards. Failures may be minimized by capturing the appropriate level of library robustness and additionally understanding the factors that may lead to a failed result" [3]. The equipment can analyze materials thru most types of packaging materials such as polyethylene bags and crystal vials. Nonetheless, the Truscan RM equipment cannot analyze thru paper bags or opaque polyethylene containers, which would require a sample to be extracted from the original packaging container and placed into a vial for the Truscan RM to be capable of analyzing the material. Therefore, there may not be a considerable limitation in the Truscan RM capability or the Raman testing method.

CONCLUSION

The technology's specificity for a wide range of materials, its ease of method development and validation, and the ability to directly transfer methods between instruments enable handheld Raman spectroscopy to both improve the quality of raw materials testing while reducing cost [3]. The current testing process suffers from high-cost factors such as needing a more controlled environment to protect material integrity, employer exposure to materials, and time delay because of testing, more personnel, and equipment to comply with product demand. In contrast, the portable Raman method is a non-invasive testing procedure with less risk of cross-contamination of materials, and it can be performed outside an external laboratory setting like the Incoming Sampling Area. Testing materials without removing samples from packaging is valuable for the company's financial goals, saving time and resources. Moreover, with no associated cost related to sample preparation, travel time, and results processing, the future manufactured lots can be released on time. This testing improvement method reduced the processing timeframe from 144 hours to 24 hours. Handheld Raman spectroscopy is an excellent alternative to traditional incoming raw-material inspection by high-pressure liquid chromatography, wet chemical methods, and NIR and mid- IR spectroscopy [1]. Addressing the company's needs to reduce cycle time and cost from the current testing procedures for introducing new products while maintaining quality promotes a continuous improvement mentality through the organization and a benchmark against its competitors.

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