Strategy for the Implementation of Raman Technology in the Raw Material Incoming Area

Ada G. Ortiz
Master of Engineering in Manufacturing Engineering
Edgar Torres, Ph.D.
Industrial Engineering Department
Polytechnic University of Puerto Rico

Abstract *— State of the art new technology to identify raw materials is available for the manufacturing industries to improve and accelerate the identification process. This document will cover the Raman technology, theory concepts, benefits and advantages with the implementation. In addition, a comparison between the conventional identification methods versus the Raman technology will be discussed.*

Key Terms *— High Performance Liquid Chromatography, Near-Infrared, Raman Spectroscopy, Raw Materials.*

INTRODUCTION

The identification of Raw Material is an essential and important step for any industry in order to obtain the desire results in the creation of a product. For regulated industries, such as pharmaceutical, the identification of Raw Material is part of the quality control in order to prevent any type error or misunderstanding of similar or mislabeled components. Any type of error in this type of industry can cost from lives of people thru large quantities of wasted material and money.

There different methods to perform the identification of Raw Materials that include a wide range of methodologies as HPLC, wet chemistry thru Near-Infrared (NIR) and Raman Spectroscopy. The first two methods mention involve process that requires and consume longer periods of time, qualified personnel are needed, and usually damage (destroy) the material been tested. The last two methods NIR and Raman Spectroscopy are like the "state of art" technologies involving sophisticate system that can be identified materials in seconds and have as advantage that the material been identified can stay in the package and there's no need to open it.

A large quantity of industries has implemented changes to improve their process by choosing Raman Spectroscopy technology to identified materials. Other industries still used the traditional methods. When the demanding of a product increase, industries need to execute changes in order to satisfied the necessity. Sometimes those changes include implementing new technology that helps industry to improve process and stay in the market.

RESEARCH DESCRIPTION

This research study and analyzed the actual method of a pharmaceutical to identified Raw Material in the incoming area. Evaluates an alternative that is more efficient without compromising the quality and provides a strategy for the implementation of Raman Technology in the Incoming Area for Raw Material Identification.

RESEARCH OBJECTIVES

Increase detectability having a reliable method of quality control, reduce costs associate with waste material, reduced cycle time, conduct at-line screening for fast material released are some of the objectives of the strategy for the Raman Technology implementation.

RESEARCH CONTRIBUTION

The implementation of Raman Technology in the process would bring benefits in many aspects. Raman Technology has the characteristic of identifying raw materials without the need to open the package. Implementing a system with that characteristic would contribute in maintaining the integrity of the raw material, eliminate the necessity of having rooms with control environment for

sampling, protects the safety of personnel by not exposing them directly to the material. Quality, reliability, reduction of time, faster results (at-line-release) and cost reduction are considered contributions after implementation of the system.

LITERATURE REVIEW

Raw material identification can be done using different methods that involve different techniques and technologies. Having and actual method that perform a task and trying to implement a different one that can bring more benefits it's something that needs to be done cautiously and taking in count all the facts that can affect the process. Making a research on the actual process, method used and the new technology would be helpful to understand how changes can be implemented.

For raw material identification different technologies can be use. What technology would be better would depend on the industry and the materials that are going to be identify. To facilitate the decision making process it would be convenient to understand benefits, disadvantages and have some source of background information.

In simple words as describe by Ruth Cordoba Rodriguez Ph.D. "According to ICH, a raw material is a general term use to denote starting materials, reagents and solvents intended for use in the production of intermediates or APIs. Raw materials do not have a unifying denomination: In-process material, source material, component, constituent, ancillary reagent, stating material, excipient." [1]. Ph.D. Cordoba in her own words describes raw materials as "Any element or component used in the manufacture of a biotechnology product that comes in contact with the API or the API stating material. A raw material may be reactive or non-reactive with the API." [1]
General sources of information describe raw materials as any materials used in the manufacture of pharmaceuticals, including those that do not remain in the end product.

Figure 1 present the supply change of raw material in flowchart we can see an overview of the lifecycle of the raw material that goes from the source thru the final destination which are the patient.

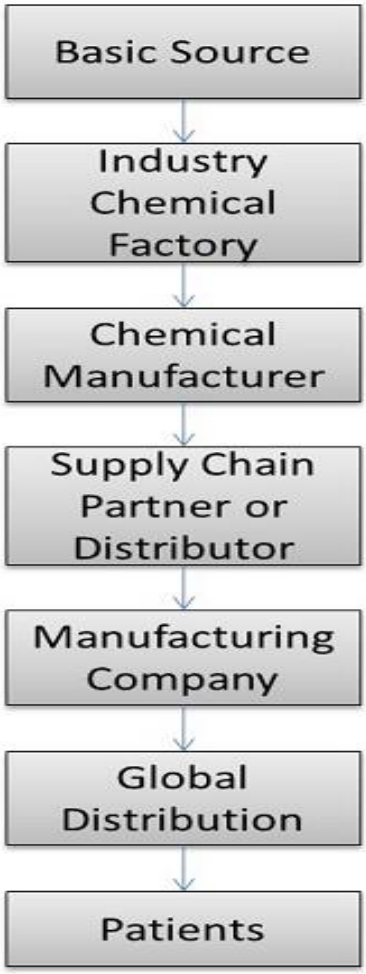

Figure 1
Supply Change of Raw Material

Raw materials arrived to incoming area of manufacturing after passing several stages. One of the critical stages of the raw materials supply chain lifecycle is to perform an inspection in order to verify that these materials meet with manufacturer acceptance criteria and comply with agencies quality regulations. In order to perform this inspection a sampling process must be carry out or an inspection method must be used. Whichever method use materials should be handle in a manner to avoid contamination with other substances and other factor that can affect identity, strength, and quality.

Identification of materials can be done using a representative sample or testing the total amount of material. According to American Pharmaceutical Review “The industry is moving away from a representative sampling approach to a total traceability of the incoming materials. A few years ago this was not considered a problem, because there were smaller numbers of providers; there were typically in-house production facilities, or the origins of the materials were easier to trace. However, nowadays, these issues have become critical factors by impacting operational costs and factory efficiency. In addition, factors such as continuous changes in manufacturing locations, samples coming from all over the world, and many companies emerging or consolidating their resources, can contribute to product quality. Under this scenario, it is easy to understand why regulators require tighter control of the safety and quality of all materials in a pharmaceutical company’s production chain.”[2]

There different methods and equipment to perform this inspection such as HPLC, NIR, Raman, etc.

As describe by Tom Kupiec in his article Quality-Control Analytical Method: HPLC “Chromatography is an analytical technique based on the separation of molecules due to differences in their structure and/or composition. In general, chromatography involves moving a sample through the system over a stationary phase. The molecules in the sample will have different affinities and interactions with the stationary support, leading to separation of molecules. Sample components that display stronger interactions with the stationary phase will move more slowly through the column than components with weaker interactions. Different compounds can be separated from each other as they move through the column. Chromatographic separations can be carried out using a variety of stationary phases, including immobilized silica on glass plates (thin-layer chromatography), volatile gases (gas chromatography), paper (paper chromatography) and liquids (liquid chromatography). High-performance liquid chromatography (HPLC) is a type of liquid chromatography used to separate and quantify compounds that have been dissolved in solution. HPLC is used to determine the amount of a specific compound in a solution. For example, HPLC can be used to determine the amount of morphine in a compounded solution. In HPLC and liquid chromatography, where the sample solution is in contact with a second solid or liquid phase, the different solutes in the sample solution will interact with the stationary phase as described. The differences in interaction with the column can help separate different sample components from each other.”[3]

Figure 2 shows the basic components of High-performance liquid chromatography (HPLC).

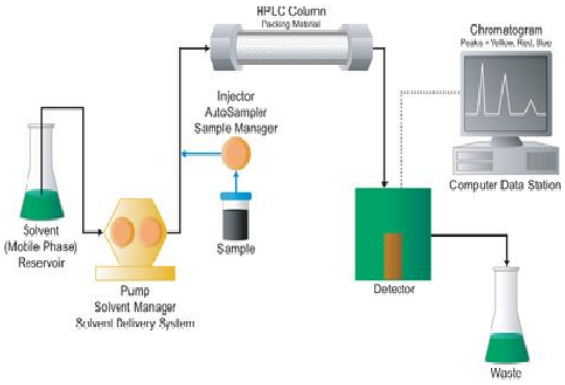

Figure 2
HPLC System

“A reservoir holds the solvent [called the mobile phase, because it moves]. A high-pressure pump [solvent delivery system or solvent manager] is used to generate and meter a specified flow rate of mobile phase, typically milliliters per minute. An injector [sample manager or autosampler] is able to introduce [inject] the sample into the continuously flowing mobile phase stream that carries the sample into the HPLC column. The column contains the chromatographic packing material needed to effect the separation. This packing material is called the stationary phase because it is held in place by the column hardware. A detector is needed to see the separated compound bands as they elute from the HPLC column [most compounds have no color, so we cannot see them with our eyes]. The mobile

phase exits the detector and can be sent to waste, or collected, as desired. When the mobile phase contains a separated compound band, HPLC provides the ability to collect this fraction of the eluate containing that purified compound for further study."[4]

Another option to perform raw material identification is the technology called NIR (Near-Infrared). According to Thermo Scientific "NIR is a spectroscopic method that uses the near-infrared region of the electromagnetic spectrum and is based on overtones and combinations of bond vibrations in molecules. In NIR spectroscopy, the unknown substance is illuminated with a broad-spectrum (many wavelengths or frequencies) of near infrared light, which can be absorbed, transmitted, reflected or scattered by the sample of interest. The illumination is typically in the wavelength range of 0.8 to 2.5 microns (800 to 2500 nm). The light intensity as a function of wavelength is measured before and after interacting with the sample, and the diffuse reflectance, a combination of absorbance and scattering, caused by the sample is calculated."[5]

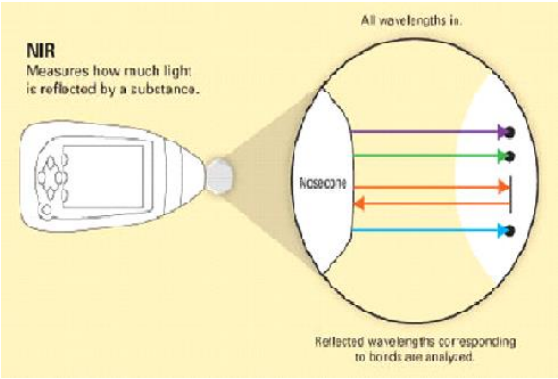

Figure 3
NIR - Light Reflected by a Substance

"Light is absorbed in varying amount by the sample at particular frequencies corresponding to the combinations and overtones of vibrational frequencies of some bonds of the molecules in the sample. Specifically, the bond vibrations between oxygen and hydrogen (OH), carbon and hydrogen (CH), and nitrogen and hydrogen (NH) result in NIR absorbance bands. The bands seen in the NIR are typically very broad, leading to spectra that are more complex to interpret than FTIR spectra; it can be difficult to assign specific features to specific chemical components. Careful development of a set of calibration samples and application of multivariate calibration techniques is essential for near-infrared analytical methods. NIR can typically penetrate much further into a sample than FTIR, and unlike Raman, is not affected by fluorescence. Thus, although NIR spectroscopy is not as chemically specific as Raman or FTIR, it can be very useful in probing bulk material with little or no sample preparation."[5]

As describe by Yubing Tang, Ph.D. "The differences between NIR and the traditional analytical procedures are the use of chemo metrics and development of multivariate model, statistically relevant samples for model development and comparable samples for model validation, and reliable and suitable software for data analysis." [6]

Similar to NIR but having other benefits another technology used for material identification is Raman Spectroscopy that has the name of his discoverer who was Dr. Raman. According to general information and as described by Todd Blonshine (CEO) of Mustard Tree Instruments "Dr. Raman was an Indian civil servant working in the count Department in the early 1900 when he discovered that sunlight interacted with materials to produce a characteristic patter. He study and published that effect and was awarded a Nobel Prize in 1930 for the technology that bears his name called Raman Spectroscopic This technology can be implement in different ways for this project we would be focusing on raw material identification". [7]

As define in Encyclopedia Britannica, "Raman Effect is a change in the wavelength of light that occurs when a light beam is deflected by molecules. When a beam of light traverses a dust-free, transparent sample of a chemical compound, a small fraction of the light emerges in directions other than that of the incident (incoming) beam. Most of this scattered light is of unchanged wavelength. A small part, however, has

wavelengths different from that of the incident light; its presence is a result of the Raman Effect." [8]

According to Thermo Scientific Raman overview "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. [9]

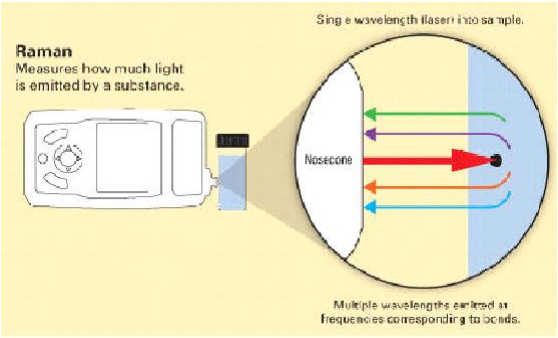

Figure 4
Raman - Light Emitted by a Substance

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. [9]

As describe in the company Horiba Jobin Yvon, "Raman can be used to analyses aqueous solutions since it does not suffer from the large water absorption effects found with FT techniques, the intensity of spectral features in solution is directly proportional to the concentration of the particular species, Raman spectra are generally robust to temperature changes, Raman requires little or no sample preparation. It does not need the use of Nujol, or KBr matrices and is largely unaffected by sample cell materials such as glass, The use of a Raman microscope such as the LabRAM provides very high level of spatial resolution and depth discrimination, not found with the FT methods of analysis. These advantages and its highly specific nature, mean that Raman has become a very powerful tool for analysis and chemical monitoring. Depending upon instrumentation, it is a technique which can be used for the analysis of solids, liquids and solutions and can even provide information on physical characteristics such as crystalline phase and orientation, polymorphic forms, and intrinsic stress." [10]

METHODOLOGY

As part of presenting a proposal for the implementation of Raman technology in the incoming area it is essential to have a clear understanding of what are the industry needs, where they are and where they expect to be.

Analysis of the actual process would need to be performed. As part of it an assessment that includes evaluation of the facility, quantity of personnel, equipment needed to perform identification and time consumption can be complete. Execution of the assessment will contribute in the comprehension of company status regarding raw material identification process.

Have good understanding of the different technologies including advantages and disadvantages.

Technologies such as FTIR, NIR & Raman are being use for the identification of materials. Is important to have knowledge of the materials that are been used in the manufacturing of the products to make comparisons and select the most

appropriate technology to improve the process and that satisfied customer needs.

In the process of selecting a new technology there are a few factors that had to be taken in consideration such as: the impact this new technology would can had on the actual process.

RESULTS AND DISCUSSION

The strategy for the implementation of Raman technology in the incoming area is presented to a pharmaceutical industry that has the necessity to change their actual system in order to satisfy the strong customer demand that their products had acquire. As part of the solution a critical to quality diagram was performed in order to have a clear understanding of customer needs and bring the most appropriate solution. Figure 5 is the CQT diagram of this problem.

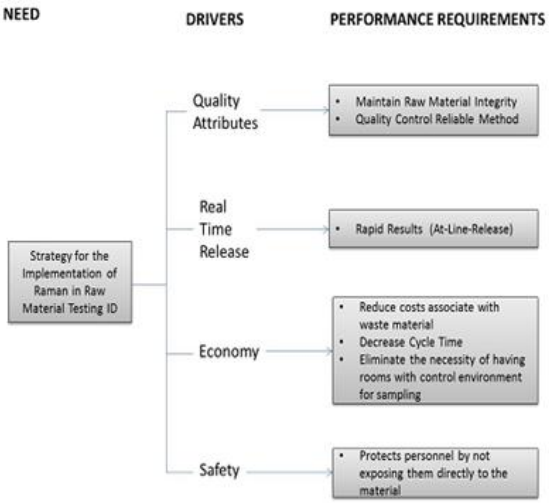

Figure 5
CQT Diagram

The actual method that is been used to perform the identification of raw materials in the incoming area is HPLC. This method complies with quality standards and regulations. As part of the steps to perform the material identification this method involve to take a sample from the raw material container to the laboratory and that sample has to be discarded. Usually when the lots of raw material arrive, this pharmaceutical make identification of materials taking a representative sample using an equation.

One of the pharmaceutical customers has presented the requirement of testing all the materials that are going to be used for the lots of products that they will purchase. In order to comply with that customer requirement the pharmaceutical will need to test all raw materials. Using HPLC will not be cost effective since they would be a serial of factor that would affect the operation such as needing more area of controlled environment in order to protect material integrity, employer exposure to materials, and time delay because of testing, more personnel and equipment in order to comply with product demand.

Figure 4 is a flowchart similar to a diagram of Thermo Fisher Scientific that represents the traditional or actual process vs the process that uses Raman technology for material implementation.

Figure 6
Traditional Process vs the Process that Uses Raman Technology for Material Implementation

After making the analysis of the entire situation it was found that acquiring a new technology such as Raman was a solution to the problem. Since there several types of devices that make raw material identification a research of them was performed to select the most appropriate technology that is Raman. As presented in the figure 4 implementing the new technology would decrease time for performing the inspection, the inspection could be made in the incoming area since this technology offers the benefit of not having to open the packages or containers to identify the materials.

CONCLUSION

Raman technology in the manufacturing industries to identify raw materials in the incoming area has been demonstrated great benefits and advantages in comparison to the traditional methodologies by decreasing the identification time, enabling cost-effective solution, and preserve integrity demonstrating a new way to meet the recent FDA directives concerning Process Analytical Technology (PAT).

REFERENCES

[1] Cordoba, R., Ph.D., (n. d.), "Raw Materials in the Manufacturing of Biotechnology Products: Regulatory Considerations", *Raw Materials Products: Regulatory* Considerations. Retrieved from http://c.ymcdn.com/sites/ www.casss.org/resour ce/resmgr/imported/WCBPCMC09 CordobaRodriguezSlides.pdf.

[2] *American Pharmaceutical Review*, "Cost & Benefits of Handheld Raman for Quality Control Testing of Incoming Raw Materials in the Pharmaceutical Supply Chain", January 30, 2013. Retrieved from http://www.americanpharmaceuticalreview.com/1504-White-Papers-Application-Notes/129832-Cost-Benefits-of-Handheld-Raman-for-Quality-Control-Testing-of-Incoming-Raw-Materials-in-the-Pharmaceutical-Supply-Chain/.

[3] Kupiec, T., Ph.D., (Analytical Research Laboratories – Oklahoma City, Oklahoma), "Quality-Control Analytical Methods: High-Performance Liquid Chromatography", International Journal of Pharmaceutical Compounding, Vol. 8, No. 3, May/June 2004.

[4] *Waters: The Science of what's Possible*, "How Does High Performance Liquid Chromatography Work?" (n. d.). Retrieved from http://www.waters.com/waters/en_PR/ How-Does-High-Performance-Liquid-Chromatography-Work?/nav.htm? cid=10049055.

[5] *Thermo Scientific*, "NIR Thecnology", (n. d.). Retrieved from http://www.thermoscientific.com/content/tfs/en/ about-us/general-landing-page/nir-technology.html.

[6] Tang, Y., Ph.D., "A Regulatory Perspective on NIR Method Robustness", January 25, 2012.

[7] "What is Raman Spectroscopy?" [Motion picture], *Mustard Tree Instruments*, 2012.

[8] *Encyclopedia Britannica*, Raman Effect | Physics, Last Updated January 23, 2014. Retrieved from http://global.britannica.com/EBchecked/topic/490453/Raman-effect.

[9] *Thermo Scientific*, "Raman Technology Overview", (n. d.). Retrieved from http://www.ahurascientific.com/product-technologies/raman/.

[10] *Horiba Jobin Yvon* (Raman Application Note), "Raman Spectroscopy for Analysis and Monitoring", (n. d.). Retrieved from http://www.horiba.com/fileadmin/uploads/ Scientific/Documents/Raman/bands.pdf.