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Indexed in Elsevier Bibliographic Database (Scopus and EMBASE)
SCImago Journal Rank 0.129
Impact factor 0.67*

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PROCESS ANALYTICAL TECHNOLOGY IMPLEMENTATION-PROGRESSION FOR A PHARMACEUTICAL INDUSTRY

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ABSTRACT

Process Analytical Technology (PAT) has been introduced as an advent of new tool which has given an opportunity for all the pharmaceutical manufacturers to improve upon their quality and compliance. The application of this technology in pharmaceutical manufacturing ensures the quality of raw material attributes that too at-line, in-line or on-line, which was difficult earlier, thereby decreasing the chances of error and significant savings in time required for testing. In Total, Process Analytical Technology lays a way for producing a standard product which is in line with Quality and thus creating a satisfaction with customer needs and making a good brand image for the organization. In this article, Process Analytical Technology has been introduced briefly and explained its different tool in order to illustrate how application of this technology ensures quality of pharmaceutical products and implementation will enhance the organization image.

KEYWORDS: Process Analytical Technology, Quality Product, Near Infrared Spectroscopy

SARAVANA KUMAR .V
Quality Assurance, Hospira Healthcare India Private Limited, Chennai, India.
INTRODUCTION

Conventional pharmaceutical manufacturing is generally accomplished using batch processing with laboratory testing conducted on collected samples to evaluate quality. This conventional approach has been successful in providing quality pharmaceuticals to the public. However, today significant opportunities exist for improving pharmaceutical development, manufacturing, and quality assurance through innovation in product and process development, process analysis, and process control. Pharmaceuticals continue to have an increasingly prominent role in health care. Therefore pharmaceutical manufacturing will need to employ innovation, cutting edge scientific and engineering knowledge, along with the best principles of quality management to respond to the challenges of new discoveries. Process Analytical Technology is one among them.

The advantages of PAT is
- Increased Productivity by real time measurement
- Reduction of process rejects/waste
- Enhancement of Product Release in a better time
- Personnel Errors can be avoided
- Process Improvement

The first Step away from off-line testing (lab separated from production area) would be on-line testing. This is the movement of testing equipment dedicated for the process, to the production line for generating rapid results. An advantage is the elimination of transfer of samples involving time delays. [e.g. Dissolution, Assay, Friability, Hardness]. The Next Mode approach for the measurement is On-Line Testing which either draws samples or monitors periodically. [e.g. Online TOC Meter, Online pH Meter]. Another Mode is known as in-line testing, which places probes in constant contact with drug product which will give a better understanding of process and also the control. The goal of Process Analytical Technology (PAT) is to understand and control the manufacturing process and these need to be consistent and compliant to the current drug quality systems. Ensuring that the instrument to be used performs correctly is the first step in developing an instrumental methodology. The European pharmacopeia and the guidelines of the Pharmaceutical Analytical sciences Group (PASG) recommend that NIR instruments be qualified as per the manufacturer instructions, which should include at least the following.
- Checking for wavelength accuracy by using one or more suitable wavelength standards exhibiting characteristic maxima at the specific wavelength regions of interest
- Checking for wavelength repeatability by using one or more suitable standards (e.g. polystyrene or rare-earth oxides). The repeatability of measurements should be consistent with the spectrophotometer specification.
- Checking for repeatability in the response by using one or more suitable standards (e.g. Reflective thermoplastic resins doped with carbon black). The standard deviation of the maximum response should be consistent with the spectrophotometer specification.
- Checking for photometric linearity by the use of a set of transmittance or reflectance standards (e.g. Spectralon, carbon black mixtures).
- Checking for the absence of photometric noise by using a suitable reflectance standard (e.g. White reflective ceramic tiles or reflective thermoplastic resins, such as Teflon).

A NIR identification library should encompass all the raw materials used by the manufacturer in order to be able to identify all possible substances and avoid or minimize errors. The method to be used should allow the unequivocal identification of each compound present in the library and the exclusion of those not present. It should also be able to distinguish between very similar compounds used in different applications (e.g. Products with different particle sizes, polymorphs, products in different grades or from different suppliers). In our present study, we have explored the possibilities of implementing the PAT opportunity in existing system of
manufacturing plant with the help of Online measurement and NIR measurement. For this study, PAT applications were implemented as process controls and not as design help for developing new products.

**MATERIALS AND METHODS**

The Instrument which are involved in PAT applications are selected for the study and subjected for Qualification

**Table 1**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Check Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Major Components are securely anchored and protected from any distress</td>
</tr>
<tr>
<td>2</td>
<td>No Physical Damage</td>
</tr>
<tr>
<td>3</td>
<td>All access ports are available</td>
</tr>
<tr>
<td>4</td>
<td>The Utilities associated with the instrument are fully integrated</td>
</tr>
<tr>
<td>5</td>
<td>All the safety features of the instrument were identified and installed properly</td>
</tr>
<tr>
<td>6</td>
<td>Installation of the unit is as per manufacturer recommendation</td>
</tr>
</tbody>
</table>

**FT-NIR (Bruker)**

(i) **Installation Qualification**

After Identification of Risk associated with the instrument for using in regular operation through Quality Risk Management determination, the identified instrument were subjected for installation verification with the objective of following checkpoints.

(ii) **Operational Qualification**

After installation, the unit was subjected to operational qualification in order to certify the operational performance and this study

- Verifies the Unit consistently operates within a specified set of parameters under normal operational conditions.
- Assures that the Unit performance is adequate to support the process for which the unit is intended for
- Demonstrates the completeness and adequacy of procedures

**Table 2**

<table>
<thead>
<tr>
<th>S. No</th>
<th>Check Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Calibration of the sub instruments associated with the unit (eg, gauges etc)</td>
</tr>
<tr>
<td>2</td>
<td>Simulation and Verification of Safety Features Functionality</td>
</tr>
<tr>
<td>3</td>
<td>Password Integrity Check</td>
</tr>
<tr>
<td>4</td>
<td>Data Acquisition Test</td>
</tr>
<tr>
<td>5</td>
<td>Single Point Calibration/Multi Point Calibration</td>
</tr>
<tr>
<td>6</td>
<td>Response Efficiency Verification</td>
</tr>
</tbody>
</table>

(iii)**Performance Verification**

The Performance Verification Check for the qualified instrument was carried out with the following test
Table 3
Check Points for the Performance Verification Check

<table>
<thead>
<tr>
<th>S. No</th>
<th>Test Performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Resolution</td>
</tr>
<tr>
<td>2</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>3</td>
<td>Energy Distribution</td>
</tr>
<tr>
<td>4</td>
<td>Wave Number Accuracy</td>
</tr>
<tr>
<td>5</td>
<td>Photometric Accuracy</td>
</tr>
<tr>
<td>6</td>
<td>Scan Time</td>
</tr>
<tr>
<td>7</td>
<td>Alignment</td>
</tr>
<tr>
<td>8</td>
<td>Linearity</td>
</tr>
<tr>
<td>9</td>
<td>Reproducibility</td>
</tr>
<tr>
<td>10</td>
<td>Signal to Noise</td>
</tr>
<tr>
<td>11</td>
<td>Interferogram Peak</td>
</tr>
<tr>
<td>12</td>
<td>Wavelength Uncertainty</td>
</tr>
</tbody>
</table>

(iv) Method Equivalency \(^ {13,12} \)
After Necessary Qualification, method equivalency of the instrument was performed by creating a library by using standard drug for the identification test by using this NIR instrument and challenged with different drug and the results were noted.

RESULTS

1. Installation Verification

<table>
<thead>
<tr>
<th>S. No</th>
<th>Check Points</th>
<th>Y/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Major Components are securely anchored and protected from any distress</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>No Physical Damage</td>
<td>Yes</td>
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<td>6</td>
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<td>Yes</td>
</tr>
</tbody>
</table>

2. Operational Verification

<table>
<thead>
<tr>
<th>S. No</th>
<th>Check Points</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Calibration of the sub instruments associated with the unit (eg, gauges etc)</td>
<td>Meeting acceptance criteria</td>
</tr>
<tr>
<td>2</td>
<td>Simulation and Verification of Safety Features Functionality</td>
<td>Meeting acceptance criteria</td>
</tr>
<tr>
<td>3</td>
<td>Password Integrity Check</td>
<td>Password Protected</td>
</tr>
<tr>
<td>4</td>
<td>Data Acquisition Test</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>5</td>
<td>Single Point Calibration/Multi Point Calibration</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>6</td>
<td>Response Efficiency Verification</td>
<td>Satisfactory</td>
</tr>
</tbody>
</table>

3. Performance Verification Test
(a) Resolution Test

![Resolution Test Spectrum](image)
(b) Sensitivity Test

(c) Energy Distribution Test

(d) Wave Number Accuracy Test
(e) **Photometric Accuracy Test**

![Photometric Accuracy Test]

(f) **Scan Time Test**

![Scan Time Test]

(g) **Alignment Test**

![Alignment Test]

(h) **Linearity Test**

![Linearity Test]
(i) **Reproducibility Test**

![Reproducibility Test](image)

(ii) **Signal to Noise Test**

![Signal to Noise Test](image)

(iii) **Interferogram Peak Test**

![Interferogram Peak Test](image)

**DISCUSSION**

The Overall aim of this work was to evaluate the feasibility of implementing Process Analytical Technology (PAT) into pharmaceutical manufacturing. In this work, PAT has been looked at in terms of steps where NIR measurement should be implemented in manufacturing. It is clear that the implementation of PAT is very expensive, but it will pay off. For this study, PAT applications were implemented as process controls and not as design help for developing new products. This work can be expanded to study into drug development in order to study the impact of PAT onto quality of design. NIR being the most common recommended PAT sensor, a FT-NIR spectrophotometer was also investigated for not such a frequent application, namely the identification of raw materials. Using the Bruker FT-NIR on raw materials (anti-biotic), it was able to distinguish the different group of raw materials correctly and there was a significant reduction in the usage of raw materials upon receipt. It is apparent that pharmaceutical companies will have to be innovative if they wish to survive the competition on the regulated markets today. From the point of view of pharmaceutical companies, they will have to invest in innovation in order to get themselves fast to the market as possible in order to prolong their window for a product. From the generics point of view, it is also essential to invest in innovative technology, as the generic company which comes first to the market, gests the biggest part of the cake.
CONCLUSION

The final result of this situation is that the pharmaceutical industry is lagging behind other related industries in implementing new manufacturing technologies which have the potential to improve product consistency reduce delays in product release, and cut overall manufacturing costs. In conclusion, PAT is an excellent opportunity for an organization to improve their Quality and rebuilding the trust in customer needs. This research work can further be initiated towards validating and standardizing this formulation for other stages in the manufacturing process.

REFERENCES

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