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Usage of Online TOC Analyzer- Process Analytical Technology Initiative

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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, Online TOC Analyzer.

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[1].

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[2].

The advantages of PAT is

- Reducing production cycle times by using on, in- and or at line measurements and controls.
- Preventing rejects, scrap and re-processing.
- Possibility of Real time analysis and product release.
- Increasing automation to improve operator safety and reduce human error.
- Facilitating continuous processing to improve efficiency and manage variability.[3]

The first Step away from off-line testing (lab separated from production area) would be at-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][4].

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][4].

Another Mode is known as in-line testing, which places probes in constant contact with drug product which will give better understanding of process and also the control[4].

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[5].

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[6].

- 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 (eg. White reflective ceramic tiles or reflective thermoplastic resins, such as Teflon).

A NIR identification library[7] 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)[8].

In our present study, we have explored the possibilities of implementing the PAT opportunity in existing utility system with the help of Online measurement. For this study, PAT applications were implemented as process controls and not as design help**.**

Materials and Methods:

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

TOC Analyzer (Siemens 500RL)

(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

Table 1 Check Points for the Installation Verification

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

(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 Check Points for the Operational Verification

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

(iii) Performance Qualification :

The Performance Verification Check for the qualified instrument was carried out by monitoring the results of TOC through online analyzer installed with the line for 6 months.

Results

1. Installation Verification

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

2. Operational Verification

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

3. Performance Qualification :

Six months data of TOC results through Online-TOC analyzer were monitored and reviewed. Based on the data, it has been found that the system is consistently producing the results and thereby reducing the laboratory errors.

Discussions:

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 which process steps, Online measurement should be implemented with utility system i.e. Water For Injection System. 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.

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 the researching pharmaceutical companies, they will have to invest in innovation in order to get themselves as 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.

"..an economical benefit for a pharmaceutical company is a gun to its head"![9]

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.

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