ROLE OF PROCESS ANALYTICAL TECHNOLOGY (PAT)

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Introduction:

According to the FDA, PAT is: "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality."

The goal of Process Analytical Technology is: "to understand and control the manufacturing process, which is consistent with our current drug quality system: quality cannot be tested into products; it should be built-in or should be by design."

Development of technology and updating the current practice in pharmaceutical industry plays a major role in compliance with the regulatory bodies. Validation is the key word in compliance of cGMP. Recently FDA attitude towards process improvement is a key drive of Process analytical technology (PAT.); simply putting from PAT is real time testing and adjustment based on a full understanding of how the components affect the final products.

Process analytical technology has been described as the pharmaceutical industries drive to provide real-time information to characterize and control process variation and manufacturing capability. Process analytical technology is a system for designing, analyzing, and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality. It also involves the use of raw material properties, manufacturing parameters, and process monitoring and chemo metric techniques to produce finished products of acceptable quality.

PAT will save the pharmaceutical industries money, time, product, and

hours in less testing. PAT made us to understand of all of the chemical process and how each of the components will effect the final products, which will leads to overcome the huddles in process production and regulatory compliances by improving the process methodology.

Process analytical technology can be applied to bulk formulation, inbound logistics, Active ingredients manufacture, Fill and finish, packing and outbound logistics.

The potential benefits of PAT are to provide processes which consistently generate products of predetermined quality in an efficient and expected form. reduction of cycle times using on-, in-, or at-line measurements and controls, prevention of rejection product and waste, real time product release, increased use of automation, cost savings, Regulatory relief, facilitation of continuous processing using small-scale equipment, resulting in improved energy and material use and increased capacity.

Mapping and Image Studies:[1]

On a micron or sub-micron scale, solid samples such as powders, pressed tablets or cast films typically exhibit non-homogeneous mixing of components. This results in regions that are disproportionately more concentrated in individual components, which can have major impact on stability, delivery and other physical properties of the product. SSCI's powerful analytical techniques provide a wealth of chemical and physical information on specific microscopic regions of solid samples. Some of the most prominent techniques are:

Infrared spectrosopy (FTIR)

Raman Spectroscopy

Near infrared spectroscopy (NIR)

X-ray powder diffraction (XRPD)

Electron diffraction (EDS)

Atomic force microscopy (AFM) and Micro thermal imaging While traditional application of these techniques involves examination of a single location in the sample and subsequent collection of the chemical or physical information from only that isolated area, new imaging techniques involve automated data collection from multiple locations over a large area of the sample. This allows visualization of qualitative distribution, identification of majority or trace components, or more accurate quantitative analysis.

Imaging[2]

Imaging is a general term for collection (usually automated) and analysis of data from a large number of locations on a sample. Collection of the data array can be accomplished in several ways. The two most common methods of collecting data are use of an array detector, where data for the entire image are collected simultaneously, and automated mapping, in which analysis is carried out a number of discrete points. SSCI Inc. makes use of both methods of data collection. SSCI scientists can carry out distribution analyses where each measurement represents an area as small as from 50 um to 1 A depending on the technique. Small particles or domains can be observed that would not be resolved with single analysis of the entire area. Distribution of a single component is easily visualized. Investigation of interfacial interactions is possible by observing differences between adjacent pixels. The array can be processed repeatedly, observing different chemical or physical signatures. Use of these techniques can produce any number of diagnostic presentations of the total sample area.

Imaging over a large area provides a more representative analysis of the sample for quantitative applications. Each pixel of the image provides a full spectrum that can be compared to spectral databases of known compounds for specific identification. Trace particles as small as a single pixel can provide a pure spectrum of a contaminant that would be undetectable in a single analysis of the entire sample area. Individual spectra from each pixel allow quantitative distribution within the area analyzed. Reprocessing provides a more accurate quantitative analysis of the bulk material.

FTIR Imaging

FTIR is well accepted as a methodology for chemical and structural analysis of organic products, providing a unique "fingerprint" spectrum of each molecule. The resulting spectrum is also diagnostic for subtle changes in the chemical or physical properties of the sample. Each FTIR spectrum represents an area of the sample as small as 10 um, and distribution of a single component is easily visualized. With proper selection of conditions, FTIR can overcome limitations of Raman and NIR. FTIR is

often limited by the presence of water or the need to sample through glass, either of which produces significant spectral interferences.

SSCI scientists have extensive experience analyzing solid-state composition in final dosage form.

Raman Mapping[3]

As with FTIR, Raman spectra are unique, allowing unambiguous chemical identification. Raman is highly sensitive to the local molecular environment such as changes in crystal structure or subtle chemical modifications, but Raman does not suffer the material limitations inherent to infrared spectroscopy since both glass and water exhibit minimal Raman spectral interferences. Each Raman spectrum represents an area as small as 1 um. Raman occasionally suffers from fluorescence, a sample-dependent spectral interference.

NIR imaging

Near infrared spectroscopy offers many of the advantages of FTIR and Raman, but overcomes some of the limitations. NIR offers the same advantage over FTIR as Raman, in that neither glass nor water interferes with the analysis. Each NIR spectrum represents an area as small as 1 um. NIR spectra result from absorption of overtones and combination bands from the mid infrared region, therefore, chemical or physical differences detected by FTIR also affect NIR data. NIR occasionally suffers from a lack of spectral specificity that is available with FTIR or Raman.

X-Ray Powder Diffraction Mapping

X-ray diffraction addresses an entirely different aspect of solid analysis and provides highly reliable analysis of the solid-state form of a material. An XRPD mapping study can, for example, provide information about the solid form composition at different regions in a tablet or identify the presence of a trace amount of a particular solid form. Each diffractogram represents an area as small as 50 um. XRPD offers limited chemical information as compared to FTIR, Raman or NIR.

EDS Imaging[4]

Energy dispersive spectrometry (EDS) combines the advantages of scanning electron microscopy (SEM) and elemental analysis. Samples interrogated by SEM can be analyzed for elemental content by EDS under similar conditions of magnification and sampling

environment. Each point represents an area as small as 1^{A}.

AFM and Micro Thermal Imaging

AFM and micro thermal techniques offer physical resolution of surface structure as small as 1 A and present a topographical representation of the sample surface with much greater resolution than SEM. Contact and non-contact AFM provide topographical imaging of the surface of conductive and non-conductive materials, as well as surfaces that are soft and pliable. Micro thermal imaging adds a significantly different dimension, imaging the sample based upon differences in thermal conductivity of the materials on the surface.

Stability, Solubility, Dissolution

Stress testing can reveal differences in the physical and chemical stabilities of various solid forms. Modes or rates of degradation can often be associated with particular solid forms such as polymorphs or solvates, since certain lattice types and modifications are more prone to degradation than others. We conduct high-temperature, high-humidity, and light-exposure degradation studies to identify and quantitate physical and chemical changes (XRPD and HPLC, respectively).

Our cGMP degradation studies can determine both the chemical stability and the solid-state stability of your drug substance, drug product, or chemical.

Dissolution rates often vary considerably with solid form. Dissolution tests are often used to ensure that production processes are under control. We determine dissolution rates and equilibrium solubilities using intrinsic and non-intrinsic methods

P.A.T. and Pharmaceutical Quality by Design

Process Analytical Technology (PAT) is a system for designing, analyzing, and controlling manufacturing processes based on 1) an understanding of the scientific and engineering principals involved and 2) identification of the variables which affect product quality. The PAT initiative is consistent with the current FDA belief that quality cannot be tested into products, but should be built-in or by design. According to the FDA draft guidance, the desired state of pharmaceutical manufacturing is that:

- Product quality and performance are ensured through the design of effective and efficient manufacturing processes
- Product and process specifications are based on a mechanistic understanding of how formulation and process factors affect product performance
- Quality assurance is continuous and real time
- relevant regulatory policies and procedures are tailored to accommodate the most current level of scientific knowledge
- risk-based regulatory approaches recognize both the level of scientific understanding and the capability of process control related to product quality and performance

The primary goal of PAT is to provide processes which consistently generate products of predetermined quality. In so doing, improved quality and efficiency are expected from:

- reduction of cycle times using on-, in-, or at-line measurements and controls
- prevention of reject product and waste
- real time product release
- increased use of automation
- facilitation of continuous processing using small-scale equipment, resulting in improved energy and material use and increased capacity

Building Quality into Products[5]

Effective PAT implementation is founded on detailed, science-based understanding of the chemical and mechanical properties of all elements of the proposed drug product. In order to design a process that provides consistent product, the chemical, physical, and biopharmaceutical characteristics of the drug and other components of the drug product must be determined. Although the science of analyzing for chemical attributes such as identity and purity is mature, certain physical attributes such as solid form, particle size, and particle shape are more difficult to analyze and control. SSCI is uniquely experienced to address this aspect of PAT. Given a compound of interest, our scientists routinely:

- Determine the solid forms attainable and their relevance to manufacture and use
- Select the optimum solid form
- Develop analytical methods to verify the presence of, and quantify the concentration of, the selected form in API
- Investigate the physical properties of the solid such as particle size, particle shape, stability, ease of drying, filterability, solubility, dissolution rate, etc.
- Develop a manufacturing process that consistently provides the desired form of the API having the desired physical characteristics
- Aid in setting API specifications
- Determine excipient compatibility
- Aid in formulation design
- Develop drug product manufacturing strategies that are consistent with the solid properties of the API
- develop analytical methods to verify the presence of, and quantify the concentration of, the selected form in drug product
- aid in setting drug product specifications

SSCI scientists have extensive experience solving solid-state problems in drug products.

Process Control[6]

Once the properties of the drug product components are understood, the processing variables that control the relevant properties must be identified. Identification of these variables necessarily requires a multivariate approach. From a solid-state point of view, PAT implementation involves the design of manufacturing processes based on a thorough scientific understanding of the solid-state properties and stability of the components of the drug product at critical points throughout manufacturing. Then, measurement and control of the critical parameters integrates a broad spectrum of analytical technologies interfaced to production plant control networks and incorporated into standard procedures.

SSCI works with clients to establish specific process understanding and design process analytical control

strategies. Building upon the current SSCI reputation for meticulous cGMP pharmaceutical research and analysis, SSCI can assist clients in all aspects of PAT implementation, including:

- Process understanding through advanced solid-state research
- identification of critical control variables using multivariate techniques
- Development and validation of appropriate analytical methods for measuring critical control variables
- Transfer of analytical methods to on-, in-, or at-line use
- Consultation and assistance in method validation and use after transfer

Potential Regulatory Impact[7]

FDA presentations indicate their anticipation that PAT implementation will eventually change the regulatory process. Documentation of quality by design during the pre-IND meeting, the end of phase II meeting, and in regulatory submissions will allow early review and analysis of the CMC section of an NDA by the FDA. Addressing issues of concern and further quality by design can result in classification of the drug substance and drug process manufacturing process as low-risk. In some cases, this approach is expected to result in a less comprehensive or eliminated preapproval inspection. While these procedural changes will not happen overnight, they present a possibility for more rapid regulatory approval and reduced time to market.

We invite your queries on this important development in the pharmaceutical industry. We believe our extensive experience in cGMP solid-state research and analysis will help you meet the PAT challenges today and for the future.

Conclusion:

As can be seen in the above discussion, the use of PAT techniques can be a huge benefit to those who choose to use the technology. Process analytical technology provides better knowledge of raw materials, manufacturing parameters and their impact on finished product quality. This will result in more robust process, better products, more uniform dissolution results, and a huge cost savings for the manufacturer. The challenge that dissolution scientists face is to become familiar with this next

generation of pharmaceutical testing and its potential application.

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