Pharmaceutical manufacturing and the quality by design (QBD), process analytical technology (PAT) approach

Trevor Murphy, Niall O' Mahony, Krishna Panduru, Daniel Riordan, Joseph Walsh
IMAR Technology Gateway
Institute of Technology Tralee
Tralee, Ireland
Trevor.Murphy@research.ittralee.ie

Abstract— This paper is the result of a literature review focusing on the application of process analytical technology (PAT) for the pharmaceutical industry in conjunction with the quality by design (QBD) framework. PAT and the QBD framework put forward by the FDA, offer a holistic approach to manufacturing pharmaceuticals, emphasising the understanding of process variables on the end products characteristics and transmitting this information upstream to control critical process parameters that effect the critical to quality attributes of a product.

Key components of QBD are discussed and their potential impact on current manufacturing processes along with the technological capabilities of PAT and the benefits associated with real-time process monitoring and control.

Keywords—quality by design, process analytical technology, spectroscopy, chemometrics

I. INTRODUCTION (HEADING 1)

Increasing demands in the pharmaceutical industry, in conjunction with new developments in medicinal science has resulted in the pharmaceutical industries methods of manufacturing their products coming under more and more scrutiny due to the inefficiencies and wastes associated with current manufacturing processes and quality control systems. The growing complexity involved in manufacturing newly developed products and the decline in the blockbuster drug model has placed increasing strain on pharmaceutical development and manufacturing process streams.

At present, the majority of pharmaceutical products are manufactured using the batch manufacturing method which involves the breakdown of the manufacturing process into stages to allow for stage by stage analysis of the material. Upon completion of each stage, a sample of material is generally extracted from the bulk and analysed in laboratory conditions to ensure the critical to quality attributes are in line with specifications. The results of the analysis then dictate whether the material can be further processed or whether corrective actions are required for the material to achieve the desired specifications. While the batch method of manufacturing is suited to some pharmaceutical products, it remains a tedious and inefficient method for other products due to the time and labour intensive nature of the sampling and laboratory testing which has led for calls within the industry for an innovative solution for the manufacturing of pharmaceutical products.

Process analytical technology (PAT) and the quality by design framework (QBD) has been identified as the future of pharmaceutical manufacturing and the solution to the increasing demand on the industries process stream due to its ability to automate the process stream while providing information to the user on the optimisation of a given process through use of a suite of novel sensors and analysers that monitor and control through timely measurements, the critical process parameters, that effect the critical to quality attributes.

This paper focuses on the key components of QBD and PAT, their suitability for integration into pharmaceutical development and manufacturing and benefits associated with the implementation of Process analytical technology in conjunction with the quality by design framework.

II. QUALITY BY DESIGN (QBD)

In 2009 the ICH pharmaceutical development guideline Q8 (R2) [1] defined the Quality by Design (QBD) framework as a systematic approach to development that begins with predefined objectives and emphasises product and process understanding and process control, based on sound science and quality risk management. Fundamental to the QBD framework is the understanding of the raw material attributes and process parameters, their effect on the critical to quality attributes (CQA) and the identification and control of sources of variables within the process [2]. This enables quality to be built into manufacturing processes rather than testing for quality in finished products, as during development stage, quality issues can be analysed for root cause and corrective procedures can be implemented accordingly to ensure product end quality.

The QBD framework is based on 6 fundamental components that must be considered prior to the implementation of this strategy [3] [4];

- Defining the product design goal
- Determining the critical to quality attributes
- Risk assessment
- Developing design space

- Control strategy
- Product life cycle management

Defining the product design goal is the first step in implementing QBD and involves evaluating the requirements for the products design and performance. These requirements are found in the quality target product profile (QTPP) which are a set of target specifications set for each individual product. The QTPP is used to define the product design and can also be used to establish the CQA's of a product and can serve as a guideline throughout the development stage to ensure target specifications are achieved [5].

Determining the CQA is achieved through evaluation of the QTPP and is vital to ensure QBD as the critical to quality attributes are the characteristics that directly affect the quality of the final product. The framework for the products design and process understanding is achieved through the identification of the CQA's. CQA's can be utilised in the developmental risk assessment stage to evaluate root causes of quality issues.

Risk assessments must be carried out to when implementing QBD to evaluate the risks associated with manufacturing a product. The most influential factors that affect the product quality such as process parameters and CQA's must be scrutinised along with all quality control and process control systems [4].

Developing design space involves the understanding of how the combination and interaction of process variables such as raw material characteristics and process parameters effect the CQA's. Identification of critical process parameters is imperative to ensure process optimisation [3]

Control Strategy is a planned set of goals derived from current product and process understanding ,that assures process performance and product quality, allowing for identification of which material attributes and process parameters should be controlled in order to achieve the pre-determined goal of product end quality [6].

Product life cycle management involves implementing measures to maintain, improve and control product quality through a variety of strong quality control systems that provide feedback on product performance such as;

- Change management and control procedures and systems
- Validation
- Trending and analysis
- Training
- Six Sigma lean manufacturing
- Quality risk management

Product life cycle management is driven largely by data (both qualitative and quantitative), that can be used to highlight potential issues in quality, supply chain, material attributes and process parameters while also providing information and guidance on continuous improvement strategies to enhance product quality and performance.

Improper product development strategies and manufacturing control systems can have a serious impact on product quality and system efficiencies that ultimately effect the financial success and performance of a product. The QBD framework offers a number of benefits that not only improve process understanding, quality and control, but also provides a rapid response to manufacturing deviations, improves the developmental stage through reducing time and costs and reduces FDA approval times. The QBD model is an ideal foil for implementing process analytical technology (PAT) due to its systematic data driven approach to pharmaceutical development and manufacturing.

III. PROCESS ANALYTICAL TECHNOLOGY (PAT)

Process analytical technology (PAT) was outlined in 2004 by the Food and Drug Administration (FDA) as a system for designing, analysing and controlling the critical process parameters of a manufacturing process that affect the critical to quality attributes of raw and in-process materials and processes [7]. The use of PAT systems for continuous process monitoring and control in the pharmaceutical industry is steadily increasing with a number of prominent pharmaceutical manufacturers inventing heavily in continuous manufacturing facilities [8], [9]. The increasing use of PAT is largely driven by increased technological capabilities that provide improvements in process monitoring and controls, and the FDA's directives for good manufacturing practices [7], [10], [11].

The goal of PAT is to consistently generate products with a predetermined level of quality [12] and enable pharmaceutical manufacturers to transition from the tedious and empirical methods of batch manufacturing, consisting of time and labour intensive off-line sampling and analysis, to a more continuous and dynamic method of manufacturing pharmaceuticals where process sensors and analysers perform continuous timely measurements of critical process parameters (Fig.1) increasing end product quality levels [10].

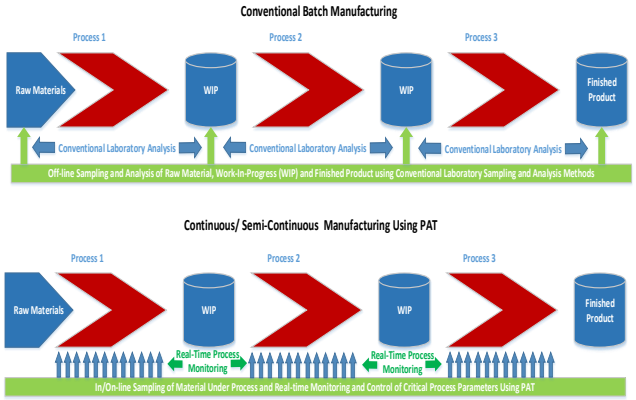

Figure 1 Batch Manufacturing Process, Continuous PAT Comparison

The key to ensuring end product quality is through the identification and management of the many variables that exist within a manufacturing process such as variations in raw-

material, mechanical performance of processing equipment and process parameters and through the scientific understanding of how these variables interrelate [13].

PAT emphasizes process understanding through the identification and real-time monitoring and control of each of these variables using specific technological tools such as sensors, analysers, probes and optical equipment located at predetermined critical measurement points that accumulate large data sets. The resulting data is then analysed and evaluated using multivariate analysis tools and transposed into an electrical signal and fed upstream to adjust plant equipment to compensate for variability in raw materials and equipment to produce a consistent product. Analysed data can also be utilised in continuous improvement strategies on manufacturing processes through simulations and process modelling that identify key areas within the process that are critical to quality. Identification and control of these key areas allow for the precise adjustment of plant equipment and raw materials allowing for the optimisation and automation of the entire process stream [14] and reducing the dependency on off-line analytics.

IV. Process Monitoring

A. *Off-line Process Monitoring*

Many of the variables within a process can be measured using off-line process monitoring techniques, which generally consist of the manual sampling of material from the process, for analysis in laboratory conditions. Off-line process monitoring has been used extensively in the pharmaceutical industry and involves rigorous quality control (QC) procedures that must be constantly repeated for each individual process such as sample collection, transport, preparation and analysis of samples, prior to documentation and archiving of generated report documents.

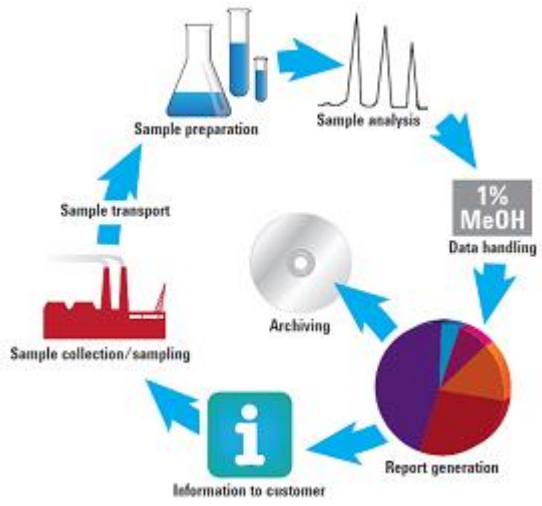

Figure 2 Workflow Diagram of Off-line Sample Analysis *[15]*

Laboratories are a critical component of current drug manufacturing and require complex, dynamic scheduling and skilled personnel to cope with the demands of the supply chain, and can have a major impact on the overall supply chain service level through its influence on cycle times, delivery times and quality levels [16]. The time and labour intensive nature of offline laboratory analysis can also be inefficient and a waste of valuable resources due to lengthy process time frames from sample collection to results of analysis. The process of off-line analysis also contains a large portion of non-value added (NVA) process steps and according to a 2013 Agilent Technologies survey [15], only 6% of the off-line analysis process cycle time is spent on analysis with 27% of the time spent on data management and 61% of the time spent on sample processing.

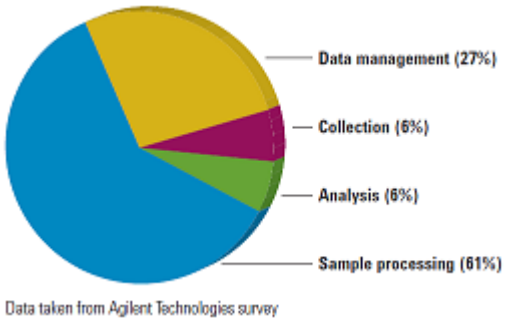

Figure 3 Agilent Technologies survey on time allocation of typical offline analysis *[15]*

The manual aspect of this method of sampling and analysis can also be prone to a variety of errors, ranging from human error in sample preparation to administrative errors in documentation and reporting that can further effect the supply chains service level [15], [17]. A reduction in the source of these errors can be achieved through the implementation of PAT systems in manufacturing processes resulting in real-time release testing, improved cycle times and product end quality while also relieving pressure on lab analysts. NVA lab processes such as data management and administrative duties such as documentation and reporting can be significantly reduced through on/in/at-line monitoring and control of critical process parameters which can reduce the complexity of lab scheduling and improve lab performance.

B. *On/In/At-line Process Monitoring*

The central point to PAT is the generation of product quality information in real time and the use of that information to control the critical process parameters of a manufacturing process. Methods of obtaining this information generally depend on the process in question and its suitability to various process monitoring solutions such as on-line, in-line and at-line process monitoring. Evaluation of the critical to quality attributes and identification of key measurement points within the process generally dictate the suitability of on, in or at-line process monitoring critical measurement points within the process.

C. *At-Line Process Monitoring*

At-line process monitoring consists of the movement of process dedicated testing equipment to the production line. The close proximity of the test equipment to the process reduces the time lag resulting from the transport and documentation of

samples from the process to the laboratory. This allows for a reduction in the reaction time to perform the necessary counter measures to ensure product end quality. It is generally observed that at-line process monitoring equipment, while more robust and insensitive towards process environments is less precise than off-line lab test equipment [18].

D. In-Line Process Monitoring

In-line process monitoring requires no sampling and takes timely measurements of material in the process stream through use of a variety of either invasive sensors such as immersive probes or non-invasive sensors such as optical sensors. Advances in fibre optic sensor technology has vastly improved the performance of optical sensors for industrial operations and is replacing the need for more traditional sensors for process monitoring with the ability to measure almost all physical measurands of interest [19].

The wide dynamic range of measurands and remote sensing capabilities of fibre optics allow for the removal of expensive sensory equipment from or near hazardous environments that manufacturing processes generate through use of optical fibres embedded at critical process measurement points or through immersive fibre optic probes. This allows for precise measurement solutions in previously unobtainable or undesirable process locations such as areas of extreme temperatures, pressures or the measurement of corrosive or hazardous materials, resulting in accurate real time data on critical to quality attributes to process analysers.

E. On-line Process Monitoring

On-line process monitoring involves the redirection of a sample of material through automatic extraction systems or recirculation loops, where the sampled material is conveyed to the sensor locations and either returned to the process stream or safely disposed of. This method is generally used in instances where modification required for the integration of in-line process monitoring is either too costly, impractical or where a higher degree of precision is required, as on-line process monitoring offers an opportunity to condition the sample before analysis to achieve higher quality results [18].

To summarize, manufacturing process parameters, raw materials, plant equipment and end product quality should be carefully evaluated prior to selecting the most suitable process monitoring techniques to ensure accurate measurements are achieved. Pre-determined measurement locations within a manufacturing process may be difficult or impractical to reach, consist of extreme environments or pose risks of exposure to harmful substances. The variety of process monitoring techniques in conjunction with the increasing range and versatility of sensory equipment ensures that a viable measurement solution can be obtained for the vast majority of key measurement locations within a manufacturing process. Non-contact sensors, immersive probes and optical sensors can provide data on almost every key aspect of the manufacturing process such as physical, chemical and biological attributes and when integrated into a PAT system through either at/in/on-line methods, can provide large continuous data sets to process analyser that drive process understanding, optimisation and continuous improvement of process and quality.

V. ANALYTICAL TECHNIQUES

The discipline of process analytical chemistry has grown significantly during the past few decades, due to the increasing appreciation for the value of collecting process data [20] coupled with the technological advances in computing large data sets [21]. As a result, the accuracy, variety and flexibility of analytical techniques used in the pharmaceutical industry has steadily improved. The most commonly used analytical techniques in pharmaceutical manufacturing, development and analytical chemistry is spectroscopy and chromatography. There is a wide variety of both spectroscopy and chromatography techniques in use in industry such as NIR, MIR and Raman spectroscopy and high performance liquid chromatography (HPLC), gas chromatography and thin layer chromatography. For the purpose of this paper, the focus will be on NIR spectroscopy and Raman spectroscopy due to their non-contact, non-destructive and remote sensing capabilities that can provide real-time data on a wide range of physical, chemical and biological properties in a manufacturing process and their suitability for integration into PAT systems.

A. NIR Spectroscopy

NIR spectroscopy is a simple non-contact, non-destructive analytical technique that can provide multi-constituent analysis on virtually any matrix while providing levels of accuracy comparable to that of primary reference methods [22]. The low absorption co-efficient of NIR's allows for deep penetration of the radiation in the sample that can provide information on both sample thickness and volume parameters [23], [24] while providing real time, precise and repeatable measurements requiring no sample preparation. Another advantage of the penetration depth of NIR's is the increased volume of material that is analysed reduces sampling error in the system [25]. NIR absorption spectra can often be complex due to the overlapping NIR absorption bands and require mathematical procedures such as chemometric data processing for data for analysis.

NIR spectroscopy techniques are becoming the most widely used analytical technique due to their ability to be placed off-line, at-line, on-line or in-line [26] using optical couplings that allow for easy integration into manufacturing process streams. For continuous monitoring of manufacturing processes NIR spectroscopy has been successfully deployed online to monitor a number of processes in the pharmaceutical industry [27] [28] such as;

- **Reaction monitoring**, monitoring the chemical reactions of liquids and solids
- **Powder blending**, measuring blend homogeneity in a bulk solid
- **Solvent monitoring**, monitoring the mixture of solvents in a solvent recovery process
- **Moisture measurements**, measuring the amount of moisture during granulation, drying, and purification stages of solids

NIR is an important PAT tool for continuous monitoring when utilised in conjunction with multivariate and statistical

analysis tools and can provide both qualitative and quantitative assessments of materials composition and chemical reactions. The data acquired from NIR spectroscopic techniques can then be utilised for continuous improvement and optimisation of both process control and product quality.

B. Raman Spectroscopy

Raman spectroscopy has been an established analytical method in pharmaceutical development and general analytical chemistry for many years used to provide a fingerprint by which molecules can be identified. Similarly to NIR, Raman spectroscopy is a non-contact, non-destructive analytical technique with remote sensing capabilities that utilises fibre optics to integrate into process streams and hazardous environments.

The principle of operation of Raman spectroscopy is based on the inelastic scattering of monochromatic light, usually from a laser that interacts with molecular vibrations, phonons or other excitation systems [29]. When light interacts with a material, the light energy is altered and the frequency changes, the resulting Raman effect is weak and requires highly sensitive spectrometers to analyse the effect and produce data.

Raman spectroscopy is the most widely used analytical technique in pharmaceutical development due to its ability to rapidly characterize the chemical composition and structure of a solid, liquid, gas, gel, slurry or powder sample through providing detailed characteristics of their vibrational transitions. The interpretation of data is also easier than that of NIR spectroscopy and does not compulsorily call for multivariate modelling as simple modelling of the peak heights or ratios can often achieve the desired goals [30].

Raman spectroscopy is ideally suited for application in PAT systems due to the flexibility of the technique to operate online or inline whilst providing accurate and repeatable real-time measurements of materials under process and providing both quantitative and qualitative data to enhance process monitoring and control. Typical applications of Raman spectroscopy in the pharmaceutical include [31];

- Blend uniformity
- Active pharmaceutical ingredient (API) concentration measurements
- Raw material verification
- Contamination & impurity measurements

Recent advances in Raman spectroscopy has increased the versatility and suitability of this technique for application in continuous process monitoring systems such as PAT. The proven accuracy and precision of these instruments allow them to be utilised in highly regulated industries such as pharmaceutical development and analytical chemistry to provide real time data on key characteristics of materials for continuous process monitoring and continuous process improvement strategies.

C. Selection of Process Analysers

While similarities exist with NIR and Raman spectroscopy there are some fundamental differences between the two methods that effect their suitability to certain applications, however the complimentary nature of NIR and Raman spectroscopy ensures that the vast majority of measurement applications would be suitable to at least one of the two aforementioned techniques. This is due to the fact that strong bands in the IR spectrum correspond to weak bands in the Raman spectrum and vice versa [32].

NIR and Raman spectroscopy both offer a non-contact, non-destructive form of real time measurements that require no sample preparation and are both easily integrated into manufacturing processes while also providing remote sensing capabilities.

Raman spectroscopy is used for highly specific analyses of materials and for analysis of liquids and generally requires simple statistical modelling to interpret the acquired data, however as the Raman affect is weak, expensive and highly accurate equipment is required for detection. Fluorescence from impurities and heating of the sample from laser radiation can obstruct the Raman spectrum and equipment must be carefully tuned and calibrated to counteract these effects [33].

NIR spectroscopy is used in the pharmaceutical industry to provide rapid measurements in areas such as raw material identification and classification, blend homogeneity and particle sizing and requires multivariate statistical analysis techniques to interpret the data collected from in process materials. NIR spectroscopic instrumentation, in comparison to that of Raman is relatively simplistic and inexpensive while maintaining a high level of precision, repeatability and accuracy. Its penetration depth into sampled material can also reduce percentage error as a larger portion of the material can be analysed.

There are a number of key factors to consider prior to selecting the correct spectroscopic technique for integration in PAT systems, such as the critical to quality attributes of the material, levels of accuracy or error tolerances required, chemical and physical stability of the material, process parameters and environment and the level and method of chemometrics required. Understanding these key factors allows for selection of the correct technique to ensure optimum levels of performance in an integrated PAT system [34].

VI. CHEMOMETRICS

Chemometrics is one of the most critical aspects to PAT systems and is used to extract, analyse and interpret chemical information from materials under process through use of mathematical and statistical methods and is driven primarily from physical and spectral data. The data, acquired from sensors and analyser located at key measurement points within the process, is computationally analysed using a variety of mathematical and statistical tools and simulations. This allows for a more in-depth understanding of chemical information and the correlation of quality parameters or physical properties of materials to instrument data [35].

Analysis of the data is achieved using specialised software packages consisting of a variety of multivariate, univariate and statistical analysis tools that are suited to a variety of applications in materials processing such as [36];

- Identification of critical to quality attributes
- Identification of multifactorial relationships between process variables
- Spectroscopic calibration solutions
- Statistical modelling for process optimisation
- Multivariate statistical process control
- Process modelling for continuous monitoring and fault detection

The fundamental principle of chemometrics is the acquisition of data, and with advances in measurement sciences and computational capabilities of data acquisition systems, it is possible to obtain and input extremely large data sets from sensors and analysers located within the process stream of manufacturing processes into chemometric software packages. This allows for a previously unachievable level of process understanding and control and drives innovation in pharmaceutical development and manufacturing.

VII. Conclusion

The pharmaceutical industry is experiencing a period of sustained growth since 2001 and continues to thrive through investments in the research and development of innovative treatments, biotechnology and biologics among others. In 2013 a report issued by the IMS institute on the global use of medicines stated that, global spending on pharmaceuticals will exceed €1.2 trillion by 2017 [37], [38] which will see the industry having tripled in size over a 16 year span. With increasing strain placed on supply chains and the decline of the blockbuster drug model, pharmaceutical manufacturers in recent years have begun to invest heavily in strategies and techniques to reduce product development times and costs while improving manufacturing efficiency, product quality and process understanding.

The QBD framework in conjunction with PAT systems backed by the FDA, not only offer a solution to continuous process monitoring and control but offer a systematic and data driven approach to pharmaceutical development and validation that acts as a guidance to pharmaceutical manufacturers that can reduce FDA approval times and increase the likelihood that FDA submission guidelines and specifications are achieved.

PAT systems, enveloped in the QBD framework provide the majority of this data through a variety of sensors and analysers that have advanced technologically in recent years to a degree where almost every aspect of a processes chemical, physical and biological characteristics can be analysed monitored and controlled. Advances in analytical chemistry such as chemometrics and the computational capabilities of equipment has provided analysts with previously unobtainable level of process understanding that can be applied to continuous improvement strategies, process optimisation and increased product quality measures.

In conclusion QBD and PAT offer wide ranging benefits to both pharmaceutical development and manufacturing through reduction in product approval times, increased product quality, significant reduction in cycle times due to on/inline process monitoring and significant financial gains as a result of reduced labour dependencies and increased efficiencies.

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