Chapter 13. Process analytical technology (PAT) and its role in the quality by design (QbD) initiative

13.1 Introduction

The pharmaceutical and related industries have been given incentive to adopt state-of-the-art process monitoring and control strategies, much like other industries have been doing for many years. Traditional arguments coming from the industry, such as "the pharmaceutical industry is different to other industries", have sometimes stifled the opportunity to become innovative, however, this situation is gradually changing. Is the pharmaceutical industry different from other industries? "Yes, absolutely"; it deals with the treatment of sick people and the need for high quality products that do their job is *imperative*. Is the pharmaceutical industry different from other industries from a manufacturing perspective? "Absolutely not"—all industries share the same issues regarding product quality and process efficiency. Within the industry, contrary arguments that try to maintain the *status quo*, may be blocking the opportunity to improve, where typically it is cited that a regulatory agency "will not accept" substantial changes to the process or product, sometimes without even "testing the water".

Indeed, it used to be a very expensive process to change the market dossier of a product if any process or product changes were to be made post approval, and this increased the resistance to make any meaningful process changes, even though they were necessary. In the early 2000s the US FDA, under the guidance of Dr Ajaz Hussain, analysed all of the warning letters issued to companies based on process deviations and instituted what is known today as the Code of Good Manufacturing Practices for the 21st Century (*cGMPs for the 21st Century* [1]). The concept and final paper was called the "Scientific, Risk-Based Approach" to pharmaceutical manufacturing. Dr Hussain highlighted the notable lack of innovation in pharmaceutical manufacturing at a conference in Singapore in 2007, where he stated that the manufacturers of M&Ms have much tighter controls over their coating process than the pharmaceutical industry has on tablet coating processes. Should this not raise concern? Is not the pharmaceutical industry held up as the gold standard of product quality and manufacturing excellence in the public eye?

Hussain's main focus was to encourage industry to adopt a paradigm shift from an 18th century approach to quality to a 21st century approach. The area of precision agriculture has utilised state-of-the-art technology for many years for fertilisation management and irrigation planning for crops using near infrared (NIR) spectroscopy and chemometrics, methods only recently adopted to any great degree by the pharmaceutical industry. cGMPs for the 21st Century was a concerted attempt to help industry realise that innovation does not stop after the R&D stage and should continue throughout the entire product's lifecycle. In order to make innovation work, a new mindset is required throughout an entire organisation, where a "can do' attitude is adopted, rather than a reactive and pre-emptive one.

The reality is that "quality costs", and cannot be considered a red line on an accountants' ledger book. Paying for quality upfront will naturally lead to cost-effective manufacture of the highest standard of product. To aid industry in the implementation of better

quality systems, the Quality by Design (QbD) initiative was established such that scientists and engineers could implement the latest advances in process monitoring and control systems with a regulatory framework to support such implementation. QbD therefore requires advanced process sensor technology and modern quality systems to enable such implementations. This is where the general premise of Process Analytical Technology (PAT) comes to the fore.

This chapter aims to provide both new and existing practitioners with an overview of the QbD and PAT initiatives, their interrelationship and how this all ties into the key analysis methods of DoE, chemometrics and TOS. The most important guidance documents will be reviewed in a pragmatic manner along with a practical, implementation approach to the pharmaceutical quality system (PQS). QbD is the embodiment of all of the concepts discussed in this textbook so far—from sampling, to appropriate technology, to the design of rational experiments right through to better process understanding and finally a system for monitoring and controlling processes to meet the highest possible levels of validity.

13.2 The Quality by Design (QbD) initiative

A key statement from the cGMPs for the 21st Century guidance is the following,

"Quality cannot be tested into products, it should be built in, or by design"

This statement powerfully outlines a paradigm shift from "Quality by Testing" to "Quality by Design". While quality control (QC) practices are highly important for many aspects of a products release, they are not all encompassing and the results generated are typically taken from a non-representative sampling scheme (chapter 3). The situation is described in full and adequate solutions are offered powerfully in Esbensen *et al.* [2].

As a key example, there is an essential mixing step in almost any solid dose pharmaceutical manufacturing process, batch or continuous. In spite of intense efforts over more than 20 years, the current state of affairs regarding adequacy and verifiability of pharmaceutical mixing and tablet homogeneity is at an impressive standstill. The situation is characterised by two draft guidance documents, one of which has been withdrawn, and the second never approved. Esbensen *et al.* [2] analysed the contemporary regulatory, scientific and technological situation and suggested a radical way out calling for a paradigm shift regarding sampling for QC of pharmaceutical blends. In synergy with the QbD/PAT efforts, blend uniformity testing should only be performed with properly designed sampling approaches that can guarantee representativity—in contrast to current regulatory demands for severely deficient *thief* sampling. This was shown to be the only way to develop the desired in-process specifications and control for content uniformity and dosage units meeting desired regulatory specifications. Their exposé shows how process sampling based on TOS constitutes a new asset for meeting the requirements of section 211.110 of the current Good Manufacturing Practices regulations [3]. This approach was called upon to establish the desired science-based, in-process specifications allowing independent approval or rejection by the quality control unit. A strategy for guaranteed representative sampling and monitoring with "built in" automated measurement system check, variographic analysis, was shown to facilitate comprehensive quality control of pharmaceutical processes and products.

It has been the authors' experience in some companies where, when a single failure has been detected in a sample, the instinctive reaction is to keep on sampling and testing in an effort to retain the batch. This is the ugly face of quality by testing and does not adhere to the principles of QbD.

So then, how is QbD achieved?

Three key terms have resulted from the QbD initiative and these are,

- **Critical process parameters (CPPs)**, which have been determined to have the most impact on product quality. Methods such as factorial designs and optimisation designs (Chapter 11) can be used to understand the main effects and interactions of the CPPs that influence quality.
- **Critical quality attributes (CQAs)**, which are the key product performance and efficacy characteristics of a product that make it effective for its

intended purpose. These are typically the response variables of a designed experiment or a multivariate quality approach and can, in many cases, be attained using PAT.

- **Quality target product profile (QTPP):** A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product ICH Q2(R1) [4].

These critical features lead to another major concept in QbD, namely the **Design space**. The definition of design space comes from the important guidance document issued by the International Conference on Harmonisation (ICH) entitled Q8, Pharmaceutical Development ICH Q8(R2) [5],

"The multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality"

Stated in a manner that is consistent with this book, the definition of design space may be rewritten as follows,

"The use of methods such as Design of Experiments, Multivariate Analysis and Statistical Process Control that have established the effects and interactions of the CPPs such that the CQAs have been assured at the point of manufacture in real time"

This means that a process oriented rather than a product-oriented approach to quality is required which has been stated to be **the** underlying premise of PAT. Following on from the definition of design space, the concept of desired state is defined as follows from ICH Q8(R2),

"Product Quality and Performance achieved and assured by Design of Effective and Efficient Manufacturing Processes"

Stated in a different way, within the design space, lies the "desired state".

It is now apparent that the key concepts of QbD can be achieved through the use of DoE and MVA, however, other approaches can also be used, but may not be as effective as these.

QbD, like PAT is not a single approach or methodology. It is the development of a new skillset that can be modified and adapted based on the problem at hand. The embodiment of QbD has recently been realised in continuous manufacturing systems (CMS) currently approved by the US FDA for the manufacture of solid dose products in a real-time release (RtR) environment. Each product/process combination has to be solved in its own unique way and reliance on a single technology to solve every problem is not an option. This is exactly the right attitude which is one of the first issues taught in the PAT curriculum, Dickens [6].

13.2.1 The International Conference on Harmonisation (ICH) guidance

To further bolster the pragmatic guidance for implementing a QbD strategy, the four documents issued by ICH listed below form the foundation of an excellent framework,

- ICH Q8, Pharmaceutical Development [5]: This document outlines the key aspects of utilising the tools of QbD primarily for secondary manufacturing. It defines the design space and provides practical examples for implementation.
- ICH Q9: Quality Risk Management [7]: This document defines a number of tools to be used to mitigate the risk that the many input and output variables from a process will cause serious harm to the end user of the product. It is an effective strategy for defining CPPs and CQAs that then need designed experiments to assess for main effects and interactions, but its most valuable use is to prescreen out any low risk factors so that they don't use up valuable experimentation budget on unimportant variables.
- ICH Q10, Pharmaceutical Quality Management System (PQS) [8]: This document defines strategies to support IT and control engineers when implementing a real time QbD system for process monitoring or control. It is most useful when combined with the guidance of GAMP®5 [9] particularly for the validation of computerised systems. The PQS is the central theme behind continuous improvement (CI), corrective and preventative maintenance (CAPA), overall equipment effectiveness (OEE) and early event detection (EED).
- ICH Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) [10]: This document is the primary manufacturing equivalent of

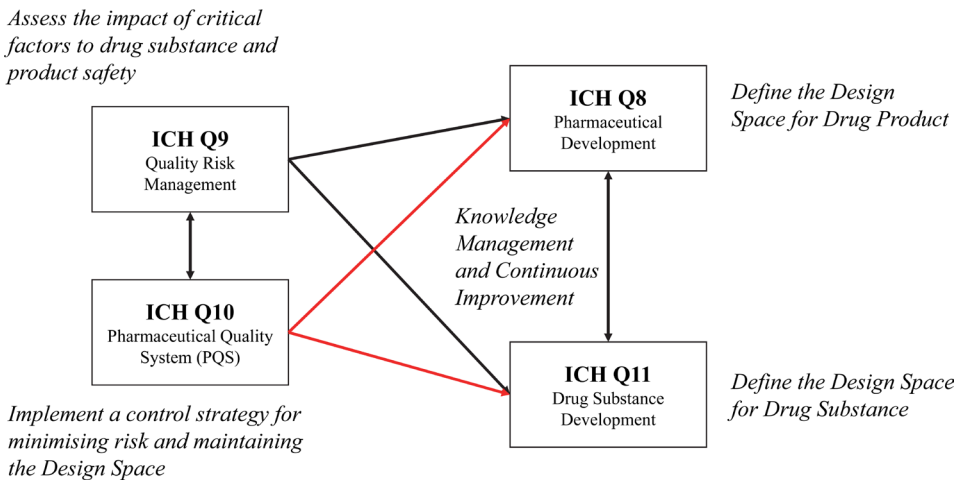

Figure 13.1. Interrelationships of the ICH guidance documents specific to QbD.

ICH Q8 which extends the principles of QbD to biotechnology/biological products and their manufacturing processes.

Figure 13.1 shows the interrelationship between the ICH Q8-Q11 documents.

As with most good initiatives in the pharmaceutical and related industries, an ocean of guidance documents has appeared from everywhere and many groups/societies have produced so much documentation that the overall initiative is at the risk of becoming the great talk fest rather than a pragmatic step towards better manufacturing. An anecdote coined by the authors of this text a number of years ago was "PAT is not idle chat".

13.2.2 US FDA process validation guidance

Possibly the single most important guidance document to support the QbD initiative is the US FDA's 2011 Process Validation Guidance [11]. Condensed to its simplest form, this guidance has two main focusses,

1) All new submissions to the US FDA must be based on the QbD approach.
2) The three batch validation approach is no longer acceptable and continuous verification is now a requirement.

The only real way to achieve continuous verification is through the implementation of an effective PQS which in turn monitors and controls CPPs and CQAs through the use of PAT and methods such as statistical or multivariate statistical process control (SPC/MSPC), which in turn have been established through methods such as DoE and risk mitigation. Following on from the three-batch validation process used until only recently, time to market was typically the main driver of the validation effort. With quality taking backstage, the validation effort was typically biased in such a way to ensure absolute success. To explain, during a validation effort, a company would require its best process operators to manufacture the validation batches, the raw material suppliers were asked to provide their known best batches of material and the laboratory personnel used to perform the analytical data were typically the most experienced analysts. What resulted was a "best case" situation of manufacturing, which typically ended in non-ideal situations, i.e. inexperienced operators, following standard operating procedures (SOPs) to the letter would end up with non-conforming batches…. Why? There are many things that can go wrong in batch production that are out of the control of most companies when a serious material issue comes up, however, when a validation effort is biased, the process has not been tested for robustness and typically batch issues will follow, either for the operation at hand, or in downstream operations.

13.3 Process analytical technology (PAT)

The classical paragraph cited from the 2004 PAT Framework Guidance document [12] is the definition of PAT stated as follows,

"The Agency considers PAT to be a system for designing, analysing, 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."

A common misconception regarding PAT is that it is a means of bringing the laboratory to the process. This misconception is no different to "quality by testing". The answer to what PAT is can be found by careful inspection of the definition above. PAT is an *enabler* of QbD in the sense that correct technology adoption can reveal insights into new and existing processes and these insights allow the modification or even replacement of existing equipment in favour of equipment that will minimise the risk of manufacturing failures. This is performed by analysing the data obtained and making scientific, risk-based decisions driven by objective data that will allow the implementation of a control strategy, particularly through the development of a PQS, refer to section 13.4 for more details on the PQS and its construction.

Therefore, PAT is not necessarily a single spectrometer generating quantitative data for a quality control test, it is a complete *holistic* means of continuous improvement and early event detection such that *proactive*, rather than *reactive* quality decisions can be made. This is the intended meaning of "timely measurements". It must also be noted that valid (i.e. representative) raw material characterisation is one of the most important aspects of a true PAT initiative and correspondingly a QbD system. Many companies have adopted NIR and Raman spectroscopy for identification of raw materials. This in itself does not constitute PAT. It is only the replacement of a compendia monograph test by an alternative identification test. What can an identification test reveal about the materials processability? Absolutely nothing! In addition, comes the fact that NIR and Raman probe heads only see a very small fraction of the material flow; this may, in many circumstances, lead to a significant fundamental sampling error (FSE) a.o. see chapter 3 and Esbensen and Paasch-Mortensen [13].

It is only when the technology is used to predict the materials quality attributes and characterise its processability that this usage can be considered a PAT. This information then has to be used as a CQA in some form that will be an input (or a CPP) to another unit operation. The authors have used the following analogy to a "jack-in-the-box" when speaking about raw material understanding. If a raw materials inherent variability is high, this is like stuffing a spring into a box and closing the lid. Since the current way of thinking is to keep all processing parameters fixed, the process is not allowed to adapt to the raw materials characteristics. Therefore, when the box is opened, the spring expands violently and this expansion of variability is what typically happens to a product when it is manufactured based on a fixed process model understanding—which is unrealistic. This situation is depicted in the top pane of Figure 13.2.

The QbD/PAT approach is first to understand the material and devise better campaigning strategies of materials to products. Then, based on the raw material characteristics, allow the process to become flexible and be able to *adapt* to the *de facto* existing material variants, then when the final product is released, it should have the lowest variability in performance characteristics and the highest quality possible, as depicted in the bottom pane of Figure 13.2.

13.3.1 At-line, online, inline or offline: what is the difference?

These definitions have caused much confusion to practitioners over the years and this section aims to provide a definitive, once and for all definition of what these terms mean and why they are implemented as such.

1) **At-Line**: The physical taking of samples from a process line via a pre-established protocol to a measurement system that is in *close proximity* to the process for the quasi-real-time assessment of a series of samples for quality characterisation and detection of process deviations. These samples are typically not returned to the main product stream

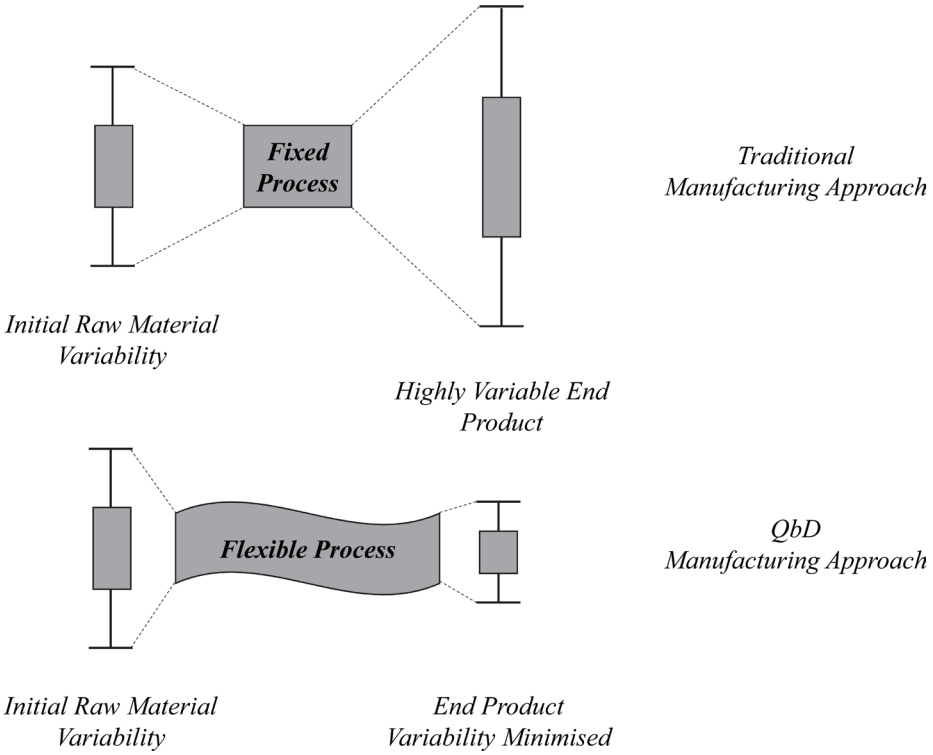

Figure 13.2: Product variability using traditional and QbD approaches to manufacturing.

after analysis. This approach may or may not be of sufficient speed to perform the needed PAT role.

2) **On-line**: The introduction of a system that can *bypass* the main product flow, or a scaled-down fraction hereof, and hold a sample in a stationary manner such that a longer analysis time can be applied, or if the sample requires preconditioning, before an analysis method is applied. These samples may or may not be returned to the main product stream, depending on whether any modification to the product's integrity has been made. The functioning of the bypass valve is the critical element in this approach. It is necessary to have demonstrated that the bypass flow is indeed representative of the main flow, an issue often overlooked or actively suppressed, see chapter 3 and below.
3) **In-line**: The placement of the analysis system directly **in** the main product stream that has been demonstrated to produce representative (or fit-for-purpose representative) measurements of the product as it exists in the process. Theoretically, this approach is meant to minimise the major sampling errors for such measurements as no samples are extracted from the line, unless a sampling port has been designed such that the sample measured is the one collected. It is often overlooked that **reference samples must** be extracted from the same flow in order to provide for a *bona fide* multivariate calibration. The requirement that in-line measurement systems have indeed eliminated all *sensor sampling errors* is a requirement very often overlooked or suppressed. This critical issue is analysed and exposed in full in Esbensen and Paasch-Mortensen [13].
4) **Off-line**: The physical taking of samples from a process, via a pre-established protocol to a remote (usually a QC laboratory) for detailed analysis using a number of analytical and physical tests. Results are typically nowhere near real time and are typically

not used for process correction, except only in certain, fast cases.

5) **Remote sensing**: The first impulse on reading "remote sensing" may well be a satellite platform equipped with appropriate sensors (LANDSATs, or the many more advanced Earth Observation satellites (NASA; NOAH), space probes (e.g. New Horizon) or planetary rovers, e.g. Curiosity, which is equipped with a ChemCam (chemical camera) that a.o. employs the **The Unscrambler®** software. However, with PAT a pathlength of 800 km is not being used, but one of cm to mm only. Any sensor system interrogating the process material through a *non-contact* interaction is a remote sensing approach. A prime example would be a NIR-camera located 80 cm above a conveyor belt transporting wood shards, the analyte in question being "instant moisture determination" (at least from the uppermost few mm of the lot material being carried through the field-of-view of the camera). Other applications concern, e.g., NAA (neutron activation analysis) for density determination, or "clamp-on" impedance sensors intended to characterise the flow regimen of compound oil/water/gas flows in pipelines. For a broad catalogue of PAT modalities in the present context, see Bakeev [14].

13.3.2 Enablers of PAT

NIR spectroscopy has been the major PAT used until recently and has enjoyed the status of being the preferred technology for use in the pharmaceutical industry, mainly due to its versatility and non-destructive sampling. In more recent times, there has been an emergence of other spectroscopic and non-spectroscopic tools that have found their way into the PAT practitioners' toolkit including Raman spectroscopy, terahertz spectroscopy, improvements in mid-infrared spectroscopy, particle size analysis (PSA) and many more tools (particularly based around imaging) are becoming available all the time.

Near infrared (NIR) spectroscopy for PAT

NIR spectroscopy has found widespread usage as a means of raw material identification. This is because of the speed aspects of the technology and for lot sizes of 100+ containers per delivery, laboratory testing times could be reduced by up to 90% compared to traditional pharmacopoeia monograph testing. However, since NIR is also sensitive to the physical characteristics of materials, Plugge and Van der Vlies [15], raw material performance attributes were soon being predicted from the identification scans. This is the differentiating factor distinguishing a simple ID test to making it into a PAT. The instrumentation available in the early days of pharmaceutical NIR were primarily holographic grating based instruments, Swarbrick [16], which meant they were not amenable to simple implementation into a process environment. Many studies were performed on pilot scale equipment to show that NIR could provide detailed insights into processes such as solid dose blending, fluid bed drying a.o. However, it was not until the emergence of diode array (DA)-based instruments that PAT took a next major step towards monitoring processes in real time.

The DA instruments offered a distinct advantage over both grating-based and Fourier transform (FT) instruments of speed and no moving parts. This made them more robust to manufacturing conditions, however, the long-term stability of these early instruments was poor compared to the research-grade instruments, and their early adoption was limited to a small number of PAT groups. Unfortunately, only a small number of the most progressive of companies allowed risk-based implementation of NIR into production equipment.

There were a number of groups who developed elaborate systems using grating-based and FT systems for rotating blenders and stationary driers. With the FT instruments proving to be more reliable when scanning moving powder samples, Berntssen [17], these systems became the first choice for implementation and fibre optical cable interfaces to multiplexed spectrometers became a popular choice. With the birth of the age of mobile phones and wireless connectivity, this soon made its way into NIR analysers. This opened up for many new opportunities to monitor powder blending processes in rotating blenders. Whatever the configuration (IBC, V-blender, double cone blender etc.) interfacing the NIR to the vessel(s) is possible using standard sanitary fittings and the inclusion of a sapphire sight window at the optimal

sampling point. Methods such as PCA and moving block standard deviation (MBSD, and related methods) have been successfully used to monitor and stop the blending process when the endpoint has been reached [18, 19]. However, keeping the reader on his/her toes w.r.t. the lessons learned in chapters 3 and 9, what is the typical size of the analytical volume relative to the full volume of the vessel in this scenario? It is not *a priori* given that many spectra obtained from a sensor grab sampling approach necessarily averages up to a full representative signal of the entire flow in front of the window (but it is always possible to test this hypothesis specifically by a replication experiment, see chapter 9 for more details).

The PAT aspects of monitoring blending operations stem around the fact that powder mixing processes are the least understood of all mixing phenomena, Muzzio [20]. Sampling inside the bed is typically achieved using a method known as thief sampling (a fancy name for grab sampling, chapter 3) that a.o. results in *forced* segregation of the blend and all thief sampling is therefore principally non-representative data for blend uniformity Muzzio [21]. In the case of dynamic blending systems, the principle of mixing is based on cascade flow, where the powder bed folds over itself in the blender and eventually uniformity is supposed to be achieved. Sampling in this case by NIR is relatively simple, since the cascading powder blend forms a front (similar to the crest of a wave as it breaks on a beach), placing the instrument into the blender at any point in the direction of rotation will lead to a measurement of the powder as it exists in the process. Blanco *et al*. [18] have reviewed the methods used for determining blending endpoints and have found that methods based on PCA are the most robust for assessment. This is because PCA can separate major sources of variation (i.e. macro-mixing phenomena due to overall blending of a mixture) from minor, but still important, sources of variation (i.e. micro-mixing phenomena that are highly important for blends that contain a small amount of the active ingredient). This information is achieved through the spectral loadings generated in PCA and their interpretation. The complete, very complex issue: assumptions vs myths vs facts regarding mixing processes were analysed by Esbensen *et al.* [2].

Again, as was stated previously, PAT is not a single tool or approach to all problems and in many cases the running of multiple endpoint models on a single process may lead to better understanding. The following important information can be obtained through the application of NIR into a dynamic blender,

1) The macro (i.e. large-scale blending) uniformity of the mixture.
2) The micro (i.e. interstitial blending) uniformity of important blend ingredients.
3) The attrition that may occur and leads to process issues downstream.

Continuing from point 3 above, when NIR spectra are allowed to be collected on a process for an extended period, a typical sinusoidal pattern of blending may be observed. This cyclic behaviour is the result of mixing/de-mixing processes that can either be attributed to attrition (i.e. the breaking down of the particle size of the mixture ingredients and their redistribution) or it is simply the end result of what mixing can achieve on a mixture that contains differently sized particles; the extra little mixing achieved is immediately nullified by counteracting segregation resulting in a non-vanishing steady-state situation characterised by a significant residual heterogeneity, i.e. homogeneity cannot be achieved completely regardless of mixing time [2].

If the particle size becomes too fine, some powder blends are more likely to segregate (others are not), but more dust is produced and if/when the powder is being compressed, issues such as punch sticking can cause production issues, more downtime and less process efficiency.

For many years, the ultimate goal of NIR was to monitor the content uniformity of tablets as they come off the tablet press as a 100% inspection system. While this application would prove to be an excellent way to enhance batch traceability and allow a reject system of tablets that did not conform to specification, is this really a PAT implementation or is it just bringing the QC lab to the process? In any case, the tablet ejection speeds are just too fast in order for a reliable NIR measurement to be taken and a new strategy was sought for this application. At the top of the punches of a tablet press, there is a system known as the feed frame. This is where powder from a container is either gravity fed or vacuum fed to the press and the powder is fed

into the tablet dies. There is an excellent opportunity to place an NIR probe (particularly the micro-instrumentation based on linear variable filter (LVF) technology, Swarbrick [16], which has a small instrument footprint and is robust to the dusty conditions of a tablet press). Placing such a sensor just above the powder may lead to quasi-100% inspection of the tablets. A tablet unit dose is considered to be a 100% statistically representative sample (this is because a tablet press is (for all intents and purposes) a large spinning riffler and if each tablet was to be tested at-line, or on-line using an external system, the process would take weeks to complete. The purpose of the feed frame system is to ensure uniformity of delivery to the press and if any deviations are observed, this information must be related back to the flow characteristics of the powder, either in gravity fed operations (through mechanisms such as rat holing or percolation) or vacuum transfers where segregation may be influenced by static or other factors. This is the PAT aspect of the tablet press monitoring application and the information obtained is used for process improvement, not a replacement of QC testing (this is a secondary benefit of PAT and should always be viewed in this way).

Case study, NIR for fluid bed drying monitoring and control (real-world PAT implementation)

In one implementation, a FT instrument was coupled to two fluid bed driers (FBD) using a multiplexer in a manufacturing facility of generic products for one of its product formulations. The manufacturer was experiencing a major bottleneck and downstream processing issues for this product and isolated the FBD as the root cause of the problem.

Careful analysis of the data being generated by QA suggested that the loss on drying (LOD) of the product was not only missing target more times than not, but also the uniformity of moisture in the powder bed was also non-uniform. This issue suggested that the initial three-batch validation approach was not robust enough to pick up this process flaw! The secret to this processing issue was found through the use of NIR. After a strict design of experiments procedure was carried out to optimise the position of the fibre optic probe in the drier, initial trials on real production batches were conducted. The method of PCA targeted at the 1930 nm (moisture) region of the spectrum was observed in scores and loadings space. This showed that the product was dry in 10 min (compared to the validated 40 min specification). It was interesting to note that the SOP for the process stated that after 10 min, the process should be stopped, the granules should be remixed and the bed placed back into the FBD for continued drying. This raised concerns as the need for extra manual handling could introduce potential contamination.

After a review of the data generated by NIR, when the bed was spatially sampled (unfortunately grab sampled in this case, chapter 3), the data revealed that the side walls, where the NIR probe was located were typically much drier than the inner sections of the bed. This indicated a lack of fluidisation in the process and this was why there was a need for manual remixing of the granules. The next step was to perform an engineering study on the process to better understand why the bed was not fluidising in the first 10 min.

In a modern FBD, the air vents to the bed are usually vertically oriented with respect to the FBD column, providing the most efficient airflow to the wet mass. Also, these modern FBD systems have a dehumidification system that controls the moisture level of the heated air that dries the powder. In this particular case, the FBD was an older system with a side air vent and no dehumidification system. These were the major causes of the lack of robustness in the process and an engineering solution was required to initiate fluidisation without manual intervention. This was provided in the form of a feature of the drier known as the “product loosening” button that automatically induced a fluidised bed, however, it was not used in the past as there was no way of triggering when to apply the button until NIR came along.

To assess if this functionality was the key to the problem, NIR was used to monitor when the bed reached its “dry” state and then the button was manually pressed. The function of the product loosening button is to create an instantaneous pressure and release cycle that redistributes the powder without manual intervention. The observation was that the moisture monitored by NIR rose sharply and clear fluidisation was visible in the sight glass of the drier. The powder bed then dropped to near dry around the 20 min point where the product loosening button was used again.

Only a small increase in moisture was observed at this time point and the product reached a stable endpoint after only 25 min. Although the reduction of the drying time by 15 mins compared to the validated process did not seem to be a great gain in time saving, it represented a situation of greater efficiency where a product of desired state was attained.

However, the real benefits of the NIR method are as follows,

1) The FBD can be operated in a more efficient manner without complete system reengineering.
2) NIR provided a key insight into the process mechanism and allowed the engineers to understand the root cause of the problem.
3) Although only 15 min was gained on the process efficiency, this does not also take into account that the bed required manual remixing twice (10 min per remix) and if the product did not meet LOD specification after 40 min, it had to be returned to the FBD, dried for a further 5 min and an LOD taken again. The LOD test required 10 min and if it had to be performed twice with re-drying, a total time of 30 min was added to the process. NIR therefore allowed a reduction of over an hour per mix compared to the current state and with 8 mixes per batch, the math speaks for itself.
4) NIR allowed the operators to monitor the product to its desired state without any manual intervention. This resulted in less process issues downstream compared to the current implementation.
5) Greater quality was *built into* the process by design.

It was common occurrence with the product that the re-drying step was required for each mix and therefore 8 h (or the equivalent of one working shift) was required just to account for a poorly validated process. The NIR was implemented as part of a control system that automatically implemented the product loosening feature at the appropriate time, thus allowing improved granule formation, improved material flows, produced less issues downstream and as an added benefit to the organisation, allowed four extra batches to be produced per month without the need for factory expansion.

The following represents a typical cost justification for implementing PAT in a QbD environment.

- Initial system cost and development time (including salaries): 300 K USD
- Operator costs and energy consumption estimate (per hour): 500 USD
  - Typical cost on eight mixes per batch current system: 5 K USD
  - Cost to manufacture four batches per month (less materials): 16 K USD
- Operating cost based on eight mixes per batch using NIR: 1.5 K USD
- Market value of batch (internal): 200 K USD
- Revenue increase through four extra batches: 800 K USD
- Increased production less initial equipment outlay: +500 K USD
- Payback period: 1 month

These figures are based on costs and available instrumentation at the time of this development, however, with miniaturisation of instrumentation (and subsequently lower costs), the figures stated above are achievable and realistic for this type of implementation.

For a more complete description of the NIR method and its applications, the reader is referred to the excellent handbook by Burns and Cuirczak [22] and the concise reviews by Swarbrick [16, 23]

Raman spectroscopy for PAT

Raman spectroscopy has enjoyed a renaissance as an analytical tool in pharmaceutical (and other industries) over the past decade. In a nutshell, Raman spectroscopy offers the sharp spectral bands typical of the mid-IR region with the sample preparation simplicity of NIR. Unlike mid-IR and NIR, Raman is a scattering phenomenon, not an absorption phenomenon and the Raman effect is many orders of magnitude lower in sensitivity compared to absorption. The Raman effect in some cases also has to compete with absorption, particularly in the NIR region and as such, the instrumentation involved in Raman spectroscopy is much more complex than its infrared cousins.

Since the development of the notch filter [24], charge coupled devices (CCDs) and diode lasers, Raman spectroscopy has found much more application as a process tool, particularly in operations such as active pharmaceutical ingredient (API) crystallisation processes where it is extensively used to monitor the formation of polymorphs [24]. There have also been many new portable Raman instruments come onto the

market in the past few years for raw material identification. In particular, the method of spatially offset Raman spectroscopy (SORS) [24] has been implemented as a means to measure materials through packaging such as paper or plastic used to contain the materials. Using Raman as a raw material identification method does not qualify it as a PAT tool as only identification is possible. Where Raman finds usage is in situations where the specificity of NIR is not good enough to distinguish between chemical species and in situations where the system being measured is highly aqueous.

Due to the high-powered lasers used to induce the Raman effect, these systems must be built with the highest possible occupational health and safety (OH&S) regulations in mind as exposure to the laser can cause irreparable eye damage, even blindness. When installed as a PAT tool, Raman spectroscopy is typically interfaced to a process using fibre optic cables and the implementation of Raman into a dynamic blending system is not possible, purely based on current hardware limitations.

There are a number of camps that have arisen in the pharmaceutical and biopharmaceutical industry in recent time supporting Raman over NIR (and mid-IR) and claiming one is better than the other. It is the authors' experience, through conducting parallel studies of Raman and infrared systems on a low concentration aqueous chemical reaction that all technologies have the same limit of detection and quantification. The only real case where this breaks down is for surface enhanced Raman spectroscopy (SERS) [24], however, this technique is useless for real-time process monitoring due to the long periods of time it takes for the material of interest to adsorb onto the substrate before a detectable signal can be observed. SERS is capable of measuring nanogram-scale concentrations of materials showing Raman scattering and is an essential tool in drug development and understanding metabolic pathways. Back to the topic of the camps advocating one technology over the other, this is completely unfounded as the Raman and NIR techniques are *complementary* and should be used as such. This is in alignment with the premise of PAT, i.e. use the right technology for the application, one size does **not** fit all.

Finally, Raman spectroscopy can suffer from the effects of fluorescence, even for low concentrations of contaminants in a system and the effect of the fluorescence is highly laser wavelength dependent. Many modern Raman systems offer a range of laser excitation sources from those in the NIR region right through to the UV/vis region. This means that Raman instruments tend to be single purpose for a particular application, but when they perform that application, they perform it extremely well.

Case study: Raman spectroscopy for quantitation of API in a wet massing process

Wet massing (or granulation) is the process of building up the particle size of smaller or "fluffy" APIs (that typically do not have good blending characteristics) with a binder that is added in liquid form. The wet granulation equipment typically consists of a stainless-steel bowl that has a large impeller at its base that moves the powder mass around in front of a chopper that rotates at high speed to regulate the particle size of the final granules. Optimisation of the granulation process can be easily performed using Design of Experiments (DoE, chapter 11), by means of some form of factorial and optimisation design. Typical controllable factors include,

1) Impeller speed (rpm)
2) Chopper speed (rpm)
3) Rate of liquid addition ($L\,min^{-1}$)
4) Spray vs direct liquid addition

By optimising these factors, consistent granulations are achievable, but these are macro properties of the system, what happens inside the granulator at the particle level? It has only been in recent times, driven by the PAT initiative, that key insights into powder mixing processes can be made *in situ*. Technologies such as Raman, NIR and focused beam reflectance method (FBRM) for particle size analysis can now be inserted via fibre optic cables into the granulator, effectively putting a microscope into the process and gaining real-time mixing information.

In this case study, prediction of hydrate formation in the API present in the granules can lead to processing issues downstream. Raman spectroscopy in the past has not been a reliable method for quantitation on a macro level due to the typically very small beam spot size measured by the laser. Recent technology has improved this situation through the development

of process capable probes that measure over a larger sample area [25].

Mounting the smaller spot size probes into the powder bed of a granulator can lead to sticking and therefore fouling of the probe surface. This is because the probe needs to be in close contact with the powder mass in order to generate an acceptable signal for analytical measurements. The use of a non-contact probe with a large sampling window can minimise such fouling and provide more reproducible spectra in a process environment.

The quantitative results of the two probes are provided in Figure 13.3, which shows again (as is the theme of this textbook) how important sampling is at all levels and aspects of any problem.

For a more complete description of the Raman method and its applications, the reader is referred to the excellent handbook by Lewis and Edwards [24].

Other technologies for PAT, a brief overview

This section only provides a brief overview of some other PAT tools that have been used to monitor pharmaceutical processes. For a more detailed explanation of each of these methods, the interested reader is referred to the textbook on PAT, Bakeev [14].

Mid-IR for reaction monitoring

The mid-IR region of the electromagnetic spectrum lies in the lower energy region just below the NIR. It is the source of the frequencies measured in the NIR region, i.e. mid-IR is the fundamental frequencies for the *overtones* and *combination frequencies* that are observed in the NIR region.

Classically, mid-IR was the method of choice in the QC laboratory for raw material identification, but due to its high level of sample preparation and detailed analysis, it was not considered a feasible option for rapid ID methods. Also, its implementation into processes requires expensive fibre optic cables and elaborate sampling devices. It does, however, find use in reaction monitoring of APIs, particularly in non-aqueous environments. The detailed information found in the fingerprint region is very useful for understanding reaction mechanisms and there are a number of commercial systems in use for this purpose, Coates [26].

Focussed beam reflectance measurement (FBRM) for particle size analysis

Focussed beam reflectance measurement (FBRM) is an in-line method of analysis for measuring the particle size distribution of predominantly solid materials. Particularly useful for monitoring granulation or milling operations, FBRM allows for the detection of excessive fine material in the powder samples and can help in the real-time engineering of particle characteristics.

It is typically used in conjunction with a method such as in-line NIR for measuring multiple characteristics simultaneously and is finding use in continuous

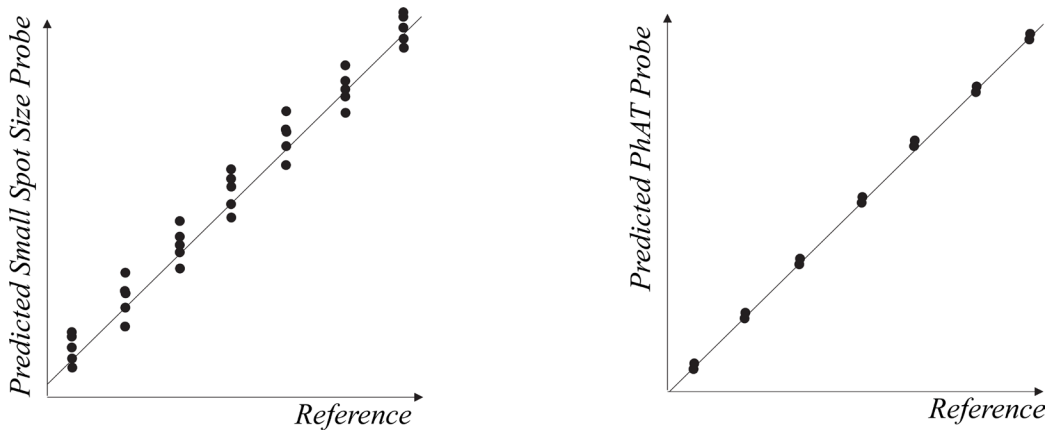

Figure 13.3: Comparison of prediction results between a small spot and a large spot Raman probe.

manufacturing systems (CMS) operations. See section 13.7 for more details on CMS.

Other than mid-IR and FBRM, methods such as UV/visible spectroscopy, terahertz spectroscopy and acoustics have been used for monitoring processes and all of these utilise multivariate methods for their interpretation and model building, Bakeev [14].

13.4 The link between QbD and PAT

QbD represents a radical paradigm shift for pharmaceutical/biopharmaceutical and even medical device manufacturing at the beginnings of the 21st century. It represents an attempt by regulatory authorities to minimise a dictatorial role in product and process development by giving manufacturers the freedom to become innovative and to teach the authorities how they are making their products. This is achieved through the design space, but the question that is being raised most often is "what is a design space?" Again, analysis paralysis can take over in companies in at the beginning of their QbD journey and risk assessments are performed that essentially block any possible progress. So, for the record, this is the most simplistic explanation of the design space,

"Measure only what is critical to quality, using the appropriate technology that will allow changes to be made in a proactive, not a reactive manner"

The term "timely measurements" was used in the fundamental definition of the PAT initiative and instils a mindset of proactive process control. Therefore, PAT is a key enabler of QbD and in many ways the two are not mutually exclusive. This is particularly true when it comes to the PQS outlined in ICH Q10 (also refer to Figure 13.1). The four key elements of the PQS are defined as follows,

- Process performance and product quality monitoring system
- *Corrective action* and *preventive action* (CAPA) system
- Change management system
- Management review of process performance and product quality

Process performance and product quality monitoring system refers to computerised systems that collect data on CPPs, batch identifiers (including unit operation identifiers), environmental conditions and any other data deemed necessary for the manufacture of high quality products. These data management systems are a key component of the PQS and more will be discussed in the section on continuous manufacturing (section 13.7).

Corrective action and *preventive action* (CAPA) *system* in the case of QbD is a proactive system usually based on advanced process control (APC) platforms. These systems manage and control the process based on measurements obtained from the process performance and product management system and they also have an intangible aspect not explored by many companies that they can provide an estimate of mean time before failure (MTBF). This is particularly useful for defining maintenance schedules that will ensure process equipment will run at its most efficient state, which leads to quality assurance. Such CAPA systems are typically based on multivariate statistical process control (MSPC) and more will be detailed on this in section 13.5.

Change management system in the case of QbD is determined by the design space established for the process, be it a holistic overview or a granular (unit operation) management system. As per the definition of design space,

"Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process."

This definition in itself provides a more flexible approach to manufacturing. Gone are the days of fixed process for variable raw materials. The process can now be developed to adapt to raw material and intermediate material changes as long as they are within the bounds defined by the design space, which is a measure of the knowledge management of the company implementing the PQS. As always, deviation from the design space (which has been shown to indicate an "edge of failure" point of the process/product) can now be assessed using multivariate controls that not only point to where the root cause of the failure occurs, but also allow a corrective process to be implemented before failure occurs. If the process significantly deviates from the design space, usual regulatory change control procedures must be initiated in order to determine the root cause of the problem.

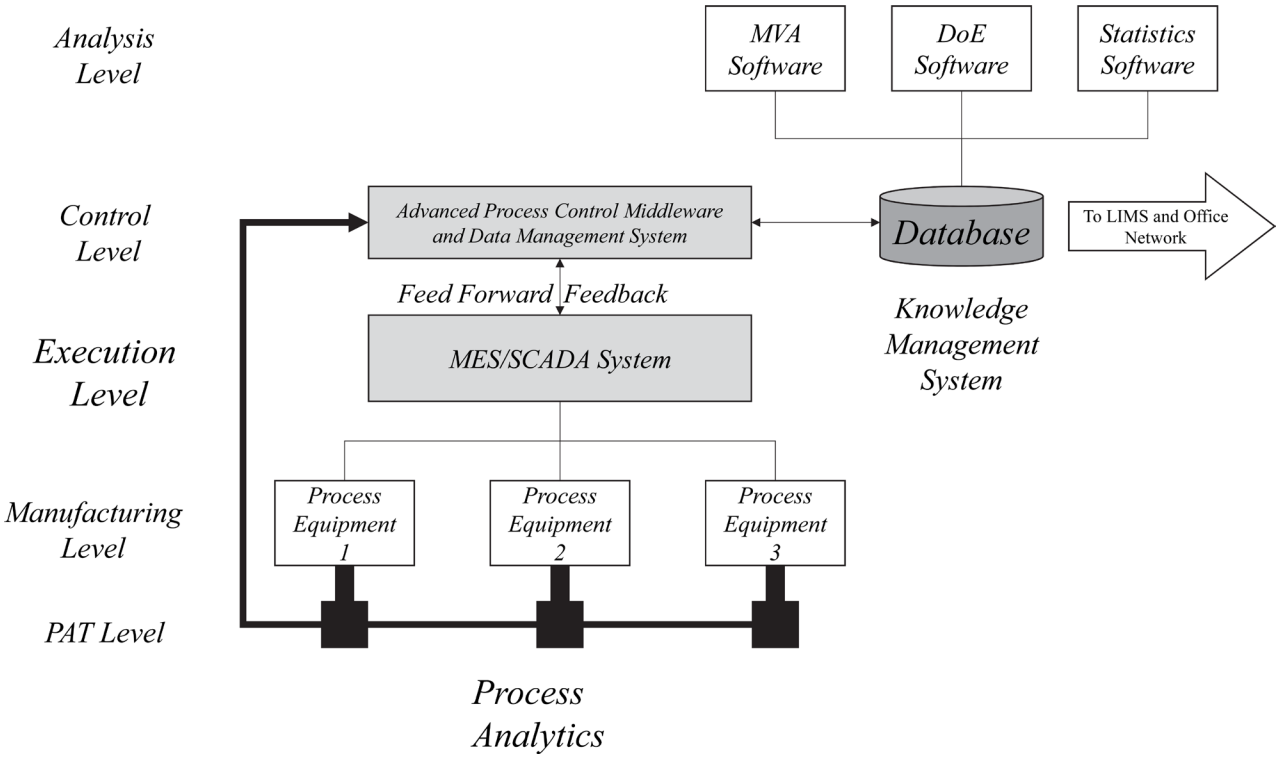

Figure 13.4: Basis of the PQS for pharmaceutical production.

Management review of process performance and product quality is better implemented through a PQS as timely information can be retrieved even during the manufacturing process. Annual reporting is now a matter of compiling the computerised results into a report template, but knowledge management only takes place if the outcomes of the reports are acted upon in a reflected continuous improvement strategy. Any deviations and conclusions can then be put into a designed experiment strategy for greater process knowledge and understanding.

This now raises an important question, what constitutes the PQS. From the authors' experience, PQS must start with as much data collection and automation as possible through the use of an advanced manufacturing execution system (MES) platform and supervisory control and data acquisition (SCADA) system connected to the processing equipment. From there, the other parts build upon this base. This is shown schematically in Figure 13.4.

The various elements of the PQS are outlined as follows,

- *PAT level:* The correct and validated technology capable of producing meaningful CQA data and for controlling CPPs.
- *Manufacturing level:* Equipment that has been engineered or modified to manufacture consistently high-quality product with minimal downtime and maintenance requirements.
- *Execution level:* A high level system that collects data from many systems and is capable of adjusting a process in real time such that proactive quality control is implemented.
- *Control level:* An advanced software platform that can take compiled data from the execution level and PAT level systems, apply MVA/DoE models to the data and feed this information back to the execution level for APC. This level also stores data into a secure database for modelling or retention. Can be linked to the office network for

annual reviews or to a LIMS system for product traceability.

- *Analysis level:* Allows access to qualified data analysts to develop process control models or gain further insights into process mechanisms for continuous improvement strategies.

Overall, this may be considered the complete knowledge management system and it meets the entire requirements of ICH Q10. It is a system that allows continuous verification to be implemented as per the US FDA Process Validation Guidelines and can be holistically qualified and validated as per the suggested guidance of GAMP®5. The system shown in Figure 13.4 is generic enough to be used as a blueprint that can be implemented into **any** manufacturing facility, the detail lies in the right technology to use as the PAT tools, the frequency of measurement, the corrective action system and how to utilise the generated data for continuous improvement.

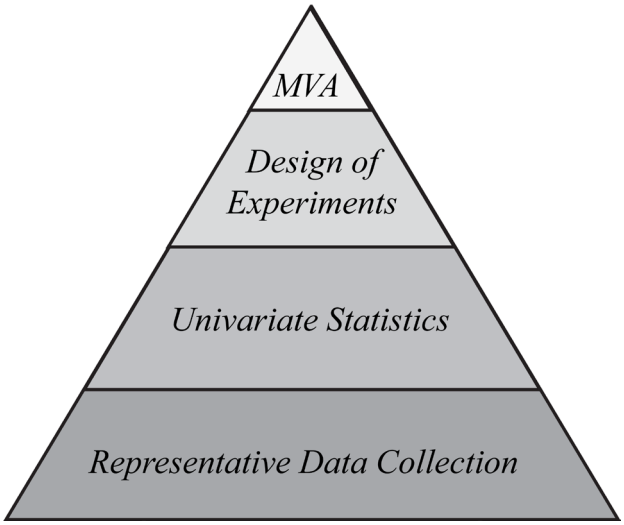

Figure 13.5: Hierarchy of data analysis for QbD.

13.5 Chemometrics: the glue that holds QbD and PAT together

Big data, mega data and more data, that's what modern process and control systems generate. It is hopefully apparent that manufacturing systems generate multivariate, time series data. Philosophies such as Six Sigma or lean manufacturing have attempted to present a over-simplistic means of controlling processes however, they cannot provide the necessary detail or insights that multivariate analysis can provide.

The currently in vogue big data solutions have provided senior managers with a dashboard approach to viewing their data. Unfortunately, this is really no different to using spreadsheet applications for a simplistic data overview, just with pretty pictures. Process scientists and engineers require a much more diverse toolkit that encompasses the simplistic views of the big data solutions with the more complex analyses required to understand not only main influences, but also their interactions, as described in great detail in chapter 11 on Design of Experiments (DoE).

To further elaborate, the data analysis approach for QbD is shown in Figure 13.5.

Starting to move from the base of the triangle up through the hierarchy, as outlined in chapter 3, representative sampling is key to any-and-all data analyses and—modelling at the top and this competence must lay the foundation of any QbD/PAT initiative. The next layer up consists of univariate data collection (this includes collection of spectra as well, even though these are multivariate in nature) and this level is used for either inputs into a DoE strategy, or an MVA approach, which may be considered the pinnacle of the data hierarchy.

The multivariate approach to data analysis is all-encompassing and allows a "helicopter" view of the overall data landscape. When used effectively, MVA can help reveal parameters useful for DoE studies when applied to non-designed data, but most importantly, the MVA approach both isolates single variable inputs when these are operative as such as well as their interactions with (many) other variables. When the parameters of interest have been isolated, a focussed univariate assessment can be made (refer to the top-down hierarchy shown in Figure 13.5). This "top-down" approach to data analysis, based on a solid sampling foundation **is the only way to fully understand data structures** and therefore to better understand the processes the data was generated from.

PAT analysers typically generate multivariate data that is modelled using chemometric approaches. Predictive models of CQAs may be developed and

used to provide understanding of the trending of a process over time. Process data typically presents itself in three major forms,

1) *Steady state processes:* Where a constant state of quality parameters it maintained over the entire manufacturing period (but there can be substantial deviations along the time line, none of which will change the general constant level). This data includes processes such as tabletting, milling etc.
2) *Evolving processes*: Where the process dynamically changes over time and is typical of biological fermentations, drying operations and coating processes etc.
3) *More irregular processes:* Processes characterised by variable loads, inputs and processing conditions (as a complex function of raw material compositions... and much more)

The chemometric models used to analyse these types of data are very different in their approaches and require profound subject-matter knowledge of the system being modelled. In recent times, the term "process signature" has gained popularity in the pharmaceutical and related industries for better understanding of how a process progresses over its course. Using methods such as PCA (refer to chapters 4 and 6), multivariate data is reduced to single points in space, defined by their scores. When PC scores are plotted over time in an evolving process, the aim of the PCA is to determine if there is a consistent pattern from batch to batch. For a steady-state process, it is expected that there will be no patterns in the data as this would indicate the presence of *systematic* influences that would change the steady state nature.

13.5.1 A new approach to batch process understanding: relative time modelling

When PC scores are plotted against each other for time-series-based data, the time dimension is removed from the data analysis, although now embedded in the "connecting line" progression linking one object (process state) to the next. In a recent pioneering publication, Westad *et al.* [27] developed a method known as relative time modelling (RTM) for the establishment of process signatures in evolving processes. Concerned by the mathematical distortions imposed on batch data by other available algorithms, the RTM method utilises the time independent nature of plotting scores together and thus allowing the definition of a *relative* batch starting point and a ditto *relative* end point for any consistently performing process. An approach with the exact same objective is Jørgensen *et al.* [28], who also ventured to *morph* unequal batch process times to a common basis through a multi-stage PLS approach. In some ways, this approach is a precursor for RTM.

Batch processes are widely used in many industries, usually in the form of chemical reactors, biological fermentations and many others. In these situations, the quality of final products is a function of the initial raw material inputs and how the process is adapted to accommodate this variability. In the past, processes were not allowed to be adjusted (i.e. before QbD) and the final product quality was much more a matter of *luck* rather than good process management. There have been numerous attempts in the past to model and monitor evolving batch processes and these typically start using three-dimensional data structures such as those shown in Figure 13.6.

In the top-left of Figure 13.6, the three-dimensional data structure is represented by the data cube (*Variables* × *Time* × *Batch*) which can be analysed in various ways. The first way is to retain the three-dimensional structure of the data and use methods such as parallel factor analysis (PARAFAC [29]) or the so-called Tucker 3 models [30]. This modelling strategy decomposes the data into three main loading directions and assesses the three-way interactions of each direction in the data set. The discussion of multiway methods is outside of the scope of the current text; suffice to say that they are relatively complex and work best when the length of each batch dimension in the matrix is equal (a situation rarely attained in practice without the use of mathematical manipulation).

Figure 13.6 also shows that three-dimensional data can be *unfolded* (more correctly *matricised*) in two distinct ways leading to two other methods currently available for the analysis of such data. These methods are,

- Unfolding the data along the time direction leads to the batch modelling approach first presented by MacGregor [31] which involves the use of dynamic time warping [32] to establish equal batch lengths.

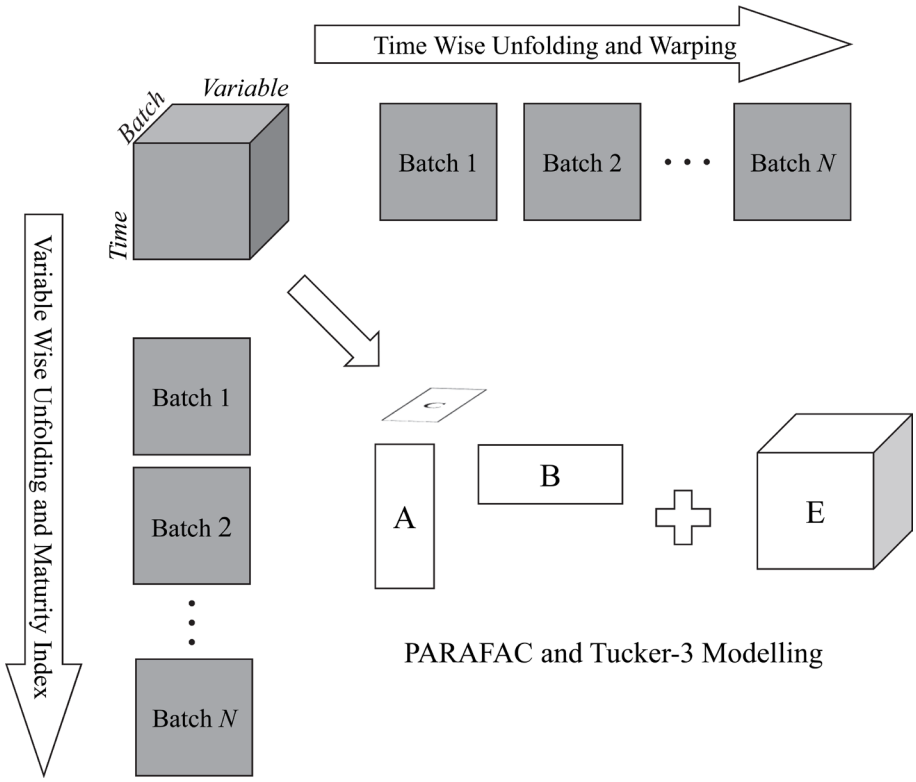

Figure 13.6: Typical batch data structure.

- Unfolding along the variable direction was proposed by Wold *et al.* [33] and eliminates the restriction of equal batch lengths by creating a two-dimensional matrix of super variables. These are regressed against a so-called maturity index and a model is created by regressing the batch data against this index to determine the endpoint of the process.

There are fundamental physical and chemical limitations on both of these approaches if the analyst is not wary. In the case of the time wise unfolding, the aim of the warping is to create a situation where each batch starts at a fixed time zero. Taking for example the process of fluid bed drying (FBD), the initial moisture state of the powder mass is hopefully consistent based on the process operators following good standard operating procedures (SOPs), however, experience has shown that there can be up to ±5% moisture variation between granulations. Now consider the development of a batch model using DTW for a data set containing the extremes, i.e. target ± 5%. Even if there are a number of training batches in the data set at target, the best the DTW can do is warp the –5% moisture batch back to target and compress the +5% moisture batch to target, but is this procedure chemically viable? Absolutely not. The chemistry of the system cannot be mathematically manipulated to be something it is not. This situation is more pronounced when biological systems are monitored and the initial chemical/biological state of the materials cannot be controlled like other processes. This is what DTW aims to achieve and is only acceptable when it can be assured that the initial state of the material in the process does not deviate to a great extent with respect to the golden target.

The maturity index approach also suffers a major flaw in the chemical/biological state point of view. The maturity index is a list of *ordered integers* used to map batch state, but by definition, the model is trying to

regress a potentially non-linear system using a linear index as the response variable. While this approach has merits in some situations, it may only have limited scope in a process where the progress can be linearly modelled, otherwise multiple phase models must be developed. The maturity index approach also requires the starting point of the materials to be of small variability compared to the target. While this sounds like it should be the case in a pharmaceutical/ biopharmaceutical environment, experience dictates that monitoring biological processes is akin to analysing "soup".

The method of RTM is **not** influenced by unequal batch lengths, does **not** require an absolute time zero and can handle **non-identical** residence time (i.e. does not require equal time point spacing like the alternative methods). This is because the time dimension is completely removed from the procedure and a new relative time scale is back-projected to the original process time scale through the use of PCA. Subsequently, based on the technology used to measure the process, the original time scale is replaced by a chemical/ biological timescale that best represents the current state of the materials in the process.

The theory behind the RTM approach is simple to explain,

1) Representative data are collected on acceptable batches using one (or many) sensors suitably aligned (refer to section 13.8.1) for data analysis.
2) Data is categorised as a two-dimensional table in an unfolded manner with batch defined as the unfolding variable.
3) Run PCA on each batch and overlay each PC score trajectory on top of each other and look for consistency. Only if the process signatures overlay to a high degree can a batch model be developed. If the PCA score trajectories do not delineate a common structure, this is an indication of two possible events,
   a) The technology being used to monitor the batches is not capable of defining a stable, useful batch signature for the process, or
   b) The processing conditions are so highly variable, that a reengineering of the process may be required!
4) Using a grid search method, a common start and endpoint of the process is defined. This defines the relative start and endpoint of the model. The endpoint samples must be analysed by a reference method to ensure that the model is predicting the final state of the product.
5) Using the grid procedure, establish the mean trajectory representative of the individual batch trajectories.
6) Define upper and lower statistical bounds on the process trajectory that are used to indicate whether the process is progressing as expected or is about to deviate from the established design space.
7) Validate the method using new batches that are normal and wherever possible are capable of testing the edges of failure and even a failure state of the process. Note that this is test set validation at the helicopter level of test batches.

Consider data taken from a chemical synthesis process, where the input variables are temperature (two probes positioned to measure different parts of the process) and the pressure in the reactor vessel. It is assumed here that these are the three CPPs capable of defining batch quality and although there are only three input variables involved, it still represents a multivariate process control situation. It also provides a good case of illustrating the complexity of a simple system.

Figure 13.7 shows the individual temperature probe 1 readings for the four batches used to develop the model.

The first conclusion drawn from Figure 13.7 is that the batches are all different based on this one variable. A more careful inspection of this data indicates a lateral shift of the data with respect to each other rather than a physical/chemical difference. This is the problem with analysing batch data in the time domain. Each batch could be warped such that they all overlay in the natural time axis, but this is an unnecessary manipulation that renders the data meaningless in the chemical sense, just to fit the form of a preconceived model.

Figure 13.8 shows all three variables measured using PCA. Due to a high degree of redundancy between the sensors, the underlying dimensionality in this system is two. The t_1 vs t_2 scores plot shows that all batch data overlay to a high degree when time is taken out of the picture.

Using a grid system, the batch is broken down into component grids where a spline interpolation

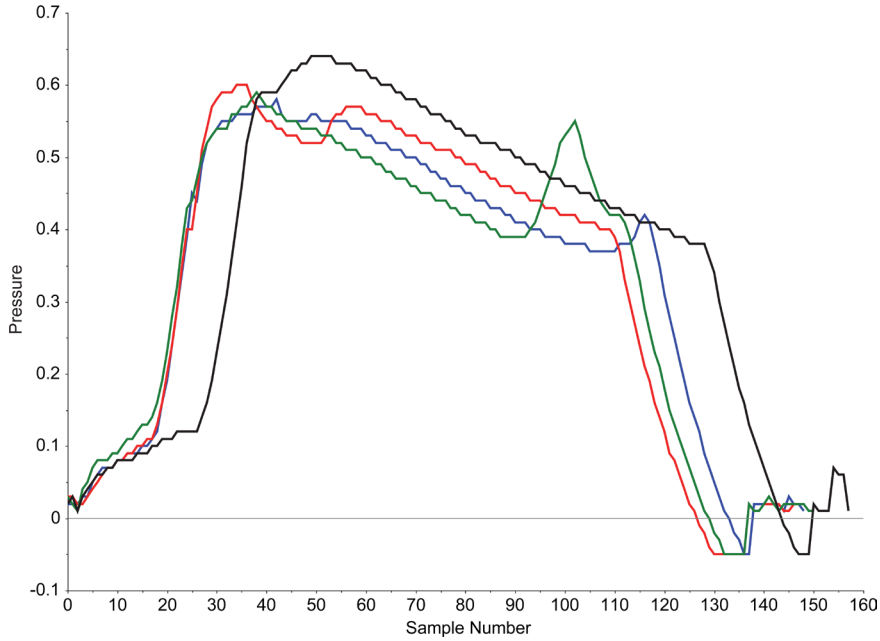

Figure 13.7: Variables measured in real time show offsets when compared on a batch-to-batch basis.

algorithm is used to define the common batch trajectory (process signature). The final batch trajectory and its design space is then calculated based on the interpolation algorithm. This is shown in Figure 13.9.

The model shown in Figure 13.9 is representative of the batch in terms of its dynamics as it evolves. Since the limits are based on the standard deviations of the batches around the mean trajectory, significance levels can be used to assess the batch. A new batch is projected onto the PC space defined by the batch model using the usual representation defined in equation 13.1. The loading matrix vector **P** represents the common process signature.

$$T_{New} = X_{New}\mathbf{P} \qquad (13.1)$$

From the newly projected score, the distance to mean trajectory can be calculated from equation 13.2.

$$D_{Trajectory} = \sqrt{\sum_{a=1}^{Aopt}(t_{new,a} - t_{new,a} \perp t_{trajectory,a})^2} \qquad (13.2)$$

where $D_{Trajectory}$ is the orthogonal distance from the new score to its projected position on the trajectory,

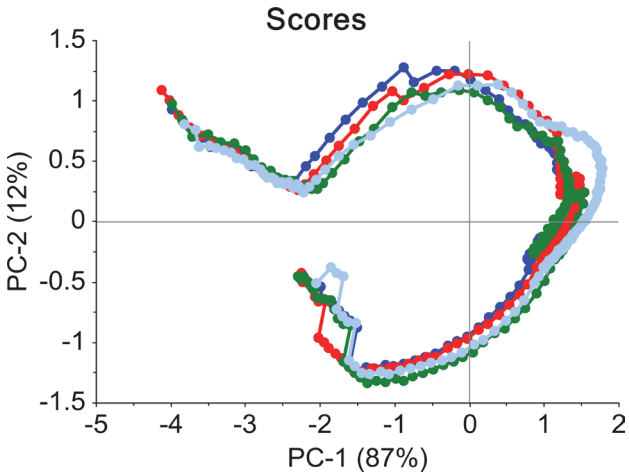

Figure 13.8: t_1 vs t_2 scores plot for the chemical reaction data.

t_{new} is the new score calculated from the batch model, $t_{new} \perp t_{trajectory}$ is the projected position on the trajectory.

During the monitoring phase of the process, the following steps are implemented into a control system such as those described in section 13.4.

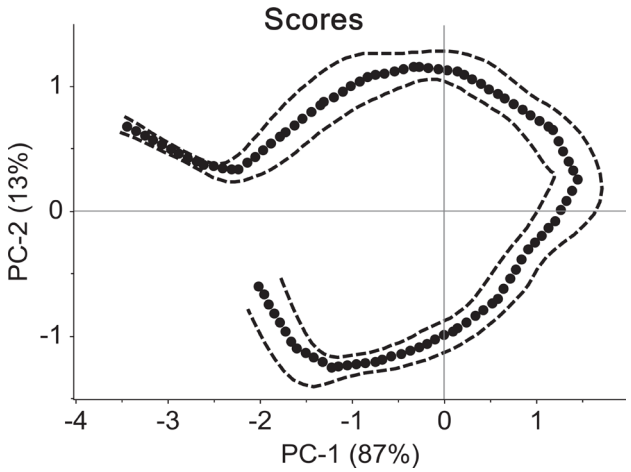

Figure 13.9: Process trajectory and limits for the chemical reaction process.

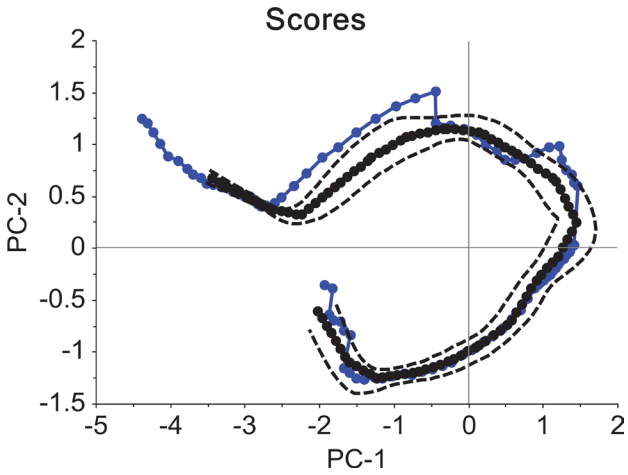

Figure 13.10: Projection of a new batch onto the chemical reaction process batch model.

1) Preprocess, centre and scale the new data before the batch model can be applied.
2) Estimate the new scores $t_{new,a} = x_{new} p_a$ for the a components used to develop and validate the batch model.
3) Project these scores onto the trajectory for estimation of the relative time, distance to the trajectory and distance to the model.

Figure 13.10 shows the projection of a new batch onto the developed batch model and the details of the projection are discussed in the text that follows.

The main observations are made as follows,

1) The new batch started prior to the common starting point of the batch model. This indicates that the conditions were immature compared to the common situation, therefore the batch model knows, through projection, that it has to wait until a point projects into the design space of the batch model before monitoring and control begins.
2) There were a few points which transgressed outside the limits of the design space (these were deliberately set), however, through use of APC, the batch can be corrected before any major quality issues occur.
3) Note that the spacing between the points is not **even**. This is the major advantage of RTM over other batch modelling approaches, if the reaction slows down, stalls or even reverses (as shown at score coordinates (–1,0), as long as the batch remains within the derived common limits, there is no reason to suggest that the batch is deviating.
4) Precise estimation of the true endpoint is possible without the risk of over-processing the batch.

When used in conjunction with an APC system, process scripts can be written to automatically correct a batch in a proactive manner before the batch limits are broken. Extension of the method is possible to spectroscopic and other data as this approach is intuitive, but most importantly it is scientifically, not mathematically grounded, therefore it fits well into the QbD approach of a scientifically, risk-based approach to batch modelling.

Finally, with respect to one-dimensional score trajectories and projection to original variables, returning to Figure 13.7 that showed the misalignment of the temperature values for probe 1, the method of RTM can also back project to original variable space, so after developing the batch model, when the temperature values of probe 1 are projected into relative time space, they all overlay as shown in Figure 13.11.

By this simple example, the merits of RTM are shown over alternative methods of batch analysis as they allow back projection into one-dimensional plots that are consistent with the data views currently accepted in statistical process control (SPC) applications. Figure 13.12 shows the *F*-residuals plot for RTM

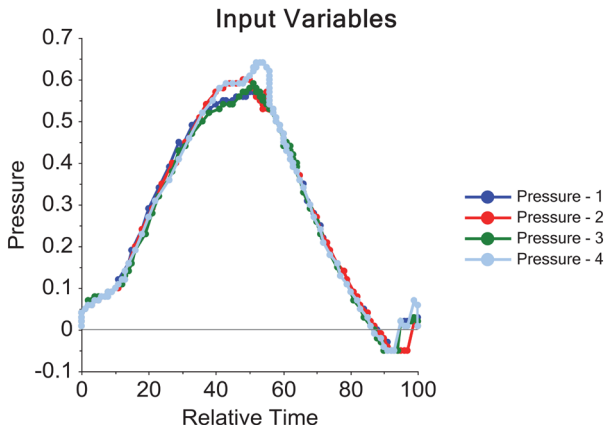

Figure 13.11: Projection of temperature probe-1 values into relative time space for chemical reaction process.

that can also be used as a multivariate statistical process control (MSPC) plot when the number of PCs for a batch model become large.

In terms of QbD/PAT, this approach forms the cornerstone of evolving process understanding and control. Combined with data fusion techniques and the PQS, monitoring and controlling evolving processes in primary and secondary manufacturing situations will be based on scientific, risk-based methods as encouraged by the latest regulatory guidance documentation and will help companies become,

- More efficient
- Less energy consuming
- More proactive towards quality
- Less wasteful in terms of scrap and batch rejection
- More able to detect root causes of problems and define a course of action based on the outputs of the PQS.
- For pharmaceutical and related industries: first to market in the development of quality medications based on more sound regulatory submissions.

On the last point, it is estimated that the time to bring a new drug substance/entity to market from phase 0 is approximately 12 years at a cost of over 1 billion USD. This is because the traditional methods used and the data analysis methods employed are all old and based on univariate statistics. Given that the populations used for the study of new drugs suffer from participant dropouts and mortality rates, the significance levels used to assess the effectiveness and safety of the drug are all very outdated. Chemometric and DoE methods offer the much-needed empirical approach to data analysis where group models can be

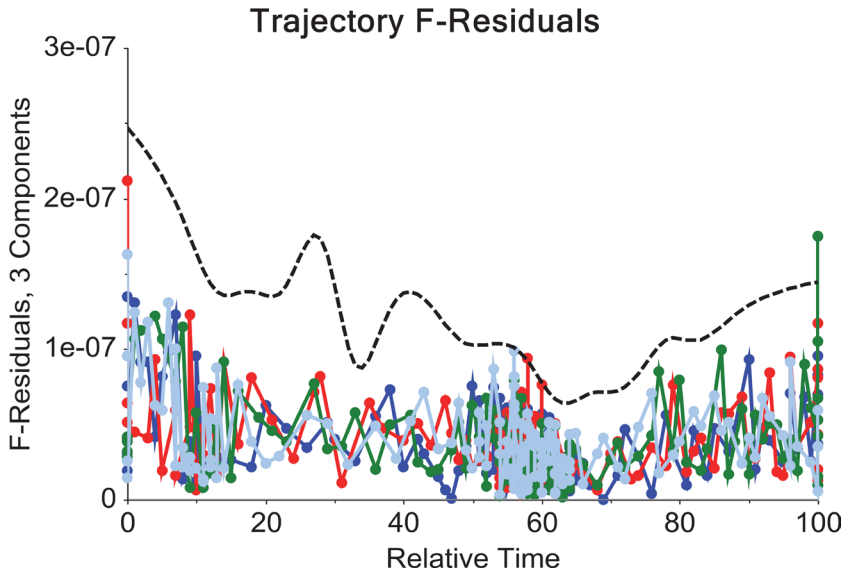

Figure 13.12: RTM F-residuals plot for chemical reaction process.