



Kick-starting PAT to achieve Quality by Design in cGMP Bioprocessing

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Summary

In 2002 the FDA announced a revolution in how they intended to regulate drug manufacturing. Their initiative promoted a continuous, process-centric approach to validation to replace the current product-centric one. Now known as Quality by Design (QBD) it incorporates, among other initiatives, process analytical technology (PAT) as a key tool for designing and optimizing manufacturing processes. Furthermore, the FDA took clear aim at eliminating the stagnation in the adoption of new manufacturing technology that their previous approach had encouraged. Many companies still have been unable or unwilling to seize this initiative and turn it into a key element of their strategic plan. Part 1 of this white paper explores and clarifies the new distinctions and exactly what they mean in practice. In the Part 2 some 'low-hanging fruit' PAT opportunities are identified that can be immediately implemented in order to ensure a successful and profitable kick-start to QBD activities.

A Historical Perspective on the FDA's Initiative

Interestingly, the process-centric approach now being promoted by the FDA has been in their guidelines for many years yet, in practice, they chose to regulate in a product-centric manner. This is far from a new story. Many other industries have been through the realization that end-of-line inspection can neither predict nor improve product quality or yield, but can only separate, *post hoc*, non-conforming material from conforming material.

For example, this author has extensive experience in electronic hardware design and manufacture for military, aerospace and telecommunications, all of which, like food and drugs, are heavily regulated 'lifeline' industries. Well into the late 1970s simple components for electronics equipments were made by manually controlled processes, qualified using three successive, so-called qualification batches and thereafter subjected to QC sampling plans that attempted to optimize the number of measurements required to pass a batch. (*Google 'AOQL' for more*). At limit, the whole batch might have to be individually measured to segregate good product from bad. With the advent of Moore's Law in the late 1970s (the doubling of the complexity of integrated circuits every eighteen months) and the resulting rapid transition to noise-immune, high-speed digital circuitry, the components were no longer 'simple' and pre-testing of many of the functions deep in the structure became impossible. This heralded the introduction of statistical **process** control to replace the previous statistical **product** control. The results have been astonishing. By 1990 a \$1 chip,



made by the millions for commodity applications, was thousands of times more powerful and reliable than those from the 60s and 70s. The legacy of the previous approach, in practical terms, translated to, in one example, the US Air Force, in the early 1990s, stripping out and repairing analog avionics, navigational and weaponry control systems from one of their mainstream, but aging, fighters after each and every flight. The mean time between failure (MTBF) of some of the onboard systems was as low as 6 hours – often less than the duration of a sortie! This at a time when digital personal computers, each much more powerful and reliable than any of the 1960's designed and implemented systems, had already become commodity. The USAF reasoned that while the cost of re-designing these systems would be relatively simple and low cost, the corresponding multiple years of re-validating of the systems to the still arcane validation protocols would be prohibitive. Hence the old, dysfunctional technology continued to be shored up for several more years.

I trust the reader noticed some striking similarities with the current status of drug manufacturing. One can compare the emerging biopharmaceutical industry with the emergence of the digital integrated circuit industry. Previous electronic products had been relatively simple and easily testable for function. These were now being joined and replaced by products exponentially more complex in structure and function. This in turn forced the approach to manufacturing processes to, almost overnight, transition from black art to manufacturing science. However, without a change in validation paradigm, validation effort became overwhelming.

The change involved was revolutionary, not evolutionary, and those caught in the middle of it often had difficulty in seeing how the proposed changes apply to their field. A similar debate is currently raging in the bioprocessing industry. It is, however, crystal clear that the complexity does require a different approach. It is also important neither to understate, nor to over-state, the complexity involved. The approach proposed by the FDA initiative represents current, campaign-tested, best practices with the best chance of: a) making the significant gains as claimed, and b) setting a higher baseline of understanding from which further best practices can emerge.

Bioprocessing can ride heavily on the coat-tails of several other highly-regulated, 'lifeline' industries which have left a rich legacy of tools and techniques for establishing Quality by Design.

A Closer Look at the FDA's Initiative

Overview

In their August 2002 (Final Guidance - September 2004) initiative "Pharmaceutical cGMPs for the 21st Century - A Risk-Based Approach" the FDA proposed a major change in how they would prefer to regulate the manufacturing of drugs. At least initially the initiative is voluntary, but the FDA is clearly committed to encouraging its adoption by offering reduced regulatory oversight burden and faster approvals for those that adopt the approach.

While the agency's focus was mainly upon the safety of drug products, it also acknowledged the need to replace the existing procedures with procedures that would:

- make oversight more focused, effective and less oppressive
- encourage the adoption of newer and better technology
- enable robust supply of more affordable drugs

To achieve this they initially proposed a three pronged approach:

- Systematically focus attention on those areas that directly impact drug quality and safety via the use of appropriate risk assessment tools.(see ISPE Guidelines)
- Use of the tools of manufacturing science to achieve profound understanding of the manufacturing processes and their control including a strong emphasis on process analytical technologies (PAT) - see later.
- Foster Continuous Improvement (CI) and then capture and retain the gains made via the implementation of a modern (ISO 9001-2000-based) quality management system.

The focus of this paper will be the emphasis on manufacturing science and particularly PAT.

Enter Quality By Design - The Desired State.

More recently the industry has realized that the scope of the initiative and its emphasis on PAT did not go far enough so the emphasis has moved to achieving Quality by Design (QbD) for which PAT is a major enabler.

The 'Desired State' (i.e. Ideal) that is the mutual goal of industry, society and regulators has been expressed as:

'A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight.' (*Janet Woodcock, FDA, Oct 5, 2005*)

The Desired State is best achieved by implementing the systematic, holistic and scientific approach to product and process design and development known as Quality by Design (QbD). Its scope is broader and integrates manufacturing process design and development with product design and development from the start.

Note: Quality by Design is not a new term. It was introduced by quality guru J M Juran in a 1992 book promoting a systems engineering approach to quality planning. In it he formalized the concurrent engineering approach to product design and the process design by which it would be delivered.

Under the Quality by Design approach to drug delivery:

- The product is designed to meet patient requirements as established by clinical testing.
- The process is designed to consistently meet product critical quality attributes.
- The impact of starting materials and process parameters on product quality is understood.
- All critical sources of process variation are identified and controlled.
- The process is continually monitored and updated for consistent



Validated Design Space

Successful application of QbD is facilitated and witnessed by the establishment of a Validated Design Space, the working definition for which is as follows:

‘The multidimensional combination and interaction of design input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality. The Design Space is proposed by the the applicant and is subject to regulatory assessment and approval.’
(ICH Q8 - Nov 2005)

Initially Design Spaces for individual unit operations are likely to be established and then later integrated into a design space representing the whole process train, and ultimately, the whole product life-cycle.

A preliminary design space will also be defined as broadly as possible during early process development to clarify the bounds of the process explored during clinical trials. It is then expected that the design space will subsequently be modified (tightened within the initial bounds) for manufacturing introduction in the light of further development results. Later, during production, the process may be further adjusted for efficiency, or any other of number of valid reasons, as long as it remains within the validated design space and adequate documentary evidence of continuing product quality is available. This will not require a supplemental regulatory filing. However, changes that do exceed the design space will. Thus the design space concept is at the heart of the FDA’s commitment to actively promote new technology adoption and continuous improvement.

The limits of the validated design space should preferably bear a known relationship with verified process limits rather than be arbitrarily set..

Univariate versus Multivariate Process Analysis and Control

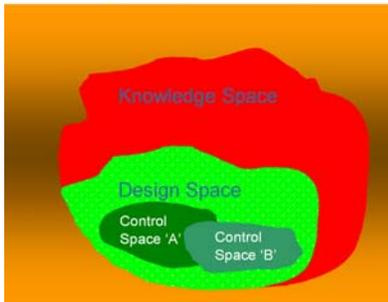
Clearly, as the complexity of the scope of the design space increases, the more sophisticated the statistical tools required to analyze and visualize the resultant data. Multivariate and multi-dimensional tools become *de rigueur*. Hence the FDA argued that only by significantly increasing process knowledge and understanding, as represented on this pyramid of manufacturing science capability, can product quality be assured by design. A process can be said to be profoundly understood when:

- All critical sources of variability are identified and explained
- Variability is managed by the process (see later)
- Product quality attributes can be accurately and reliably predicted *a priori*

The approach is to use increased understanding to develop more and more accurate models of the system upon which to apply mathematical optimization techniques.

This requires the use of modern, multivariate tools such as Design of Experiments (D.o.E.), Response Surface Designs, Principal Components Analysis (PCA) and Partial Least Squares (PLS) analysis to characterize the process and its design space. The latter two methods make it possible

Knowledge-Design-Control Space



Note: The design space is multi-dimensional and cannot adequately be represented in 2D or 3-D

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The degree of process understanding is inversely proportional to risk.

Multi variate processes require multivariate analysis tools



to summarize the process' health using several key indicators as a “dashboard”. Ultimately, in the case of a full product train, these indicators would represent possibly hundreds of monitored variables and make it possible to drill-down to root cause(s) when a deviation occurs. Indeed, early warning of an incipient deviation is often possible.

Control Chart Limitations

Some manufacturers believe they already have statistically based process control and produce control charts to prove it. But, control charts can have significant limitations and are often misunderstood:

- 1 It is frequently found that the parameters being tracked by control charts are not critically related to product quality, and vice versa.
- 2 They have typically been used to track end-product quality. This is statistical **quality** control (SQC) - not statistical **process** control (SPC).
- 3 Being univariate by design, control charts cannot fully describe what are inevitably multivariate processes. This leads to a significant risk of passing bad, or failing useable material.
- 4 The approach of using control charts to track historical process performance in order to set process limits is seriously flawed. Rather than defining a verified, multi-dimensional, design space it provides only an arbitrary specified workspace with little useful diagnostic insight into root cause when a deviation occurs.

It is believed that up to eighty percent of parameters that are measured on control charts are not relevant and eighty percent of those that could usefully be logged on control charts aren't - Anon.

What is Process Analytical Technology (PAT) ?

To improve process knowledge the FDA introduced a sub-initiative called Process Analytical Technology with the working definition:

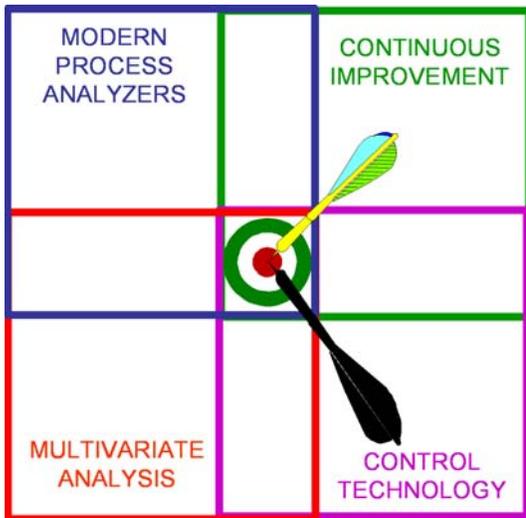
“Process Analytical Technology (PAT) is a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.”

It implies measuring, in real-time, the progress of key process variables and knowing the process deeply enough to decide exactly if, when and how to intervene if it starts to go off track. Contrast this with control charting of the final product quality where the process is already completed and it is too late to intervene.

The Four Tools of PAT

PAT is a system comprised of several elements used in concert; it is much more than just the new measurement technologies that many early adopters initially focused upon. The FDA has captured this by defining the four main tools of PAT.

When all four of these elements of the PAT tool kit are used in balance, the full benefits of PAT can be achieved.



When all 4 parts of the PAT tool kit are used in balance, the full benefits of PAT can be achieved.

1 Modern process analyzers (sensors/ instrumentation):

e.g. pH, NIR, Raman, Humidity, UV, Conductivity, Dissolved Oxygen, rapid bio-assays, cultures, etc. These are complemented by Comparability Protocols (another sub-initiative).

It is essential that the capabilities of each instrument is understood and verified in depth. In the hands of a competent control engineer the accuracy and reproducibility achievable are often several orders higher than the basic manufacturer's specification would suggest. Getting access to this level of instrument performance can often make or break a PAT application.

2 Multivariate analysis:

As implied earlier, multivariate processes require multivariate analyses such as DOE, Response Surfaces, Principal Components Analysis, Partial Least Squares Analysis etc.

It is essential to realise that multiple univariate analyses are not equivalent to multivariate analysis.

Several layers of development are usual including:

- Scouting experiments
- Screening experiments
- Main DoE
- Taguchi Robustness experiments
- Verification DoEs
- Response surface plotting etc..

The toolbox is rich but as with all tools they are most valuable in the hands of an expert. The author highly recommends that a seasoned industrial statistician oversees the application of these tools.

The output from these tools indicates which parameters are critical to product quality and those that are not. This is vital information to the designing the appropriate control system.

Another output is a system model (equation) that can be used to further optimize the process.

3 Control Technology:

Once the process is understood in depth it is possible to select the most appropriate control strategy, e.g. feedback, feedforward, batch, PID, real-time adaptive, model predictive control, etc.

The output from these tools is a control scheme identifying how each parameter will be controlled or accommodated by the system and explicitly how this will be achieved.

- Critical, adjustable
- Critical, fixed and monitored
- Non critical, fixed and monitored
- Non critical, not controlled, not monitored

4 Continuous Improvement and Data Analysis:

The use of multivariate analysis lays the foundation for continuous improvement. Tools used include data mining, EVOP, correlation studies,



learning systems etc .

Three Promises of PAT

1 Product Excellence through Process Excellence:

Product excellence is defined by predictable product performance and safety. "Quality by Design" (QBD) achieves this.

The pay-offs are that reportable deviations (or worse, consent decrees) can be eliminated plus the process becomes intrinsically 'Lean' - i.e. waste-free - thereby minimizing costs of goods sold and increasing competitive edge.

2 Continuous Validation:

The PAT approach kills the myth that running 3 conformance batches achieves the objectives of validation. It replaces it with what is essentially continuous validation.

The current reality of our industry is that we run ~2.5 sigma processes followed by extensive final product QC to achieve 5.5 sigma product quality. While this ensures that safe products are delivered, it is hugely wasteful, yields unpredictable process outcomes and offers little process understanding. This makes it very difficult for the FDA to effectively oversee.

The 'desired state' is to have 6 sigma processes and almost zero final product QC to achieve 6+ sigma product quality. The FDA can readily assess the depth of process understanding underpinning such a manufacturing process design and thus can relax the degree of regulatory oversight when appropriate evidence has been presented.

3) Real-time Product Release:

This is the use of process/product knowledge and validated in-process controls history to release final product. In this way long duration final QC assays or cultures can be eliminated along with the associated work-in-progress (WIP).

This may be particularly important for the quality of short shelf-life products.

Although many view this promise as unattainable it is in fact already widely used and approved by the FDA for post-production sterilized products and also for the clearance of viruses, host cell proteins and DNA. (The post process inspection of drug products for the absence of viruses etc. is demonstrably very much less reliable than the use of processes validated to achieve the desired clearance.)

Real-time release is already a reality for certain products/processes. e.g. viral or host cell protein clearance

PAT System Attributes

The following are the key attributes of a PAT-based system:

- Sensors located in-line, on-line or at-line.

- Automatically measures a useful key attribute of the process, environment, a process intermediate or the final product at a critical process control point.
- Has the built-in intelligence to determine if, when and how to intervene in the progress of the process to improve final product quality.
- Operates in real-time or close-to-real-time.
- Programmable with electronic data i/o and records (21 CFR pt 11).

The system should also be accurate and reproducible, verifiable and validatable, reliable, safe, affordable and have a compact form-factor.

The most distinguishing attribute is the third one: the built-in intelligence to determine if, when and how to intervene in the progress of the process to improve final product quality. Such intelligence can only come from extensive understanding of the process being controlled. The ability to intervene, rather than just monitor, is what really sets PAT applications apart.

Key Attribute of PAT Control

Has the built-in intelligence to determine if, when and how to intervene in the progress of the process to improve final product quality. i.e. adaptive control.

Six Sigma

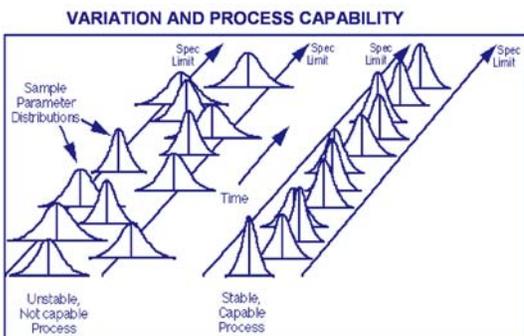
A Systematic Approach to Manufacturing Science via Variation and Defect Elimination

Working Definition: 'Six sigma is a widely used, systematic strategy and set of manufacturing science tools designed to optimize processes, and hence product quality, by eliminating, or eliminating the opportunity for, variation and defects.'

A couple of underpinning concepts are important to remember:

- 1 "You can't improve what you don't measure": this emphasizes the dependence upon data driven decisions.
- 2 It is important to "Measure and control the right things, the right way, at the right place, at the right time". If any one of these elements is missing the measurements and any inferences drawn from them are likely to be invalid.

While PAT does not mandate the use of Six-Sigma it is included here as a best practice that has proven capability for streamlining the transition to QbD. It does this by providing the tools and infrastructure to identify critical process elements to focus upon and then ensures the selection of the most appropriate tools and methodologies to deliver the desired results.



Variation is clearly the enemy of accuracy and reproducibility, the major determinants of process capability.

Variation and Process Capability.

The reason for six sigma's focus on variation elimination is graphically captured here.

The process on the left is clearly out of control and incapable. A drug company's worst nightmare is for the three conformance batches to be, purely by chance, like the distribution of the frontmost run on the left side. This would cause havoc in subsequent production when the true long-term variability of the process finally emerged. The process on the right is much less variable and thus in control (tight distribution) and capable



(consistently within the product's specification limits). Variation is clearly the enemy of accuracy and reproducibility, the major determinants of process capability.

Systematically peeling away the different layers of variation-based noise permits more accurate understanding of the process of interest.

Variability and Process Development

The intention of DoE in PD is typically to quantify the effects of different parameters upon the output of a process in order to rank-order which are the most critical factors to achieving the particular product quality(ies) of interest. Spurious variation of any of the parameters acting upon the experiments, whether consciously included in the experimental design or not, adds to the 'experimental noise floor' against which any response in the experiment must be compared before its significance can be assessed. It thus behooves a developer to systematically remove as much noise from variation as possible in order to maximize the resolution of his experiments. It is also interesting to reflect that the resolution of the DoE method is such that it can also identify that a significant parameter has been missed and not been included in the experiment since its effect then shows up as excessive noise in the analysis.

Common vs. Special Cause Variation

Before attempting to eliminate variation it is important to distinguish between the two types of variation, one of which cannot be eliminated

Special cause variation is variation which has a traceable, rectifiable root cause.

An example of special cause variation would be if room temperature variation is shown to be a cause of process variation and hence product variation. The remedy is likely simple; for example, climate control the room, or, carry out the process in a temperature controlled insulated vessel.

Noise: When a special cause can be attributed but the variation is difficult or impossible to eliminate we designate it as a "noise" variable. An example of special cause "noise" might be the change in stationary phase over time until the media is retired and the column repacked. Here the process can be made robust to such noises by including them in DOE experiment which identifies where to operate the process that it is least sensitive to their influences. (i.e. Taguchi Robustness Engineering). Thus 'noise' is a special case of special cause variation. Note that in a multi-step process stream the output of one stage is the input of the subsequent one and is considered as a 'noise' input.

Common cause variation: When all sources of special cause variations have been eliminated or slated for minimization, any remaining variation is random in nature and cannot be eliminated. This is called common cause variation. Trying to compensate for common cause variation in an in-control process actually adds more variation and potentially puts the process out of control.

Common-cause variation is random in nature and cannot be eliminated. Trying (knob-twiddling) to compensate for common cause variation in an in-control process actually adds more variation and potentially puts it out of control

Variation Elimination

The '6 M' SOURCES OF VARIATION OF A SIMPLE LIQUID BLENDING STEP:

Measurement (Instrument bias, linearity, accuracy (repeatability), precision (reproducibility), stability, limit of detection, distinct categories ...)

Materials (raw material impurity profile, contamination, consistency, homogeneity, concentrate strength, ageing, stability, materials of contact...)

Men & Women (training, attention lapses, mixing errors, measurement errors, incorrect tank hook-up, accuracy, reproducibility of measurement/response etc...)

Machines (Dimensions & tolerances, wear, control system, scale, control accuracy, repeatability and responsiveness, data collection and manipulation rates and techniques....)

Methods (procedures, process design, undocumented procedures, inconsistent application/interpretation...)

Mother Nature (physics of mixing vs. scale, seasonal climate variations, solubility limitations...)

Potential sources of variability are myriad

Potential Sources of Variation

Before looking at how to eliminate variation it is useful to study its various sources.

As this "6M chart" suggests, the potential sources of variation in accurately blending just one liquid input feedstock to a typical pharmaceutical process are myriad.

Similarly, for each all the other elements of the process there are typically an overwhelming number of potential additional sources of variation.

Variation Elimination

There are two basic approaches to variation management. "Deterministic" and "Adaptive".

Deterministic Approach to Variation Elimination: (How to Work Harder ... and still fail!).

It can be expressed as "Identify all potential contributors to variation and allocate part of total allowable variation budget to each. Then ensure that each individual element stays within its variation budget. BUT ... with a very tight total variation budget target (say 0.1%) and myriad potential sources of variation, some of which can't be controlled - this approach is impossible to implement".

Adaptive Approach to Variation Elimination: (Work Smarter)

Design the system for variation stack-up elimination via judicious adaptive adjustment at critical process points.

It can be expressed as, "It may not be possible to accurately predict or control exactly what will cause variation in any given case, but it is likely quite possible to measure the total variation immediately prior to a critical step and remedy it."

This is clearly an opportunity for realtime process measurement and adaptive control ... in short PAT!

Summary Part 1

The FDA's Pharmaceutical cGMPs for the 21st Century initiative has recently morphed into a more broadly reaching goal of Quality by Design from its initial emphasis on PAT. QbD adds the emphasis on a full life-cycle perspective and on concurrently engineering both the product and the processes by which it is to be made right from very early in the development cycle.

Many industries, including other heavily-regulated 'lifeline' industries, have already made this transition from relying on final product QC to creating quality product via process understanding and control. The transition for the biopharmaceutical industry is perceived by some to be much more difficult than for the small molecule pharmaceutical industry by virtue of the complexity associated with biological systems. In reality, this complexity



only strengthens the argument for the need for a more scientifically and statistically based approach.

Many tools and proven implementation strategies are available as a legacy from those pioneering industries.

PAT is a major enabling technology for Quality by Design as it allows the precise determination of a Validated Design Space. Without PAT the need for dependence upon the end-of-process QC approach remains.

The initiative represents current best practice and is expected to deliver significant commercial benefits over and above improved quality and safety.

PART 2

Opportunities for Kickstarting PAT activities

Overview

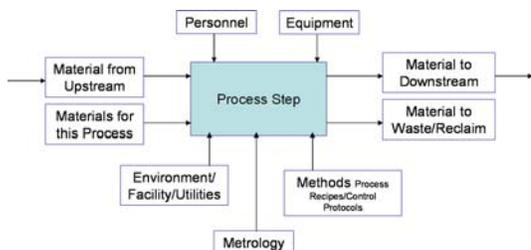
We have seen that QbD requires a holistic approach to product and process development. PAT also requires in-depth knowledge of the product/process relationship in order to optimally design the process. So what can we do immediately that will kick-start the PAT activities?

The answer lies in the generic aspects of pharmaceutical processes and the widespread use of generic hardware technology platforms. We can start work immediately on introducing equipment that has the ability to minimize this unwanted variability. We need to identify processes that currently have significant opportunity for variation.

Much of the early attention on PAT has focused upon:

- Novel, real-time metrology technologies for application to the principal process vessel such as reactor or fermentor etc.
- Dry powder formulation (80% of pharmaceuticals are tableted.)

Looking at the generic process model sketch we can categorize the potential sources of variability under the same headings as the process inputs and outputs. Much of the variability in pharmaceutical processes can be attributed to input material variability and variability associated with current equipment and metrology shortcomings.



Our two examples of 'low-hanging fruit' projects to successfully kick-start PAT activities come from these areas. We shall look at two closely related activities, both involving delivery of accurate and reproducible liquid feedstock to (bio)pharmaceutical processes - one of Technikrom's core competences.

They are:

- mobile phase blending for liquid chromatography
- Buffer concentrate dilution to maximize productivity and capacity within limited floorspace constraints.

Before looking at these examples it is useful to look at the role of automation in PAT applications.

Manual versus Automated Processes for PAT

A large proportion of current bioprocesses are subjected to reliance upon manual control. While their brains are extraordinarily flexible and adaptive, human beings are incapable of maintaining focussed attention for any significant period of time - indeed, their attention is predictably **unreliable**. Furthermore humans are predisposed to trying to 'improve' processes they are operating, despite instructions to just follow the existing method exactly. Multi-tasking assignments further decrease this already poor performance. This shows up as increased process and product variation..

Automated processes can dramatically reduce the variation associated with manual processes.



automated equipments are essential for most PAT applications.

On the other hand, modern process control hardwares and softwares have essentially 100% (attention) availability, can carry out tasks exactly as instructed time after time and can multi-task and also process huge amounts of complex data essentially in real time. After early teething problems they are now proven robust, commodity items. Thus automated equipments are essential for most PAT applications.

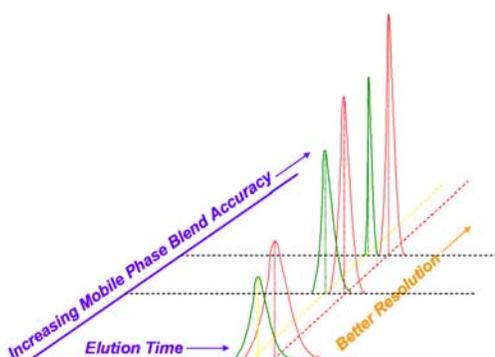
PAT Kickstart Application 1 Buffer Blending for BioProcess Liquid Chromatography

Current Status

Buffer make-up variability is a very significant contributor to variation in almost all production-scale pharmaceutical processes. We shall see that this variation is proportional to scale of operation and it has been accepted and institutionalized as being an inevitable consequence of large scale blending and storage of liquid feedstock.

Despite this, buffer preparation is not valued as a strategic core competence and is often relegated to junior staff.

The resolution of Liquid Chromatography (LC) systems is severely compromised by band broadening and shifting of elution profiles. All the systematic causes can be traced to the variability of some key parameter(s). Analysis reveals that a small decrease in variability of the mobile phase can cause a large improvement in product resolution and reproducibility, which, in turn, correspondingly affects product quality and profitability. Thus, for LC, mobile phase accuracy and reproducibility are known as key leverage variables - prime candidates for accurate process control.



Mobile phase accuracy and reproducibility are key leverage variables - prime candidates for accurate process control.

The Challenges of Buffer Preparation and Blending

It is desirable to remove all possible variation from our processes. Consider the variation associated with preparing and mixing buffers. At lab scale (i.e. less than 5 liters) every step can be precisely managed and the outcome is accurate.

Lab-scale Mixing (<20 Liters)

Mobile Phase Long-term Accuracy: +/- 1%
Mobile Phase Long-term Reproducibility: +/- 1%

Raw Material Quality:	Highest (USP, Analytical)
Weighing Accuracy:	Excellent (<0.01%)
QS step accuracy:	Excellent (<0.01%)
Temperature control:	Good (RT) to Excellent (Bath)
Mixing Efficiency:	Excellent Dissolution Excellent Homogeneity
Cleaning Diff./Cost:	Low (Autoclave)
Cleaning Validation:	Straightforward
Shelf Life:	Make on Demand
Sampling Challenges:	Low (Good mixing)
Metrology Challenges:	Low (Single measurement standard)
Transportation/Cost:	Easy/None
Storage Space/Cost:	Minimal/Low



If, every day, a technician makes five liters of a mixed buffer mobile phase solution for a bench scale prep run, we expect the accuracy and long-term reproducibility to be well within +/-1%.



Pilot/Small-scale Production Mixing <1000L

Mobile Phase Long-term Accuracy: +/- 3%
 Mobile Phase Long-term Reproducibility: +/- 3%

Raw Material Quality: Average (Bulk +/- 0.25 % purity)
 Weighing Accuracy: Good (<0.5%)
 QS accuracy (weight): Good (<0.5%)
 Temperature control: Good/Poor
 Mixing Efficiency: Average Dissoln. & Homogeneity
 Cleaning Diff./Cost: Low/High (Disposable Bags)
 Moderate/Medium (Tanks)
 Cleaning Validn.(Time/Cost): None/C. of C. from Vendor (Bags)
 Moderate/Moderate (Tanks)
 Buffer Shelf Life: Moderate (1% of batches scrapped)
 Sampling Challenges: Moderate to Low
 Metrology Challenges: Moderate (5+% of batches scrapped)
 Transportation: Cumbersome
 Storage Space: Moderate



As we move to pilot scale (i.e. hundreds of liters) the volumes involved start to tax the practical limits of certain elements of mixing, and precision, accuracy and reproducibility fall to within +/- 3%.

Large-scale Production Mixing >1000 Liter

Mobile Phase Long-term Accuracy: +/- 5%
 Mobile Phase Long-term Reproducibility: +/- 5%

Raw Material Quality: Average (Bulk +/- 0.25 % purity)
 Weighing Accuracy: Average (< +/-1%)
 QS accuracy (weight): Average (< +/-2%)
 Temperature control: Good (+/- 2 deg C, HVAC RT)
 Poor (> 20 deg C External tanks)
 Mixing Efficiency: Poor Dissolution assurance
 Poor Homogeneity assurance
 Cleaning Diff./Cost/Delay: High/High/High
 High/High
 Buffer Shelf Life: Moderate (2% batches = scrap)
 Sampling Challenges: High (Temp./ Conc'n Gradients)
 Metrology Challenges: Moderate (10% batches scrap)
 Transportation Diff./Cost: High/ High
 Storage Space S/Capital: Very High/Very High



When moving to large-scale tank-farms, where thousands or even tens of thousands of liters of buffers are common, the challenges are quite large. Many industry pharma engineers, when informally polled, concluded that +/- 5% variation is a reasonable, possibly optimistic, estimate of what is typically delivered from such tanks at their facilities.

Variance Stack-up Sources $S^2_{Total} = \sum s_i^2$

Source	Bench Scale	Pilot/Small Mfg.	Large Mfg.
$s^2_{raw\ material(s)}$	V. Low	Low	Med
$s^2_{weighing}$	V. Low	Low	Med
$s^2_{liquid\ addition}$	V.Low	Low	Med
$s^2_{temp.\ related}$	V.Low	Low/Med	Med/High
$s^2_{mixing\ inefficiencies}$	V.Low	Low/Med	Med/High
$s^2_{cleaning\ inefficiencies}$	V. Low	Low	Med/High
$s^2_{storage/helr-life}$	V.Low	Low	Med
$s^2_{sampling}$	V.Low	Low/Med	High
$s^2_{metrology\ procedures}$	V. Low	Med	High
$s^2_{metrology\ equipment}$	V.Low)	Low/Med	Low/Med
$s^2_{transportation}$	V.Low	Low	Low/Med

Variance is proportional to scale!

A closer look at the actual variance (a statistical measure of variation equal to the square of the standard deviation) at each of these scales reveals that the variance achieved (variation) is proportional to scale.

Shortcomings of Current Buffer Preparation Blending Equipment

Most commonly used process scale LC systems have not been designed to adaptively correct for the high variability of simple buffer feeds or pre-mixed mobile phases.

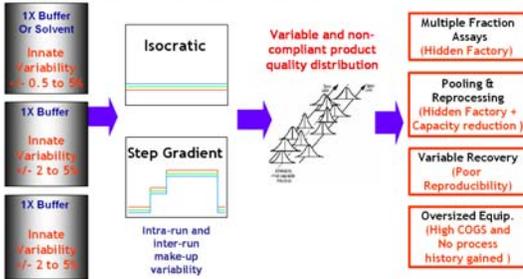
When attempting to create gradients they actually add even more variability. Therefore many large biopharma manufacturers have abandoned gradients for production.

Furthermore, the LC Processes have been made as robust as possible to the highly variable, isocratic, pre-mixed buffers. This is variation *accommodation* and not variation *elimination* prior to robustness engineering.

There is a large cost to pay for this approach due to reductions in first-pass recovery and purity.

Variation accommodation has several undesirable consequences:

Feedstock Variability: Popular LC Approaches



- It generally forces the user into the multiple fraction & assay approach (i.e. to maintain a 'hidden factory' entity) in order to find where the product is on any given run.
- It increases the amount of pooling and re-processing necessary to achieve overall recovery targets. (i.e. Creates yet another 'hidden factory' entity and reduces manufacturing capacity.)
- Run-to-run recovery varies significantly. Since the obvious lack of reproducibility is difficult to justify to the FDA, companies routinely use oversized LC equipment so that the LC processing can be carried out in one batch! The extra equipment cost incurred obviously gets low utilization and increases COGS.
- No multiple-batch statistics/history of prep-scale process capability is accrued to assist continuous process improvement.

Clearly an adaptive approach is preferred. But what does it look like?

Here we fall back on some of our earlier observations, specifically:

- Measure and control the right thing in the right way at the right place and the right time, and
- Buffer variance is proportional to scale.

Measure:

Right Thing: Accurate, 1^o Surrogate of Concentration
 Right Way: Essentially Undamped
 Right Place: Blending module just before Column (CCP)
 Right Time: Every 250 mSec

Control: Level 1 - Blending

Right Thing: Inlet Control Valves Ratio
 Right Way: Real-time, PID enhanced PLC
 Right Place: Blending module inlet
 Right Time: Process Value ≠ Set Point Value

Control: Level 2 – Release to Process

Right Thing: Divert Valve - to column or to drain
 Right Way: Real-time, digital, PLC
 Right Place: Blending module outlet / column inlet
 Right Time: Process Value = Set Point Value

The accurate physics of mixing of small volumes apply even when very large final volumes are being prepared.

The Solution to Buffer Blending

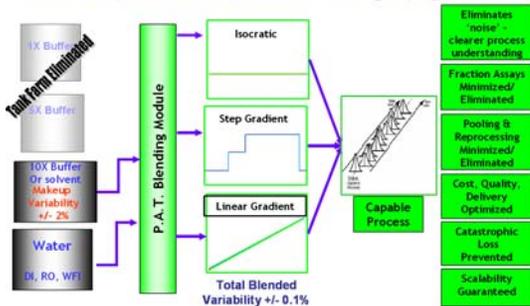
The PAT-based solution to buffer variability that TechniKrom offers is an adaptive implementation of PAT, as shown on the left:

The control scheme consists of a one measurement and two levels of controls applied to a judiciously located, low-volume blending module run in continuous mode.

In this way the accurate physics of mixing small volumes apply even when very large final volumes are being prepared.

With such “Adaptive P.A.T.™ control” it is possible to routinely achieve the +/-0.1% blend accuracy and reproducibility necessary to maximize process resolution of products from their closely-related impurities which, after all, is the fundamental intent of any separation technology.

P.A.T. Impact On Liquid Chromatography

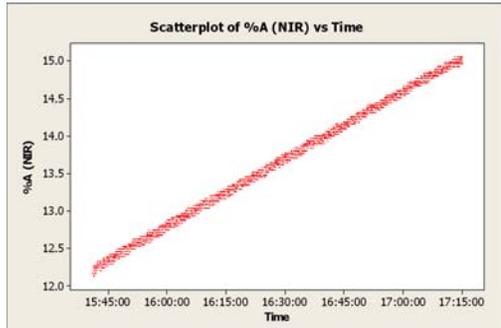


Besides eliminating several hidden factory elements (tank farm, assay lab and pooling/rework of product) this increased resolution permits the much clearer view of the underpinning process that is essential for better process understanding and improvement.

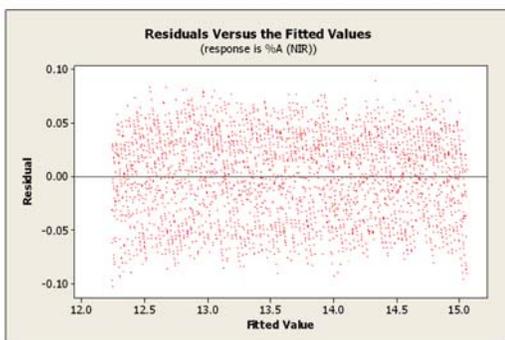
A huge bonus of this approach is that the real-time, continuous, on-line process validation provides very valuable insurance against unintentional loss of the (often extremely expensive and/or difficult to replace) product when, for example, incorrect buffers are unintentionally (or intentionally) connected. The potential business impacts associated with such losses dwarf the cost of the complete equipment associated with preparative scale LC.



LC Gradient Regression Analysis



Regression Analysis of Gradient LC



The following charts clearly indicate the +/- 0.1% accuracy achieved by one of TechniKrom's clients using PAT controlled shallow gradient blending.

These charts also support the point raised in part 1 of this paper that, in the hands of a knowledgeable expert, the performance of many sensors can be several orders of magnitude better than the nominal specification given by the manufacturer. (In this case 2% of full-scale)

The factory-calibrated sensor is regularly, locally tuned to 0 and 100%-of full-scale standards (in this case 12% and 16% concentrations of component A). It is also temperature compensated for the specific blend it is making. The data points are plotted at one second intervals, although the actual control system is handling, typically, 4 (undamped) points per second (scan rate 250 mSec) upon which it makes its realtime control decisions.

This example uses data from an installation at one of our clients who previously experienced +/- 4%, and worse, variation that completely swamped the shallow 2-3/4% concentration change over 90 minutes gradient.

PAT Kickstart Application 2 In-Line Buffer Dilution - (Potentially a 'Killer App' for Process Analytical Technology (PAT))

Current Status

Biopharmaceutical companies continue to wrestle with how to approach the implementation of PAT. The accelerated adoption of many new technologies has benefited from the identification of a 'killer app' – an early application that enables a readily-achieved breakthrough in capability. This can be a totally new capability (e.g. e-mail on the internet) or a major step-change (e.g. 10X or more) in an existing capability.

Flashes of inspiration cannot be achieved at will, but we can identify elements of existing processes that are ripe for such breakthroughs, e.g. downstream processing capacity increases have fallen far short of the 10X-1000X improvements recently achieved in upstream titers due to the inability to increase buffer capacity within existing floor space.

The current paradigm for buffer preparation is to pre-mix and store buffers in (relatively large) tanks. A new paradigm is required.

Two candidate solutions are proposed:

- 1) Reduce demand for buffers by 10X or more, or,
- 2) Change the current buffer preparation paradigm to the in-line dilution of buffer concentrates consisting of:
 - Outsourcing the preparation and validation of strongest possible buffer concentrates,
 - Storing only maximum possible strengths of buffer concentrates, and,
 - Using PAT to adaptively and accurately make, validate and deliver any desired dilution directly to the process.

Solution 1) implies moving away from the traditional buffer-hungry capture, purification and viral removal/ deactivation processes. Such a move is not on the current horizon but should continue to be pursued.

Solution 2) is eminently possible with existing patented technology but requires an iconoclastic shift in the mindset, a shift that will only take place when the pain of staying with the status quo is greater than changing. That point has already passed for most biopharmaceutical companies.

Outsourcing of buffer concentrates preparation.

In their 'cGMPs for the 21st Century' initiative the FDA wisely recommends that companies should adopt a quality assurance system in which a manufacturer takes full responsibility for the performance of his supply chain. He should enter into a 'partnership' in which the supplier's workforce effectively becomes an extension of his own. Other highly-regulated industries have successfully achieved this, often via audits and the use of 'source-inspectors.' This approach frees up the floor space/capacity previously dedicated to:

- Raw buffer ingredient procurement, incoming QC/assays and storage.
- Raw buffer ingredient measuring, 1x blending, filtering, assaying and storage in large tanks
- Cleaning and re-validation of buffer blending and storage tanks etc.
- The capacity impact of having to re-make buffers that fail QC assay.

This floor space is now used to store only buffer concentrates and not the copious amounts of associated water or the multiple different dilutions of the same buffer.

PAT-based, Just in time (JIT) Buffer Dilution

Portable, PLC-controlled blending/dilution skids of different capacities are available that accurately and repeatably dilute concentrates, using piped-in WFI, to any desired final blend.

This is an excellent application of PAT. Appropriate sensors measure the blend/dilution accuracy in real-time, as it is formed.

As with mobile phase blending above, these signals are then used in a two-part control strategy to:

- instantly, adaptively adjust the blend to compensate for any variability in the concentrate feed, and
- only release exactly the correct blend to the process.

In this way, continuous validation and real-time release is achieved.

The elimination of numerous storage tanks etc. enables the 10 X or greater increase in capacity from the existing floor space as desired for a killer app.





As a bonus, this patented approach also delivers buffers to the process to within +/-0.1% accuracy, compared to the +/- 5% accuracy of other current buffer prep approaches¹.

This accuracy permits much tighter control of the processes it feeds which translates into higher quality, efficiency, throughput and process understanding.

Conclusions

Most pharmaceutical processes suffer from significant variability due to the variability of the incoming process feedstocks such as buffers. This paper has identified how PAT-based systems can be designed to provide solutions to this problem along with a solution to the industry's capacity imbalance between upstream and downstream processes for monoclonal antibody production.

PAT mandates significant improvements in the resolution, accuracy and reproducibility from the equipment employed

The drastically reduced tolerance for variation that PAT brings means that much of the current equipment is not appropriate for use with PAT. That leaves three options:

- Live with the existing equipment, do not pursue PAT and endure the closer attention of the FDA, reduced yields and higher costs of production.
- Upgrade the existing integrated equipment with PAT front ends
- Introduce capable integrated equipment with PAT based controls.

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About TechniKrom

TechniKrom is a provider of customized world class engineering solution, including processing equipment, products and services for biopharmaceutical, pharmaceutical and fine chemical industries. We design, build and test in accordance with FDA, ISPE GAMP-4, ASME-BPE, UL, and international codes (e.g. ATEX).

Our equipment meets the highest levels of pharmaceutical processing requirements including sanitary design, +/- 0.1% accurate/reproducible mobile phase blending (isocratic and gradient), strict 21CFR11 capability, pre-delivery IQ/OQ, UL approved, EXP options, dynamic axial compression columns with the highest performance and most sanitary design, capture columns, UF/DF equipment and Biosynthesizers (oligo, peptide, RNA).

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