PAT: Misconceptions, Blind Spots and Forgotten Basics

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DOI: 10.62178/sst.004.007

ABSTRACT

Why process understanding, measurement location, and proper sampling are just as important in PAT as our beloved (but often expensive) analytical equipment: the PAT sensors. Here is presented issues that are equally important for optimal PAT solutions as the analytical instrumentation and its performance.

1. Introduction – PAT Is More Than Device Technology

In PAT implementations, identical misconceptions occur again and again in large and small companies. Described below are three typical misconceptions I have encountered many times in practice:

1. The belief that you "already know" the process
2. Neglecting the critical role of optimal measurement location.
3. The technology trap: TOS as a misunderstood foundation.

These misconceptions are closely linked: those who believe they already know the process, tend to plan sampling and measurement location less carefully – and quickly decide on a technology that ultimately does not fit optimally.

1.1 Common Reasons for Choosing PAT

The most common reason to engage with PAT is the desire to replace off-line laboratory analytical samples with direct at-, on- or in-line process measurements. This is of course justified in many projects because it clearly relieves laboratory and operational staff of many work tasks and burdens, improves occupational safety (no hazards from sampling perhaps under dangerous conditions), gives faster analysis results, supplying measurement 24/7 ... so aiming for a PAT solution is often also a powerful driver for automation.

However, before starting down this road, one would often benefit by asking oneself three seemingly simple 'what' questions (Eifert, Erens and Gerlach, 2023):

1. What is the measurement task?
2. What is the core of this measurement task?
3. What is really the core of this measurement task?

Yes – this question is deliberately asked three times, but with slightly different emphasis. Why this repetition?

This question is designed to prevent implementing an unsuitable measurement concept. Analysis of the measurement objective must start here: Why should a specific measurement be taken at exactly this process step (and exactly at this location)?

PAT Insight #1: Before assuming you already know the process, please ask yourself: What is the actual goal — not the technical one, but the value-creating goal? Many PAT projects fail when they chase numbers instead of purpose!

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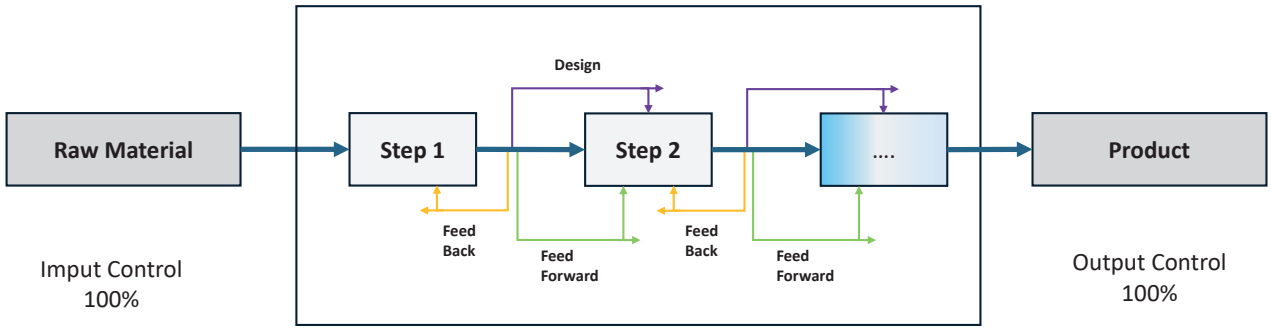

Credit: Kessler, 2001; used with permission.

Figure 1: Graphic illustrating of feedback and feedforward control loops.

2. CPP and CQA in the Context of the FDA Framework (2004)

According to the 2004 FDA Framework (FDA, 2004) Critical Process Parameters (CPP) and Critical Quality Attributes (CQA) can be used as key variables to monitor and control a manufacturing process in real time, for example in order to ensure consistent product quality. The FDA Framework was written for the pharmaceutical industry, but the definitions of CPP and CQA are highly useful across all industrial sectors.

In the context of product specification and property design, it is important that the collected measurement data are used in both feedback and feedforward control loops to automate the process – ideally without operator intervention (Kessler, 2001).

However, this approach is based on an ideal model that presupposes that processes and workflows are comprehensively known and understood.

Field Lesson #1: The smartest PAT engineers choose tools based on fitness for purpose, not on trend or brand. Sometimes a €5000 conductivity sensor adds more control value than a €50,000 spectrometer.

2.1 Dangerous Belief: "Already Knowing" the process

A typical scenario is that of a PAT expert asked whether measurement principle X or Y can be installed at a specific measurement point – usually exactly where laboratory samples have been taken so far. When the expert asks why, the answer often is: "Because there was a ball valve there, or it was the easiest location for sampling for the lab. But when asked where the process model or a proper process understanding would actually suggest to measure, it often turns out that this is not the optimal location. Nevertheless, it often happens that a new and expensive PAT technology is installed right at such a location – sometimes even replicating the laboratory measurement principle 1:1.

PAT Insight #2: Measurement in-line is not automatically real-time. True real-time means that the entire signal-to-action chain — from measurement, through data interpretation, to process response — works without delay.

The problem: The decisive question – whether this location is even suitable for capturing CPP or CQA in real time – is not asked. Instead of defining a measurement strategy, a device is selected directly (all to hastily).

2.2 Unavoidable PAT Uncertainties

In practice it often turns out that the current theoretical assumptions about the process are not correct. Here are three examples of incorrect assumptions:

- There are in practice gas bubbles where none should be
- There are solid sediments that were not anticipated
- There are in fact "wandering" chemical reactions, i.e. reactions taking place along with material transport through the pipeline(s)

Therefore, preliminary tests and trial installations (always including critical validations) are essential parts of PAT planning. Preliminary, trial tests should clarify whether a measurement location and measurement principle work under real conditions, and consequently help avoid costly misinvestments.

3. The Measurement Location Trap: TOS as a Misunderstood Foundation

Representativity and homogeneity are crucial – both in the lab and for in-line, in situ and on-line measurements. The role of sampling 'before analysis' (for laboratory analysis) is replaced by PAT measurement location selection (in-line measurements) or physical sample extraction (on-line measurements). Location errors at this stage can so easily render even the most precise measuring instrumentation worthless.

PAT Insight #3: Combine simple, robust signals instead of overengineering. Clever pairings, e.g., conductivity + density or/and refractiv index often outperform complex systems while saving significantly on cost and maintenance.

The Theory of Sampling (TOS) states that samples must be acquired, or PAT measurement locations selected, allowing PAT sensor signals to represent a complete cross-section of the streaming material.

Otherwise, systematic errors arise causing biased sampling which of course undermine any process monitoring and control (Kessler, 2001; Esbensen, 2025).

3.1 Relevance of TOS Principles for in-line, in-situ, and on-line PAT measurements

In PAT, measurement strategies are typically categorized as in-line, in-situ, or on-line, depending on how and where data are collected with respect to the process. While in-line/in-situ sensors measure directly within the process stream or reactor without physical sampling, on-line systems extract a sample automatically for external analysis.

Based on Table 1 it becomes clear that in-line and in-situ measurements avoid many of the sampling-related errors typical of conventional approaches (IDE, IEE, IPE) and often offer practical advantages. However, their actual superiority strongly depends on the homogeneity of the process material and the representativeness of the measurement location. For example, in poorly mixed systems an on-line measurement with defined sample conditioning may even provide more reliable result.

Interferences caused by gas bubbles or solid particles (e.g., catalysts) can, for instance, increase signal noise in optical measurements, even though they do not contribute to the actual analyte value. In such cases, a sample conditioning step in an on-line system can help achieve more stable readings.

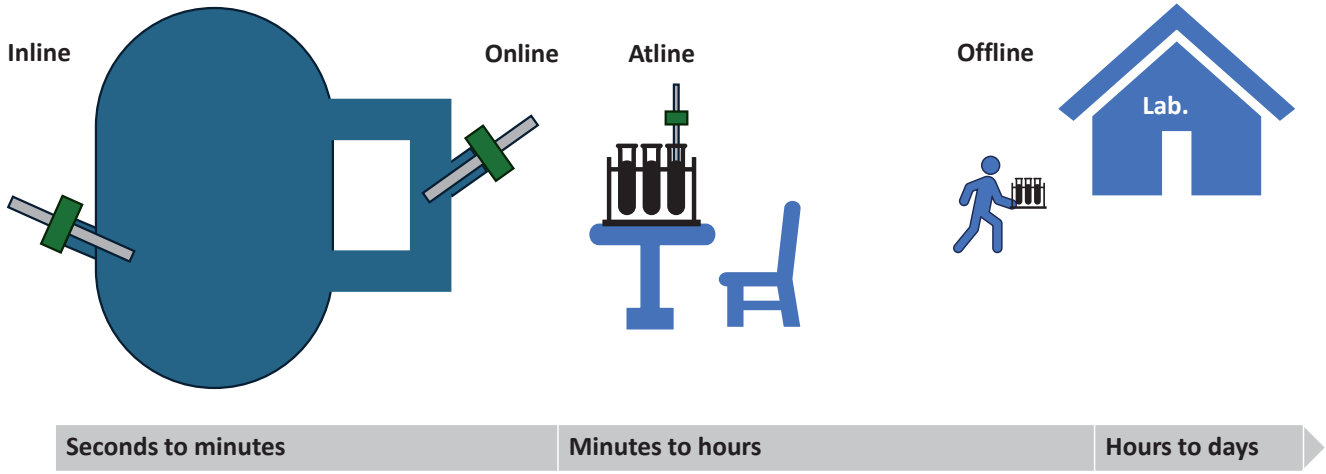

Figure 2: Graphic illustration of in-line, on-line and at-line measurement setups.

Table 1: TOS Criteria and Their Relevance for in-line/in-situ and on-line PAT measurements

TOS Criterion	Definition / Typical Source	Relevance for in-line/in-situ PAT	Relevance for on-line PAT	Comment / Example
FSE – Fundamental Sampling Error	Statistical variance due to limited sampling volume in a heterogeneous system	Partly relevant	Relevant	Sensor measures locally → reduction possible through turbulence or mixing
GSE – Grouping & Segregation Error	Occurs when components are clustered or segregated	Partly relevant	Relevant	Common in multiphase or partially unmixed flows (e.g. suspensions, slurries, melts)
IDE – Increment Delimitation Error	Caused by poorly defined sample or sampling volume boundaries	Relevant	Relevant	Sensor position, sensor field-of-view (FOV) and flow profile critical
IEE – Increment Extraction Error	Error during physical extraction of a sample	Not relevant	Highly relevant	Inline sensors have no extraction step
IPE – Increment Preparation Error	Error during sample preparation, dilution, sieving	Not relevant	Sometimes relevant	Occurs only in on-line systems with conditioning
MEE – Measurement Error	Instrumental or analytical error during signal generation	Relevant	Relevant	Calibration and environmental compensation required
IWE – Increment Weighting Error	Unequal weighting of increments or sub-samples	Not relevant	Partly relevant	In-line sensors integrate over time; on-line systems analyze discrete volumes
TEE – Transformation Error	Error due to non-representative measurement variable	Critical	Critical	Indirect measurement (e.g., refractive index or ultrasonic signal) may not fully reflect the true concentration.

Of course, this modification always comes with trade-offs, such as time delays and additional effort in system design, maintenance, and servicing

3.2 Example from practice: in-line ultrasonic concentration measurement

Inhomogeneities do not only occur in solid mixtures or during powder handling. Liquids, suspensions, emulsions, slurries and gas–liquid systems can likewise present significant challenges for PAT measurements. Local or transient variations in composition, density, or temperature will strongly influence measurement signal quality and representativity and must therefore be considered with great care.

This is particularly relevant for ultrasonic concentration measurement, where the propagation of sound depends on the local physical properties of the medium. The positioning of the sensor and the representativeness of the measurement volume are critical success factors.

Improper placement or flow conditions can lead to biased, unstable readings, especially in multiphase or poorly mixed systems.

Ultrasonic concentration measurement is a physical measurement principle based on the propagation of sound waves in liquids. A transducer emits ultrasonic pulses travelling through the medium, and from the measured sound velocity and signal damping, the measurement system (NB must be suitably calibrated, and validated) can derive quantities such as density, concentration, or compressibility.

This approach relies on well-defined relationships between sound velocity and material properties of the liquid phase. Since the propagation of sound is influenced by density, temperature, and medium elasticity, variations in these parameters are directly reflected in the acoustic response.

In contrast to spectroscopic techniques, ultrasonic methods do not provide molecular information; they measure macroscopic physical properties of the fluid. Because the sensor operates without optical access and without the need for reagents, it is often used for continuous monitoring of homogeneous and two-component liquid systems, for example in pipelines or reactors, where robust, real-time information on concentration or density is required.

Typical sources of inhomogeneity include:

- Gas bubbles: Even small fractions of entrained gas strongly attenuate or scatter the ultrasonic signal, resulting in unstable, biased readings.
- Pressure variations: In zones of reduced pressure (e.g., after valves, or at pipe outlets) degassing may occur (dissolved gases come out of solution), forming bubbles that disturb measurement stability.
- Poor mixing: In areas with insufficient turbulence or incomplete forced mixing, stratification or phase separation can occur, producing locally different concentration profiles.
- Deposits (fouling): Over time, precipitations and sediments on sensor surfaces can further dampen the signal and shift readings.

Installation recommendations from manufacturers reflect these challenges: ultrasonic probes should preferably be installed downstream of pumps. Pumps not only provide sufficient mixing but also increase the local pressure, keeping gases dissolved and minimizing bubble formation. Likewise, vertical installation positions help bubbles escape upward, away from the measuring zone. By contrast, locations directly after throttling devices, in dead zones or at pipe outlets, are especially prone to degassing; therefore, unsuitable for reliable ultrasonic measurement.

4. Manufacturer Guidelines and the Link to TOS Principles

Manufacturers of in-line ultrasonic systems explicitly address the same physical challenges described by the Theory of Sampling (TOS) — i.e., avoidance of Fundamental Sampling Error (FSE) and Grouping and Segregation Error (GSE) effects, which is caused by local inhomogeneous material and/or irregular process conditions.

The sampling and service documentation provided by ultrasonic equipment manufacturers shows critical awareness of the effects from the Increment Extraction Error (IEE) and the Increment Preparation Error (IPE).

A typical example would be from the company LiquiSonic® which instructs users to log both the controller timestamp and the distance between probe and sampling point when taking reference samples, ensuring time-aligned comparison between in-line readings and laboratory data. This structured correlation of field and lab measurements strengthens traceability and enables identification of localized inhomogeneities that might otherwise remain undetected in continuous operations.

Figure 3 shows typical installation guidelines highlighting suitable (green) and unsuitable (red crosses) positions for in-line ultrasonic concentration measurement. The reliability of the measurement strongly depends on sensor placement and local material and flow conditions. Positions (1), (3), (4), (6), and (9) are considered unsuitable, as they are prone to degassing, turbulence, or stagnant flow (e.g., near valves, outlets, or at the reactor bottom). Positions (2), (5), (7), and (8) are recommended, as they provide stable flow and opens up for optimised reproducible conditions. In particular, position (5) downstream of the pump ensures sufficient mixing and pressure to minimize gas bubble formation.

These installation principles (as illustrated by the company SensoTech), reflect general good practice for achieving stable and reproducible ultrasonic concentration measurements in pipelines and reactors.

Overall, these manufacturer's approach embodies key TOS principles in a practical, industrial context: ensuring representative measurement conditions, documented traceability, and active error monitoring. Such design features transform the TOS from a theoretical sampling framework into an operational quality assurance tool for modern PAT installations.

While these measures significantly reduce the main sampling-related errors (FSE, GSE, IDE), TOS' principles cannot be fully fulfilled in in-line ultrasonic measurements, since the sensor head here only probes only a local section of the process stream rather than the necessary complete tream section (see further below and in another article in this issue (Esbensen, 2025).

4.1 Example from practice – on-line gas composition measurements

An on-line gas measurement probe was installed immediately after a pipe bend. The results were precise – but not accurate, sometimes too low, sometimes too high.

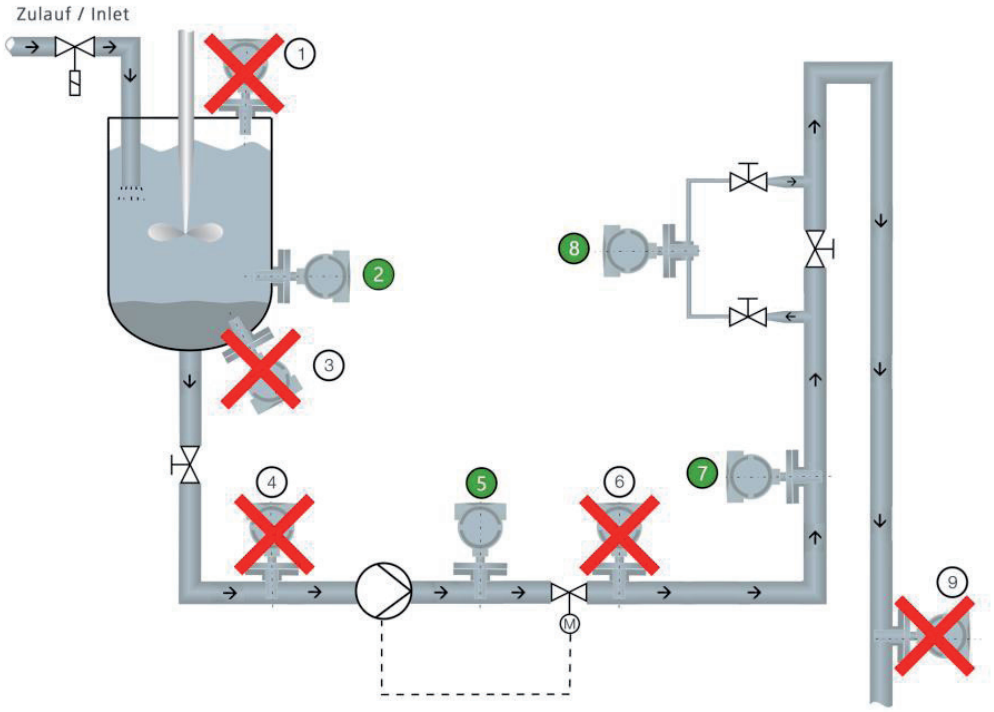

Figure 3: Recommended and unsuitable installation positions for ultrasonic concentration sensors (adapted from SensoTech GmbH installation manual).

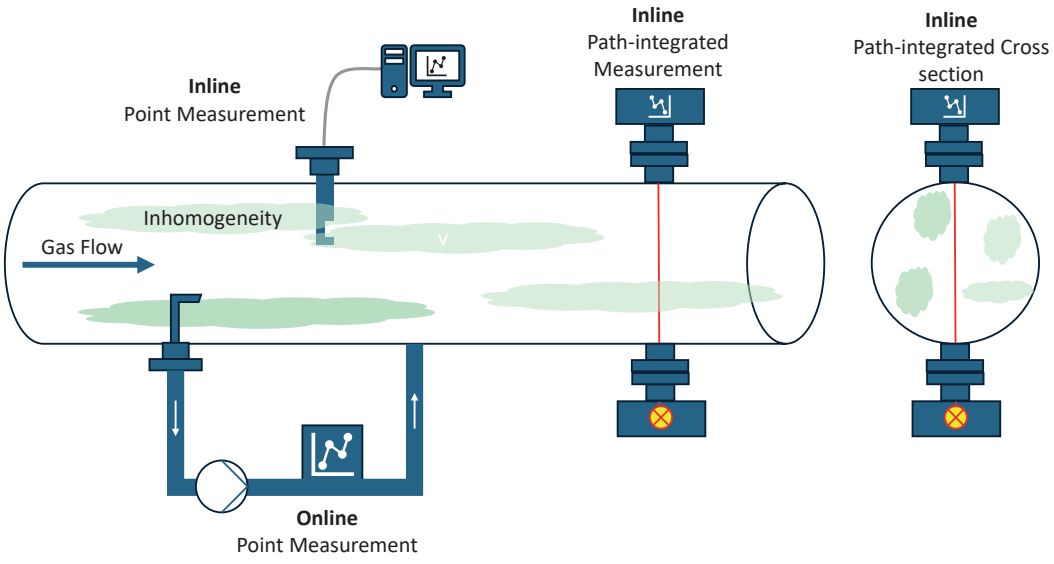

Figure 4: Illustration of on-line and in-line PAT sensor installations in an inhomogeneous gas/gas mixture stream.

The reason was that flow velocity locally influenced the gas composition, i.e., there were actually inhomogeneities even though this was a supposedly well-mixed gas flow. Indeed focused investigations revealed formation of channled flow patterns. The remedy in this case consisted in installation of up-stream static mixers, and of a different PAT probe at another measurement location. Lesson learned (a reflection of a much broader general problem): An in-line measurement would not have been better here because most in-line probes are also point measurements. Very many in-line methods, e.g., laser spectrometers, pH meters, focused PAT probes result in 'point measurements' - essentially optical grab samples (Esbensen, 2025) - that are completely unable to represent a complete stream segment (see another article inthis issue). An early overview of TOS as applied to gas and gas mixture characterisation was given by Larsen and Esbensen (2020).

5. Business Case Aspects

Selection of incorrect, non-optimised measurement location not only runs a high risk of significant wastes the equipment budget, but also invites unnecessary risks for:

- Production time losses (through misinterpretation)
- Production of scrap (due to inferior or incorrect process/product control)
- Additional costs (for unnecessary modifications)
- Reduced trust in PAT performance

The last point in particular – trust – must not be underestimated. Once lost, it is difficult to rebuild trust in technical solutions, making new projects harder to initiate, or even impossible (before a new management is in place – which is a much bigger project to undertake).

5.1 Practical Example – Costly correction of measurement location

In a chemical company, new measurement technology was installed to capture a critical quality parameter directly in the process. The investment for equipment, integration, and commissioning exceeded €80,000. The measurement location was initially identical to where laboratory samples had previously been extracted – without detailed verification of whether this location was truly suitable also for continuous process monitoring. The company was only interested in a specific analyte occuring in one of the mixture components.

After commissioning the following became clear:

- The medium at this location was not sufficiently well mixed. But this heterogeneity did not raise alarms, because it did apparently not impact on the manual sampling, as the analytical aliquot was taken after phase separation in the lab.
- Occasional gas bubbles in the product stream severely compromised the optical measurement principle. Again, this was not an issue for the subsequent manual sub-sampling for the analytical aliquot.
- Temperature fluctuations were greater than expected, significantly impairing measurement stability.

This all resulted in significantly varying, unreliable measurement results, indeed they were unsuitable for process control. After weeks of troubleshooting, the measurement point was moved several meters to another location with (more) uniform flow, (more) stable temperature, and no air entrainment. Additional modification costs surpassed €20,000.

Field Lesson #2: A short pilot (or perhaps an instrument on loan) would have revealed this problem instantly. Precautionary early testing first — even with soft sensors or simple devices — prevents expensive rework later.

5.2 How could this have been avoided?

- A targeted preliminary study of the planned new installation condition would have been an easy option e.g., focusing on flow simulation and visualization, temporary test measurement with a mobile device
- Automatic locating a new PAT measurement point at exactly the same existing lab sampling point is very often dramatically inferior to determining the optimal position analytically (for the probe and the process).
- Interdisciplinary coordination is always good, as between process engineering, plant operations, the laboratory and the PAT team - to validate theoretical assumptions against real process conditions.

Such preliminary checks can save not only the extra costs but also weeks of project delay.

6. QbD and Regulatory Frameworks

In the pharmaceutical industry, measurement strategies are an integral part of validation. Quality by Design (QbD) and Process Analytical Technology (PAT) are closely interlinked – both require a solid process understanding before any technology decision will be made.

Regulatory authorities, such as the FDA and EMA, expect that the criteria for measurement location selection and data usage are documented in a traceable manner. The QbD concept requires that all CPPs and CQAs are identified, comprehensively understood, and monitored with appropriate measurement approaches already during the development phase (FDA, 2004).
This last demand makes eminent sense: only those who understand and fully model a process from the outset can later operate reproducibly within a defined "design space."

In practice, however, this is often more difficult. Subsequent changes to measurement points, sensors, or process parameters in a validated environment are laborious, requiring extensive documentation, testing, and re-approval.

This is sometimes called the "validation pain" – the effort can be so high in practice that necessary adjustments are delayed or avoided entirely: double jeopardy! (Dahlgren et al., 2020).

The idea, of course, is to understand the process so well before validation that later changes are unnecessary. But often "all theory is grey." Even carefully planned QbD approaches encounter unexpected effects, deviations, or new insights in reality, forcing adjustments.

PAT can help here, but only when measurement points and principles are chosen so that they continue to deliver relevant and usable data even when requirements change.

PAT Insight #4: Early PAT during Research and development reduces validation pain later. Once a system is validated, changes are expensive — learning early allows simpler, cheaper sensors in production.

7. Forgotten Basics: Soft Sensors and Data Integration

In addition to classic measurement technology, using existing process data combined with operators' vast and valuable experiences offers an often underestimated way to gain additional insights and improve process control. This is where so-called soft sensors come into play.

Existing process data and the empirical knowledge of operators can be used to calculate virtual measurement values.

Surprising insights often emerge when talking to operators and specifically asking how they steer production at present.

Examples:

- Calculation of viscosity from physical measurements (temperature, torque, rotational speed, power consumption of mixers and pumps)
- Moisture estimation (from dew point and temperature measurements)
- Concentration calculations (via material balance models)

PAT Insight #5: More data do not necessarily mean better control. A signal must be representative, robust, and interpretable — otherwise it only adds noise.

7.1 Control charts as a complement:

Data obtained via soft sensors, or direct measurement, can be effectively monitored with control charts. Control charts are statistical process monitoring tools used to distinguish between random (common-cause) and systematic (special-cause) variation in time-series data. They are based on continuous plotting of measurement results (or derived quantities such as model residuals) compared with statistically defined control limits, typically set at ±3 standard deviations (UCL) from the mean (Control Line: CL). Deviations beyond these limits, or persistent drifts within them, indicate that a process may have shifted from its expected state (in a trending or in a more fluctuating fashion).

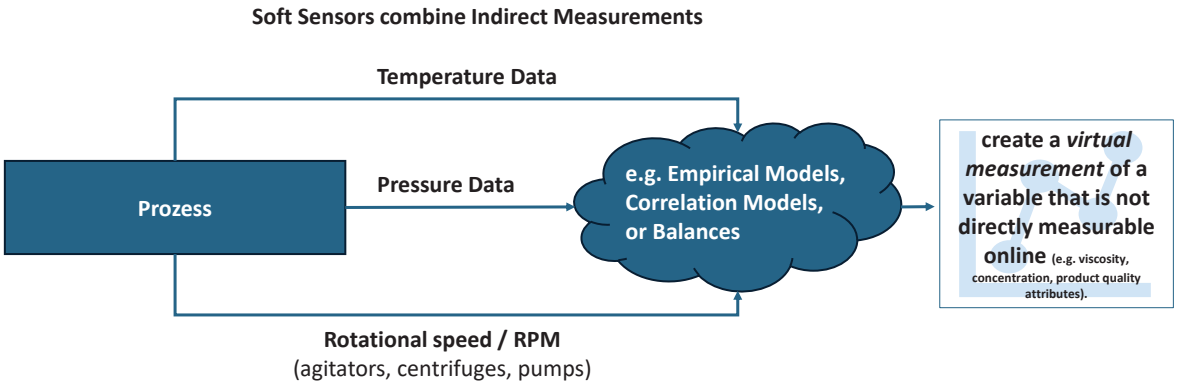

Figure 5: Schematic illustration of the soft sensor principle.

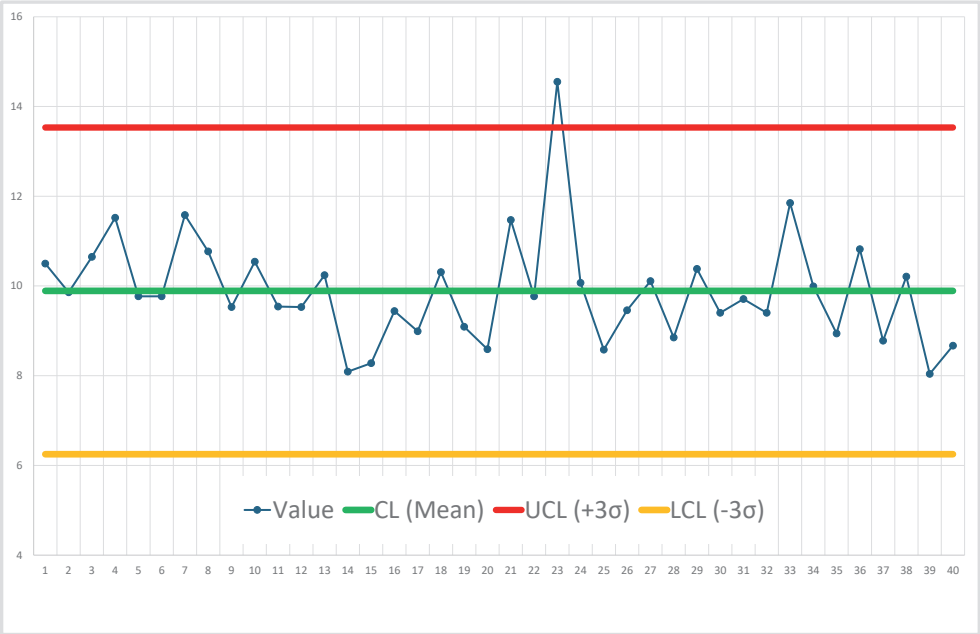

Figure 6: Illustration of control chart, typically set at ±3 standard deviations (UCL) from the mean (CL).

Several types of control charts exist, each suited to different data characteristics:

- Shewhart charts visualize pointwise deviations and are well suited for detecting sudden changes or outliers.
- CUSUM (Cumulative Sum) charts integrate small deviations over time, enabling early detection of gradual drifts.
- EWMA (Exponentially Weighted Moving Average) charts smooth short-term variability and emphasize recent data, which makes them effective for trend monitoring in continuous processes.

Data obtained via soft sensors or direct PAT measurements can be effectively monitored using such charts. They provide not only current values but also reveal trends, process shifts, and emerging deviations, quite often before they become apparent in conventional quality checks. In this way, control charts support both early process intervention and validation of long-term measurement stability. But there is also an important limitation: The quality of soft sensors and derived control charts depends directly on the quality of the data and its representativity (Esbensen, 2025). With the right methodology and motivated data analysis, meaningful monitoring values can often be determined surprisingly well and can be statistically substantiated.

7.2 Examples

In emission analytics, CUSUM (Cumulative Sum) control charts are frequently used to track slow drifts in analytical systems. They provide early indications of the need for necessary maintenance, recalibration, or instrument adjustment well before threshold limits are exceeded. Their continuous nature makes them particularly suitable for long-term monitoring of sensor stability and process performance.

Control charts are also increasingly used within Process Analytical Technology (PAT) frameworks to ensure the robustness of inline and online measurements. A common approach involves Multivariate Statistical Process Control (MSPC), where data from spectroscopic sensors (e.g., NIR, Raman, or UV/Vis) are condensed into principal components (PCA/PLS). Control charts based on principal components help distinguish random variation from systematic drift, and provide a quantitative basis for model maintenance and recalibration decisions.

Furthermore, CUSUM-type charts have been explored for monitoring residuals from chemometric prediction models, improving the sensitivity for small shifts in complex data streams.

Many examples can be found in the chemometrics textbook (Al-Rashed, Al-Mutairi & Al-Attar, 2019).

7.3 Checklist – Measurement Location Planning

A well-thought-out measurement location plan determines whether a PAT system will later be able to deliver useful and reliable data. Before a decision is made, the following points should be clarified:

- **Clear definition of the goal and benefit of the planned measurement**
  Has it been specified why the measurement is to be carried out and how the data will be used (distinguish between monitoring, control, release, prediction, alarm)

- **Are CPP/CQA known and measurable?**
  Are critical process parameters (CPP) and critical quality attributes (CQA) for the specific application clearly defined, described and directly/indirectly measurable at the planned location?

- **Flow and mixing conditions as well as process engineering constraints?**
  These topics include temperature/pressure profiles, phase states, gas bubbles, sedimentation, installations, dead volumes, delays in bypasses, cleaning/fouling, materials, safety issues

- **Theory of Sampling criteria fulfilled?**
  Ensuring representativity for in-line and on-line measurements are de rigeur. This includes sub-sampling, sample preparation, return of residual sample material. Data quality is a critial attribute spanning three domains, see Esbensen 2025.

- **Validation concept in place?**
  The following must always be planned a priori: calibration, validation, verification, acceptance criteria, maintenance, drift monitoring, data integrity, change control.

Field Lesson #3: No sensor is truly calibration-free. Factory settings and self-monitoring can help, but verification and periodic validation remain essential, especially when process data drive important and critical decisions (e.g., release decisions in pharma) (FDA, 2011; EMA, 2015).

8. What does all this mean in practice?

A measurement only has real value if it effectively contributes to monitoring, control, release, or optimization. Target outcomes can include shorter cycles, lower energy consumption, higher yield, less raw material usage and/or less scrap, and consistent quality.

A salient practical example would be the use of an in-line NIR or laser diffraction device (PAT) in the mixing segment of an emulsion production, providing an early correlation with droplet size distribution. This information allows agitator speed and dosing profiles to be adjusted during batch production instead of waiting for laboratory tests. The result is more stable quality and less rework. Another example would be regulation of an evaporator stage, not simply by temperature but directly by solids content using conductivity or NIR signals. This enables the same product quality at lower temperatures, saving energy and reducing thermal damage of the product.

The goal of a measurement should therefore never just be "to produce a number," but to enable a model or control strategy that leads to improved process management and resource use.

Equally important is to define CPPs and CQAs correctly and not to confuse them with final product specifications. CPPs and CQAs relate to what is required for process control. Final product specifications are critically important for product chances on the market, but they often do not help for production or manufacturing control.

A polymerisation example will illustrate this well: final molecular weight is determined in the lab and is decisive for, say, product release, but it cannot be measured in-line. Instead, an IR band correlated with monomer conversion can be measured in-line and used for process control. The final CQA remains a release criterion, but the CPP-related IR signal allows stable operation and fewer off-spec batches.

9. Flow, mixing, and process conditions are further decisive factors

Local inhomogeneities, installations, and operating states can massively influence the measured value.

One example was the above-mentioned gas probe installed behind a pipe bend that produced local inhomogeneity streaks caused by secondary flows. Only after installing a static mixer and relocating the sampling point to before the bend were stable values obtained. Another case would be an in-line NIR probe, disturbed by gas bubbles in the product stream. The solution was a physical bypass with degassing, a modified installation position of the window, and a slight pressure increase.

Dead volumes and delays in by-passes can also cause practical problems.

An on-line analyser with twelve meters of sample tubing had a residence time of several minutes, making process control impossible. Only by shortening the tubing and increasing the flow rate could the the delay time be reduced to under the required one minute.
Similarly, temperature and pressure fluctuations can cause spectral shifts if not accounted for in calibration, or stabilized by tempering the measuring cell. Finally, fouling and deposits on windows are a frequent reason for drift and upsets. Flushing, anti-fouling coatings, or Clean-in-Place (CIP)-capable designs are essential in these cases.

10. TOS thinking – is good for PAT

Applying correct TOS principles is often the decisive point in practice but is sadly, frequently neglected.

For example, a NIR system may be calibrated with laboratory samples extracted after filtration, while the in-line probe interacts the unfiltered stream. The result is likely to show significant systematic errors and shifts. The correct approach would be calibration with process-representative samples from the same environment. Alternatively, an online system with controlled sample preparation can be implemented to ensure that the measured stream closely reflects the true process composition.

In gas analytics, another example concerns isokinetic sampling: if the sampling velocity does not match the flow, certain particle or droplet fractions are over- or underrepresented in the extracted sample volume, leading to the dreaded sampling bias, dreaded because it can never be corrected for. In emulsions, sampling itself can change the sample when pumps or lines introduce shear which may alter droplet size distribution, an illustrative example of an Incorrect Extraction Error (IEE) in the PAT domain. In all cases, the rule is clear: contemporary process representativity is mandatory, otherwise even the most expensive measuring devices are worthless.

Validation must not be considered only at the end of a project. Acceptance criteria, test plans, and proof procedures should be carefully defined from the start of any PAT project. For an in-line sensor, this means predefining the desired limits for measurement uncertainty, recovery, stability, drift, and failure rates already during the planning phase.

The system's entire lifecycle – from initial and ongoing calibration through regular verification and maintenance to spare parts strategy and data integrity – all must be most carefully documented a priori. Any changes to the process or product recipes must feed back and influence validation through meticulous change control.

Typical pitfalls in practice include carrying "laboratory thinking" into the process, i.e., calibrating with non-representative samples, or simply reusing laboratory sampling points as process measurement locations. Equally problematic are long or poorly designed by-passes that cause delays and dead volumes, as well as ignoring temperature and pressure effects, or underestimating fouling. Countermeasures include calibration and validation with process-representative samples, flow- and mixing-aware placement of measurement points, minimizing dead volumes, considering temperature and pressure effects in the model, planning cleaning strategies, and integrating maintenance from the beginning.

The numerous practical examples above show that these issues are not merely of theoretical importance.

11. Conclusions

Some of the most often forgotten basics, misconceptions and blind spots regarding PAT system design and implementation were presented. PAT does not start with buying a 'powerful analytical device' in isolation - but instead starts with analysing the measurement task, the measurement location, and the physical and chemical process reality. Only in this way can robust, economical solutions be created that enable appropriate, improved process control.

The conclusions are clear: Before any procurement, three decision gates must be passed.

1. Is the technical suitability proven, i.e., representativity, flow and mixing conditions, T/P effects, delay time, and is maintainability demonstrated by tests and pilot trials?
2. Is the economic benefit shown and compelling, i.e., are the expected savings in scrap, energy, or time versus CAPEX/OPEX, environmental impact calculated realistically?
3. Is validation and routine operation conditions ensured with the desired bracketing attributes, i.e., calibration, proper validation, verification, acceptance limits, alarms, data integrity, and change control sufficiently documented?

Only when a system passes all three decision gates will procurement be worthwhile. Only then will the likelihood be high that a new PAT solution will genuinely and effectively contribute to improved process control.

FINAL THOUGHT

Even the best PAT setup fails without ownership. Every successful project has a PAT champion who connects proper planning, QA, TOS, lab, maintenance with production and logistics — and keeps the system alive after commissioning.

References

Al-Rashed, A., Al-Mutairi, N., & Al Attar, M. (2019). Air Pollution Analysis in Kuwait Using a Statistical Technique (CUSUM). International Journal of Geosciences, 10, 254–294.

Dahlgren, G., et al. (2020). Quality & Regulatory Solutions for PAT in Continuous Manufacturing. Pharmaceutical Engineering, September–October 2020, International Society for Pharmaceutical Engineering (ISPE). Available at: https://ispe.org/pharmaceutical-engineering/september-october-2020/quality-regulatory-solutions-pat-continuous

Eifert, T., Erens, J., & Gerlach, M. (2023). Workshop: Fundamentals of PAT in Industrial Applications – Part I: PAT Project Management – from Measurement Task to Business Case [Presentation, in German]. Arbeitskreis Prozessanalytik (GDCh) / Covestro. AK PAT Colloquium 2023, November 2023

Esbensen, H.K. (2025). Data Quality: Importance of the 'Before Analysis' Domain [Theory of Sampling (TOS)]. Journal of Chemometrics, 39(4). Available at: https://doi.org/10.1002/cem.70021

European Medicines Agency (EMA). (2015). EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use – Annex 15: Qualification and Validation. Available at: https://health.ec.europa.eu/system/files/2016-11/2015-10_annex15_0.pdf

Kessler, R. W. (2001). Lecture Notes: Product Property Design. Reutlingen University, Germany. (Unpublished lecture documentation)

Larsen, A. & Esbensen, K. H. (2020). Principles of gas sampling: TOS with critical challenges. TOS Forum, Issue 10, pp. 41–47. (doi:10.1255/tosf.126)

U.S. Food and Drug Administration (FDA). (2004). Guidance for Industry: PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance. Center for Drug Evaluation and Research (CDER), Rockville, MD. Available at: https://www.fda.gov/media/71012/download

U.S. Food and Drug Administration (FDA). (2011). Guidance for Industry: Process Validation – General Principles and Practices. Center for Drug Evaluation and Research (CDER), Rockville, MD. Available at: https://www.fda.gov/files/drugs/published/Process-Validation--General-Principles-and-Practices.pdf