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Optimal Special Edition

QbD & PAT

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Design quality into manufacturing

Maintain your quality in real time

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Brad Swarbrick
Martin Gadsby
with Faithe Wempen

About Optimal

Formed more than 30 years ago, Optimal now consists of two organizations — Optimal Industrial Automation Ltd., which concentrates on all forms of industrial automation, and Optimal Industrial Technologies Ltd., which is the products division. This latter division handles the development, support and, where required, integration of the synTQ product. Optimal Industrial Automation can also provide associated services where traditional industrial control such as PLC, SCADA, and DCS is required to support the client's PAT initiative. Optimal has extensive experience working in highly regulated industries, especially life sciences. The company's work experience in other sectors is broad ranging, with many successful projects having been executed in less regulated discrete as well as process industries. This book relates to the products division of Optimal, which is totally focused on the PAT product synTQ and its implementation in many industries.

QbD & PAT

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by Brad Swarbrick and Martin Gadsby with Faithe Wempen

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QbD & PAT For Dummies®, Optimal Special Edition

Published by: **John Wiley & Sons, Ltd.,** The Atrium, Southern Gate

Chichester, West Sussex, www.wiley.com

Registered Office

John Wiley & Sons, Ltd., The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, United Kingdom

ISBN 978-1-119-46633-8 fm (pbk), ISBN 978-1-119-46629-1 (ebk)

Printed in Great Britain

10 9 8 7 6 5 4 3 2 1

Publisher's Acknowledgments

We're proud of this book and of the people who worked on it. Some of the people who helped bring this book to market include the following:

Project Editor: Martin V. Minner

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Table of Contents

Introduction

Welcome to *QbD & PAT For Dummies*, Optimal Special Edition — your guide to understanding and implementing these strategies to improve your quality and increase efficiency.

Quality by Design (QbD) and Process Analytical Technology (PAT) are innovative approaches to improving manufacturing efficiency and quality. QbD stresses designing quality into manufacturing, rather than testing for quality after the event. In contrast, PAT enables real-time, quality-based adjustments to your process. By reading this book, you will get a better feel for the principles behind the initiative.

It's Happening Now

Since their conception in the early 2000s, QbD and PAT have been hot topics of discussion in the life science industries, but they've only recently started being widely adopted in full-scale manufacturing. Where this is happening, the companies, regulators, and consumers are all reaping the benefits.

The life science industry has been slow to adopt these methodologies. However, with more advanced technologies and harmonized regulatory guidance, the QbD/PAT-driven paradigm shift is set to be taken up exponentially.

A New Mindset

QbD and PAT represent a completely new way of working — at least to the life science industries. A new culture is required that includes complete "buy-in" from key stakeholders and senior management. Legacy methods should be reevaluated and updated.

Companies can reap huge benefits by employing a QbD/PAT approach, but implementations are not "plug and play." QbD/PAT is a team event, with a whole range of disparate but complementary skills and technologies being required.

We're pleased to say that QbD and PAT are here to stay, not only for the life science industries but also for many other processing industries. Other industries have led the way with "islands of PAT," but the life science industries may be among the first with a holistic and joined-up approach.

About This Book

Despite QbD and PAT being discussed for many years, there is still a great deal of fear, mystique, and misunderstanding around the subject. The objective of this book is to dispel these so that you can proceed confidently with a project.

We ask you to take this book for what it is intended to do: to present a basic view of what QbD and PAT is, what it can deliver to all parties, and how to implement it.

We hope that this book meets its objectives, and wish you all the very best with your QbD/PAT journey. This is the future!

Icons Used in This Book

To make it easy to navigate to the most useful information, these icons highlight key text:


TIP

Follow the target for tips that can save you time and effort.


WARNING

Watch out for these potential pitfalls on the road ahead.


EXAMPLE

Enrich your understanding with these real-life examples.


REMEMBER

Take careful note of these key takeaway points.

Read these optional passages if you crave a more technical explanation.

Where to Go from Here

The book is written as a reference guide, so you can read it from cover to cover or jump straight to the topics you are most interested in. Whichever way you choose, you can't go wrong. Both paths lead to the same outcome — a better understanding of the steps and technologies needed to move forward.

IN THIS CHAPTER

- Introducing Quality by Design (QbD) and Process Analytical Technology (PAT)
- Understanding how QbD and PAT complement each other
- Making organizational changes to prepare for QbD/PAT
- Starting out small and moving ahead

Chapter 1
Understanding QbD and PAT

In recent times, the pharmaceutical and related industries have been challenged to think about the way they approach product development and manufacturing. A definite paradigm shift is occurring with movement from the old ways of manufacturing to the new code of current good manufacturing practices (cGMPs) for the 21st century.

So why the need to change something if it already works? The simple answer is that the old ways are no longer the best practices, and can't keep up in today's market. In this chapter, you learn the basics of Quality by Design (QbD) and Process Analytical Technology (PAT), two complementary approaches for improving product development and manufacturing effectiveness. You also learn how these systems work together, and look at the kinds of organizational changes typically involved in implementing them.

Understanding Quality by Design (QbD)

Traditional product development and manufacturing methods are based on a philosophy of Quality by Testing (QbT). In this approach, products are tested *after* the event to establish

their quality. If problems are found using the QbT approach, it's usually too late to fix the current batch. The focus is on correcting the process going forward by quarantining, rework, testing, and making process adjustments. Being wrong multiple times before you get it right is an expected part of the process.

A more modern and efficient alternative is the Quality by Design (QbD) approach, which was introduced in the *cGMPs for the 21st Century* guidance and in guidance from the International Conference on Harmonization (ICH). You can learn more about those guidelines in Chapter 3. In QbD, quality is built into a product *by design.* The QbD approach can be challenging to implement because the manufacturer must know more about the products it produces, and must provide regulators with more evidence of this knowledge.

The traditional approach deals with quality in a reactive way. The regulatory body dictates minimum quality standards to a manufacturer, and in some cases the manufacturer either gets frustrated or cannot adapt to the requirements. In contrast, QbD is a proactive approach in which a manufacturer shares knowledge with the regulator about how the company manufactures. With QbD, both sides win. Figure 1-1 summarizes the difference.

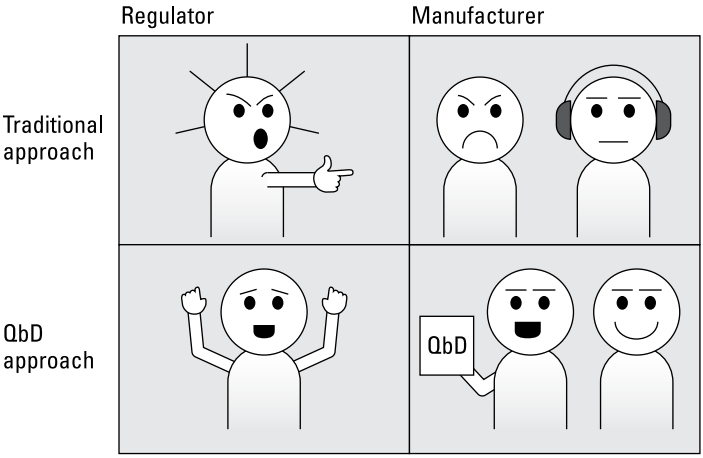


FIGURE 1-1: The traditional versus the QbD approach.

A key concept in the QbD approach is the design space, which you learn more about later in this chapter. The design space enables manufacturers to explore combinations of multiple variables and

properties using scientific, risk-based tools to avoid problems occurring. For example, inherent variability in raw material lots can be managed within the design space by applying real-time process adjustments during manufacturing. These minimize end-product variability and waste while maintaining the highest level of quality.

Understanding Process Analytical Technology (PAT)

To implement QbD effectively, you must be able to make timely measurements that relate to the health of the process and the product quality. For example, as a product is being made, the raw and in-process materials must be monitored for quality and the process adjusted accordingly. You don't wait for the product to be complete before you check it. Pulling this off successfully requires a disciplined, systematic approach to product and process development. This is where Process Analytical Technology (PAT) complements the QbD approach.

REMEMBER

PAT is about making timely measurements on the state of raw materials and intermediates generated during processing. When a PAT system detects a process drift or change within the process's design space, changes can be made so that the desired state is always maintained.

PAT tools have typically been *spectroscopic* in nature. That means they examine the interaction of electromagnetic radiation with matter to better understand the chemical (and sometimes physical) nature of the matter being investigated. Methods such as near infrared (NIR) and Raman spectroscopy are the most commonly used tools because they measure the state of a process without physically disturbing it by taking samples.

WARNING

Implementing a PAT tool into a process and taking measurements does not ensure that the measurements are representative! The manufacturer must demonstrate that the measurements are representative (that is, that a small sample accurately reflects what a larger sample would also show) using the guiding principles of the Theory of Sampling (TOS). This theory defines the proper practices and protocols for collecting representative *aliquots* (spectral data) for analysis.

QbD and PAT are highly complementary in both batch and continuous manufacturing situations (in other words, they enhance each other). QbD establishes a design space for a product/process combination that is predictive and allows process changes to be made proactively, before manufacturing deviations or out-of-specification situations occur. PAT, in turn, provides the tools for measuring and controlling quality at key steps during the process to ensure the effectiveness of the design space.

Understanding the Design Space

The design space provides a top-down, multivariate view of the process, enabling operators and/or control systems to make the right changes to maintain optimal quality.

The design space is a key feature of QbD, enabling manufacturers to define the process boundaries that define the highest level of product quality. That sounds pretty simple, but a good design space is anything but that.

A design space can be assessed by three main regions of operation, as follows:

- **Normal operating region (NOR):** This is the desired state, in which the highest quality product exists.
- **Proven acceptance region (PAR):** This is where acceptable product is still being manufactured, but process adjustments should be made to return operation to NOR levels.
- **Out of specification (OOS):** The state of the product is not acceptable. Investigations must take place to determine the reasons and decide on a course of action.

The design space is conveniently summarized in Figure 1-2.

Here's a more formal definition of *design space:* It's the multivariate combination of raw materials, intermediates, and final product properties, as well as the manufacturing parameters used to produce them, that collectively ensure the quality and performance of the product. The design space, by definition, looks at multiple variables. (That's what *multivariate* means.) Considering a single variable at a time is not a typical design space approach (unless, of course, the process is controlled by only one variable).

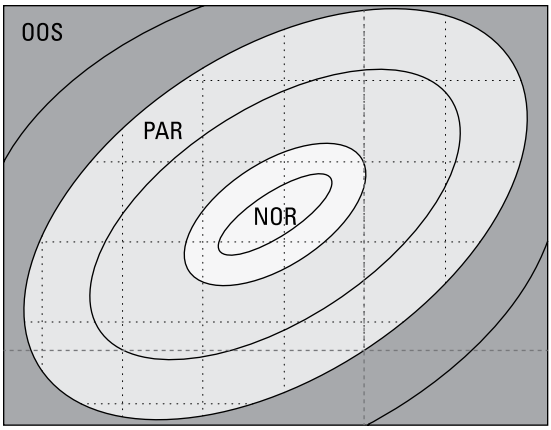


FIGURE 1-2: In the design space, NOR is the desired state. In PAR, the product is acceptable, but corrections should be made. In OOS, the product is not acceptable.

To put it more simply: The design space enables manufacturers to look at a process that has multiple variables and figure out which variables to adjust to achieve optimal quality (that is, to keep the manufacturing process in the NOR region).

PAT is a great help in keeping the process within NOR. Specialized sensors, strategically placed at key points in the manufacturing process, can deliver real-time data about chemical and physical attributes of the raw materials and intermediate products. This data, when fed into a PAT knowledge management system, can help explain why a process might be deviating. In combination with a control function, this data can implement process corrections.

REMEMBER

You can implement QbD without PAT, but we don't recommend it. Keeping a process within NOR is much more difficult without the real-time information and tools that PAT uses to supply a wealth of information almost instantaneously.

PAT stands for Process Analytical Technology, but you should think of it as the *Practical Application of Technology.* It provides deeper insights into a process in real time, enabling manufacturers to work proactively — not reactively — to ensure product quality.

Thinking About Organizational Changes

What changes are required in an organization looking to implement QbD/PAT? The biggest change can be summed up in a single word: *culture!* From the CEO to the janitor, if the organization does not live, breathe, and speak QbD, it cannot effectively move forward with it.

WARNING

Some organizations have boutique PAT groups that investigate new technology, but unfortunately, many of these groups are unable to progress from the R&D environment to commercial manufacturing. If you don't make this step, then the value is lost.

A successful QbD implementation requires a significant paradigm shift in most companies, simply because the "old way" of focusing on post-manufacturing quality inspections is so ingrained in the culture. Departments must work together, and must work with the PAT group. No more compartmentalizing, or saying, "That's not my problem." Further, the main focus must be on the safety of the product as delivered to the end-user.

The risk assessment must be useful but pragmatic, and not just a paper generating exercise. A risk assessment must isolate what are known as critical process parameters (CPPs), which influence critical quality attributes (CQAs). The CQAs identified are the attributes that effect the efficacy of the product, plus those most likely to cause the end-user harm, and are therefore most critical to control. It's essential to employ well-placed PAT sensors to monitor those factors.

From a short-term financial standpoint, an organization's top goal is to put a product out on the market as soon as possible in order to maximize market capitalization. Unfortunately, in some cases, quality is sacrificed and (perhaps inadvertently), process validation efforts are biased to pass, causing problems that may harm the company financially in the long run.

EXAMPLE

For example, say that an organization wants to release a product to market before a competitor does. Before manufacturing can begin, the process must be validated. The traditional approach to process validation requires manufacturing three validation batches that show statistically insignificant variability in analytical results.

To complete the process validation as swiftly as possible, the organization will try to create optimal conditions under which to run those test batches. It will choose its best process operators, its best analytical resources, and its best materials for the validation batches. The problem with that approach is that it isn't reality. It doesn't test what is going to happen on the manufacturing floor on a day-to-day basis. Only later, when OOS situations occur regularly, does the economic effect of traditional validation hit the factory's bottom line.

In 2011, the U.S. Food and Drug Administration (FDA) released process validation guidance that addressed the bias issue by introducing the concept of *continuous verification*. The guidance also stated that all new submissions to the FDA will be based on a QbD approach. Therefore, by extension, each batch is considered a validation batch under the continuous verification regime. The QbD/PAT approach is the most efficient way to implement continuous verification strategies.

Bottom line: It's time to start thinking in a QbD/PAT manner if you haven't already done so!

Design of experiments (DoE) is the practice of performing the minimum number of experiments to obtain the maximum amount of information. QbD is not solely DoE, but DoE is a major tool used for defining the design space. DoE must be a part of the QbD/PAT toolkit, along with statistical process control (SPC) and multivariate analysis (MVA).

Figuring Out Where to Start

As the old saying goes, a journey of a thousand miles begins with a single step. That same principle can apply to implementing QbD/PAT.

We recommend starting with raw material variability. After all, products are made from raw materials, and understanding their batch-to-batch or seasonal variability is the first step toward developing processes capable of adapting to that variability. We talk more about this starting point at the end of Chapter 2.

From there, consider extending the studies to the unit operations used to manufacture a product. Start with the operations that have historically resulted in the most downtime or quality issues for a product, and then seek to understand the link between the operations before and after the problem unit operation.

Over time, with increased knowledge, you will be able to strategically select the most important variables to measure in order to provide useful data for a PAT knowledge manager (PAT KM). Eventually you can have an end-to-end PAT system that provides information to proactively maintain the design space. These suggestions hold for both batch and continuous manufacturing operations in all industrial sectors, not just for life sciences.

IN THIS CHAPTER

- Understanding the commercial benefits
- Examining the potential quality benefits
- Exploring the development and manufacturing time benefits
- Understanding how these benefits differ between industries
- Determining the best approach

Chapter 2
Exploring the Benefits of a QbD/PAT Approach

Organizations can learn all about QbD/PAT and study the concepts for years in R&D environments, but it won't help them practically unless they implement them into commercial manufacturing processes.

In this chapter, we explain the benefits of QbD/PAT in several areas, including improved quality plus development and manufacturing times that ultimately lead to cost reduction. Although these benefits may differ between industries, the approach can be useful across a wide variety of process and product types.

Understanding the Commercial Benefits

QbD/PAT implementations take a proactive approach to quality, as Chapter 1 shows. They use early event detection (EED) systems to identify issues and correct them in real time, before they create problems. This proactivity greatly reduces waste of both time and materials, which increases profitability. For example, out-of-specification and quarantined material can be avoided,

as can worst-case scenarios such as a product recall and batch scrapping.

EXAMPLE

Here's an example. Suppose that one of the unit operations (UOs) of a pharmaceutical manufacturing process is fluid bed drying (FBD). This UO is a critical step for generating process intermediates in granulated products. The FBD process is meant to ensure a consistent particle size distribution (PSD) and consistent granule moisture levels. These two properties are the critical quality attributes (CQAs) for the FBD operation and are controlled by critical process parameters (CPPs) such as air flow, inlet and outlet air temperature, and drying time.

These CQAs are important for two reasons:

- Particle size distribution determines the blend characteristics of the granules, and therefore the uniformity of the tablets produced during compression.
- Moisture affects two important performance characteristics. If granules are over-dried, it leads to excessive fine material in the granules that may hinder effective blending. On the other hand, too much moisture may lead to microbiological growth, and represents a health risk to the product's end-user.

Incorporating a near infrared (NIR) sensor into the FBD enables manufacturers to monitor the moisture level of the bed (and in some cases, the median particle size of the bed) in real time. The NIR can be used to control and stop the drying process to keep the granules within their desired state. Such monitoring is in alignment with the principles of the U.S. FDA process validation guidance, which states that processes should not be based on fixed time endpoints, but based on when the process has produced the desired granules.

Now picture another company, one that uses traditional methods for determining endpoints, trying to make the same product. Without an NIR sensor integrated into the FBD, the company must physically sample the bed and run tests on them. This manual sampling and evaluation process results in unnecessary physical sampling of the powder bed, downtime for measuring the loss on drying (LOD) of the sample, and the potential for having to re-dry the powder if the moisture target was not reached.

The benefits are not just in short-term process expedience. PAT data can also help engineers analyze and improve processes overall. For example, in one case an NIR sensor enabled the engineering department to better understand the process and make changes that resulted in better overall fluidization of the bed. This, in turn, shortened processing time, minimized downstream processing issues, and allowed three more batches to be processed per month without factory expansion. There are many more examples of where the QbD/PAT approach can lead to real economic benefits without sacrificing quality.

Examining the Potential Quality Benefits

Time savings and quality are usually opposing objectives in a traditional sense and one has to suffer for the other. Not so for QbD/PAT! Although a QbD approach may have a steeper learning curve than some other approaches, the long-term benefits far outweigh the effort expended. In addition, the knowledge gained in learning about QbD/PAT readily transfers to other situations, so it's far from wasted effort.

So, how does QbD/PAT translate into improved quality? That's easy. With QbD, the goal is to get things right the first time, so quality is achieved more quickly initially and is maintained more readily. A *right first time (RFT)* approach greatly reduces the risk of future issues.

REMEMBER

Keep in mind that QbD is a proactive approach to quality. Within the design space, a process can be fine-tuned to minimize product variability. In contrast, a reactive approach to quality means that the problem has already occurred, and the organization must put time and effort toward trying to save the batch (which in some cases is a futile exercise). The "fighting fires" approach results in efficiency losses and investigations that stick a bandage on a problem rather than identifying its root cause.

You may have heard the old saying that *quality costs*. However, if the process is developed correctly in the first place, quality only costs once. You pay for it up front, and not repeatedly over the course of the product life cycle trying to put out fires that should not have occurred in the first place.

Figure 2-1 shows how the cost of quality (or lack of it) can be traced using the traditional and the QbD approaches.

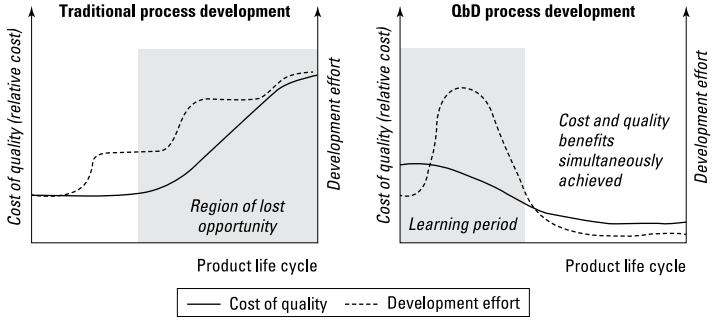


FIGURE 2-1: The real cost of quality.

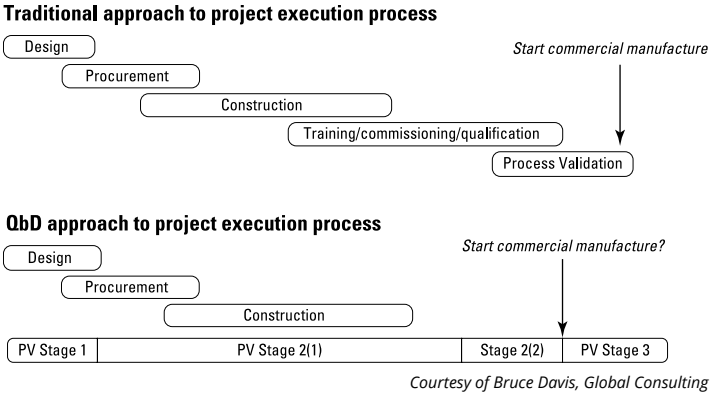
Exploring Development and Manufacturing Time Benefits

As you saw in Figure 2-1, more effort is required to develop a QbD process than a traditional one. However, that greater development effort does not necessarily translate to increased development *time*. The time of development is simply a function of how committed an organization is to taking a purely QbD mindset and not trying to carry over baggage from the traditional ways. QbD requires an all-in commitment. In our experience, hybrid approaches between QbD and more traditional methodologies don't often work.

REMEMBER

When an organization takes a traditional approach, process development effort never really ends. That's because continuous quality issues require "tweaks" to the process to attempt to fix a particular situation. However, in many cases these fixes are just patches; they only hide the unaddressed actual causes of the problems. In the QbD approach, on the other hand, manufacturers can make changes within the process design space without having to update regulatory submissions. Over time, through enhanced knowledge and understanding, a process reaches a plateau where no more improvements can (or need to) be made. This is the basis of the Pharmaceutical Quality System (PQS) defined in the ICH Q10 guidance (you can learn more about that in Chapter 3).

According to the 2011 FDA process validation guidance, manufacturing can commence at an earlier stage when using QbD compared to the traditional approach. Figure 2-2 illustrates the differences in the timelines.



Courtesy of Bruce Davis, Global Consulting

FIGURE 2-2: Commencement of manufacturing using traditional and QbD process development approaches.

In general, Process Validation (PV) Stage 1 uses QbD principles in the process design stage. PV Stage 2 (1) corresponds to the traditional Installation/Operational Qualification (IQ/OQ) stage of the process validation, while Stage 2 (2) is the traditional Performance Qualification (PQ) stage. Stage 3 is the beginning of the continuous verification process. Manufacturing can (at least theoretically) start at this point, because under a QbD paradigm, every batch is a validation batch.

How Different Industries Use QbD/PAT

The pharmaceutical and related industries are among the most regulated of industries, and for good reason: They provide products to treat medical conditions in humans (and animals). The goal of the industry is to make people well, not make them sicker!

REMEMBER

However, QbD/PAT methods themselves are industry-agnostic. There is no real difference between QbD in the pharmaceutical industry and outside of it. All industries are faced with process issues and can benefit from advanced sensors and quality system approaches to better address them. For example, oil refineries have been using advanced process control (APC) based on PAT for many years (longer than the pharmaceutical industry has been using PAT). In refining, the quality of gasoline must be monitored and controlled in real time to ensure that "octane giveaway" is minimized. The feedstocks used to blend gasoline can vary during

a blending operation, and in-line NIR or Raman spectroscopy systems have been successfully used to help ensure consistency.

The food and beverage industry has not used QbD/PAT to the extent it should. This is mainly because the industry doesn't see that its products are of high enough value to warrant the cost. If a batch of $100-a-pill drugs is bad, that's a huge expense. But if a batch of $1-a-box breakfast cereal is bad, it isn't necessarily a big deal. However, companies taking such a view are being short-sighted. Any effort that provides better understanding of raw materials, intermediates, and final product quality naturally leads to better product recognition, improved consistency, and reduced risk of contamination. The latter is especially important, with food poisoning being a real risk in the food industry. Methods such as NIR have been used for food authentication, particularly for olive oil and honey; wineries have also used NIR for authentication.

Deciding Where to Start

QbD/PAT works best when it works across the entire manufacturing process, but it's seldom implemented all at once like that. More often, a company picks a certain part of the process to start the ball rolling.

As we mention at the end of Chapter 1, a good place to start is to characterize the raw materials used in the manufacturing of a particular product. The sensors used for PAT can help in this regard. A company takes what it learns from such analysis and applies it to the unit operations that compose the process.

NIR and Raman, along with PSD measurements, are common tools for characterizing raw material attributes. The information gained from different lots, suppliers, and seasons all help in determining the choice of CPPs, so the process can adapt to the changing raw material characteristics.

WARNING

Not all uses of spectroscopic tools such as NIR and Raman are considered PAT. If these tools are used extensively in the QC laboratory — for example, to identify received raw materials — that isn't a PAT operation. When an instrument is used to assess material conformity and processability, only then can it be considered a PAT tool.

CULTURE CHANGE AND THE PAT CHAMPION

Successful implementations of PAT start with a culture change in the organization. Regulatory authorities have given industry a lot of time to get ready for the needed change in mindset, and those who are still lagging behind will find it difficult to compete in the near future.

Some organizations have defined QbD without reference to PAT, or even a complete PQS. This shows that they are not ready, and are trying to box QbD into the traditional ways they feel comfortable with.

QbD and PAT go hand in hand. If this is not the attitude and culture in an organization, then it will be a slow and painful process trying to move forward to meet regulatory expectations with a *cGMPs for the 21st Century* mindset.

The best way to move an organization into the QbD mindset is to create a "PAT champion" position in the organization. The PAT champion's job is to implement PAT tools into commercial manufacturing processes. This should not be a part-time role with the PAT champion doing other roles; it is a full-time position that works closely with QC/QA, technical services, engineering, production, and regulatory affairs to ensure that all aspects of the implementation are communicated clearly, that staff are trained in its usage, and that the technology is written into product submissions as the method of quality assurance.

In the QbD/PAT culture, only the required aspects of traditional developments are incorporated into the QbD submission. All implementations use state-of-the-art, innovative scientific tools and data management systems to ensure that the data collected turns into information and that information turns into business benefits.

Ideally, the CEO should be the main driver for a QbD-based environment because this person has the overall responsibility for the success of the organization. The CEO does not have to understand the intricacies of QbD/PAT, but must appreciate how QbD processes and submissions work. He or she must demonstrate commitment to the new manufacturing approach. Unless an organization has top-level buy-in, QbD/PAT initiatives will crawl along rather than running at full speed.

QbD/PAT initiatives ideally start at the raw material characterization stage and grow from there. This is because the raw material characteristics determine how a blend is premixed, granulated, and milled before the final blend stage is reached. This principle holds equally well for batch, continuous, and biological fermentation processes. The final goal is to reach a holistic PAT implementation using the pharmaceutical quality system (PQS) as its foundation.

WARNING

Some organizations looking to implement PAT try to start with blend uniformity on rotating blenders. They choose that, thinking that it's an easy application, but this approach can backfire on them. That's because blend uniformity cannot be truly assessed and understood in the absence of information about the raw materials and intermediates generated in the previous UOs.

IN THIS CHAPTER

- Understanding cGMPs for the 18th Century versus the 21st Century
- Grasping the paradigm shift
- Looking at regulatory approaches to QbD and PAT
- Understanding the ICH guidance documents
- Applying QbD and PAT to new and existing products
- Understanding the design space/regulator relationship

Chapter 3
Understanding the Regulatory Aspects of QbD/PAT

QbD and PAT have a strong connection to each other that has been defined through guidance provided by regulatory bodies. In this chapter, we tell you about the most important regulatory documents that pertain to QbD/PAT, and we provide some general guidance for applying them to new and existing products.

Understanding cGMPs for the 21st Century

Even though the pharmaceutical industry has produced high quality and effective drug products for many years, outdated quality

practices and the lack of real process understanding have hurt it in many areas. Such problems were highlighted in the FDA's pioneering 2004 document *cGMPs for the 21st Century*. This document was a first step by the FDA toward modernizing pharmaceutical quality regulation, taking it into the 21st Century.

The main points in this document are:

- Encourage new technology adoption (PAT).
- Facilitate development of modern, integrated quality management systems (QMS).
- Encourage risk-based approaches to quality.
- Promote the use of state-of-the-art pharmaceutical science.
- Aim for regulatory oversight consistency through an integrated quality systems orientation.

cGMPs for the 21st Century was a move by the industry from art to science — and it was long overdue. The last time cGMPs were updated before this document was in 1978!

So why has the uptake of modern systems into the industry taken such a long time, when there are countless conferences, webinars, and expert forums preaching the benefits of QbD/PAT? In our experience, cultural resistance to change has been the biggest roadblock.

All regulatory guidance documents begin with a disclaimer that the guidance is only a recommendation containing non-binding principles. They clearly state that the word "should" is intended to be interpreted only as something to be considered, not necessarily implemented. In our opinion, if regulators moved to a "must" approach, industry would make rapid progress toward implementing QbD/PAT. We discuss this in more detail later in the chapter, when looking at the FDA process validation guidance.

REMEMBER

Plenty of guidance documentation and resources are available to help a company implement a QbD/PAT approach, but there is no mystique or magic to the process. It's really just common sense! People working on QbD/PAT projects are typically well-trained scientists and engineers with a solid understanding of their organizations' practices and processes.

Wondering what documents your team should be reviewing on the QbD/PAT journey? These are the important ones:

- *cGMPs for the 21st Century*
- FDA PAT framework guidance
- ICH Q8 to Q12 guidance (discussed in detail later in this chapter)
- FDA process validation guidance
- ASTM E55 guidance documents
- GAMP 5
- Regional documentation of a similar nature

The most important of these is the first one: *cGMPs for the 21st Century*. It is the roadmap document that all organizations implementing QbD/PAT should read first because it describes the motives for all of the supporting guidance.

Grasping the Paradigm Shift

A "*paradigm shift"* is a fundamental change in thinking that alters an individual's or group's approach to a task or situation. This is summed up nicely in *cGMPs for the 21st Century*, which states "Our findings have put the Agency on a path to restructure its oversight of pharmaceutical quality regulation, thereby developing the product quality regulatory system of the future."

That statement confirmed the FDA's commitment to working with organizations to improve their quality practices. The FDA hoped that the proposed best practices would result in less overall effort and less regulatory oversight compared to traditional practices.

Here's another important statement made in the document: "The pharmaceutical industry has reached a crossroad; one path goes towards the desired state and the other maintains the current state. The path towards the desired state is unfamiliar to many while the current state provides the comfort of predictability. The agency hopes the pharmaceutical industry will choose to move towards the desired state." Although this statement was written in 2004, it is still highly relevant today.

Earlier in this chapter we talk about the difference between "should" and "must." In a paradigm shift mindset, organizations looking to implement QbD/PAT take the "must" mindset, and see the recommended changes as essential to success. Consequently, they look for opportunities to adopt PAT and computerized quality systems in order to gain real-time information from a process during all stages of the product life cycle. They then use this information to define a product/process design space, and within this space, they use the available information to move toward the desired state.

WARNING

You can't implement QbD effectively while clinging to the mistakes of the past. QbD is not an approach where organizations can just tweak and re-brand old practices as QbD systems. If your organization isn't fully committed, there is no point.

Looking at Regulatory Approaches to QbD and PAT

The QbD/PAT approach originated with the FDA, under the direction of Dr. Ajaz Hussain. He led the team writing the *cGMPs for the 21st Century* guidance.

The FDA intended industry to use these guiding principles to adopt innovative technology and scientific, risk-based approaches toward drug development and manufacturing. During the early days of QbD (the early 2000s) electronic data management systems and wireless PAT technologies were still in their infancy; the FDA was proactive in promoting their use, publishing the PAT framework guidance of 2004.

Here's an important statement from that PAT framework document of 2004:

The agency is encouraging manufacturers to use the PAT framework to develop and implement effective and efficient innovative approaches in pharmaceutical development, manufacturing and quality assurance.

REMEMBER

As this statement makes clear, PAT is not about bringing the lab to the process to "test quality into a product." Instead, it is about gaining knowledge throughout the entire product life cycle. Such knowledge enables manufacturers to develop

flexible manufacturing systems that can adapt to raw material, in-process material, and process variability within the design space to constantly maintain the desired state.

TIP

Hesitancy is the killer of progress! The FDA has made it clear that it will accept modern and innovative approaches to pharmaceutical manufacturing and development. Save time, money, and effort by understanding your products and implementing proactivity into your processes.

Another important statement from the PAT framework document is this one:

PAT is a system for designing, analyzing, and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality.

As this statement makes clear, PAT is process-centric, not product-centric. In other words, if the process can be assured to be in its design space, then the product quality is assured. That is why the following key points are so important:

- Validation alone is not sufficient to assure product quality. Implementing a QbD/PAT approach enables continuous verification, so that every batch is a validation batch.
- Quality cannot be tested into products; it must be there by design. Post-manufacture testing takes a reactive view of quality. QbD with timely PAT measurements takes a proactive view.

The FDA process validation guidance of 2011 makes clear that the traditional three-batch validation approach is inappropriate moving forward. It is too easily biased to pass a product into the market without a full understanding of the manufacturing process's long-term robustness.

REMEMBER

All processes are perfect! That's a bold statement, but a correct one. It simply means that a process produces exactly what it is designed to produce. If a process generates 5 percent failures per batch, that is how it was designed. It is only doing its job. To have the fewest number of failures, design the process using the best knowledge available.

The PAT framework document lists four key tools for successful QbD/PAT implementations:

- **Multivariate analysis tools** including chemometrics and design of experiments (DoE) tools, for designing robust product/process combinations and developing predictive models to maintain the space defined by the DoE.
- **Process analyzers** such as PAT tools for at-line, in-line, or on-line implementation. These tools provide timely and proven quality information that allow continuous improvement/verification.
- **Process control tools** utilize the outputs of PAT sensors and chemometric models to orchestrate the entire process. Orchestrations use feed-forward/feedback signals that allow modern quality systems to correct for potential deviations and then verify effectiveness of the changes (within the design space). From the PAT framework document: "Process monitoring and control strategies are intended to monitor the state of a process and actively manipulate it to maintain the desired state."
- **Continuous improvement and knowledge management tools** provide the basis for learning. Data without analysis provides no information. A PAT knowledge management system offers an organized repository of the process's history. Mining this repository and utilizing the experience gained through the QbD/PAT approach makes continuous improvement possible.

Implementing PAT in real manufacturing systems can generate the most relevant information. The following statement in the PAT framework advocates for risk analysis being used when testing PAT:

For an organization evaluating experimental on- or inline process analyzers during production, it is recommended that risk analysis of the impact on product quality be conducted before installation. This can be accomplished within the facility's quality system without notification to the agency.

What about the rest of the world? *cGMPs for the 21st Century* identified that European Union (EU) GMPs and Pharmaceutical Inspection Cooperation Scheme (PIC/S) were virtually identical in base requirements.

QbD/PAT does not aim to make new regulations or change existing ones. Instead it aims to use enhanced knowledge to better ensure quality products using scientific methods. Therefore, consensus has been reached that harmonization between the regions can be achieved. The International Conference on Harmonization (ICH) has released a number of guidance documents further supporting QbD/PAT's global adoption. We discuss those guidance documents in the next section.

Understanding the ICH Guidance Documents

At the time of this writing, four main International Conference on Harmonization (ICH) guidance documents have been released, and a new one is in draft. They are:

- ICH Q8: Pharmaceutical Development
- ICH Q9: Quality Risk Management
- ICH Q10: Pharmaceutical Quality System
- ICH Q11: Development and Manufacture of Drug Substances
- ICH Q12 (Draft): Lifecycle Management

Figure 3-1 provides an overview of the relationships among the ICH QbD/PAT documents. It follows the general path of how a QbD/PAT implementation should proceed:

Define→Design→Understand→Implement→Improve

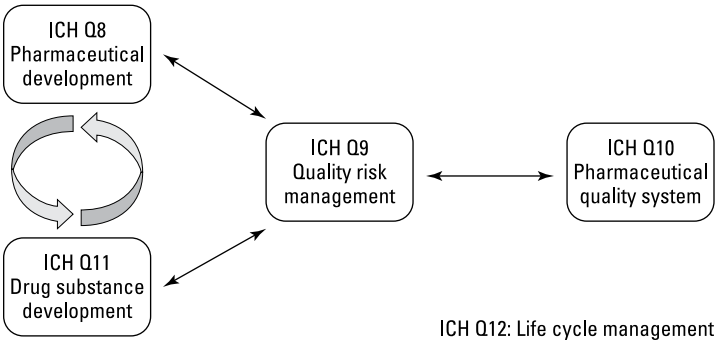


FIGURE 3-1: The steps in a QbD/PAT implementation.

Here's a closer look at each of those parts:

- ICH Q8 and Q11 set out the path toward effective drug substance and drug product development. These two documents are used together to assess compatibility of a drug substance with its formulation and its manufacturing process.
- ICH Q9 is used in conjunction with ICH Q8 and Q11 to assess the importance of critical quality attributes (CQAs) and their relationships to critical process parameters (CPPs).
- ICH Q10 aims to define a control strategy and a risk-based quality system to keep the CQAs and CPPs within the design space and maintain the desired state. ICH Q10 is used in conjunction with ICH Q8, Q9, and Q11 to implement continuous improvement strategies and mitigate the risk any such strategies may have on product quality.
- ICH Q12 is a draft intended to provide guidance for maintaining or changing the nature of a design space after it has been initially approved.

Applying QbD and PAT to New and Existing Products

The regulatory agencies have provided a path forward for moving pharmaceutical development and manufacturing from an art to a science. The FDA and other agencies have stated that manufacturers may implement alternative approaches as long as they satisfy the applicable statutes and regulations. In other words, the QbD approach does not replace or remove the requirements of cGMPs on industry. QbD/PAT is simply the best approach to meeting these requirements. For those not implementing a QbD/PAT approach, efficiency, and quality will suffer in the long run.

In its process validation guidance of 2011, the FDA stated that all new submissions to the agency will be done using a QbD approach. This statement applies to new submissions as well as legacy products and processes. In particular, cGMPs for the 21st Century states:

Process changes with critical variables that have not been sufficiently defined (e.g. processes for many older products) may require the submission of additional data or comparability protocols.

Understanding the Design Space/Regulator Relationship

A regulator cannot tell you how to make your product, therefore a design space is best defined by the applicant, who fully understands the product and its manufacturing process. The amount of regulatory oversight required depends on the product type, and the demonstrated degree of product/process understanding.

The design space's complexity depends on a number of key points:

- **The risk to the end-user:** The manufacture of high therapeutic index (TI) products, or products that may degrade into toxic related substances, requires a higher level of monitoring and control compared to over-the-counter (OTC) and similar low-risk drugs.
- **Whether the control strategy is local or holistic:** Holistic PAT systems (such as those for continuous manufacturing systems (CMS)) require several unit operations to connect, forming one steady state process environment through the incorporation of a process orchestrator such as synTQ.
- **The level of monitoring and control:** Implementation of early event detection (EED) strategies that will prevent an issue from occurring in the first place are preferred.

When a manufacturer submits a design space to a regulator, it is the quality of information submitted that is important, not the quantity. In some cases, much data and information is required to justify the submission, but if something can be said concisely, it should be.

Looking at a Regulatory Documentation Roadmap

Figure 3-2 provides a roadmap you can use to navigate through the regulatory guidance for a successful QbD/PAT implementation.

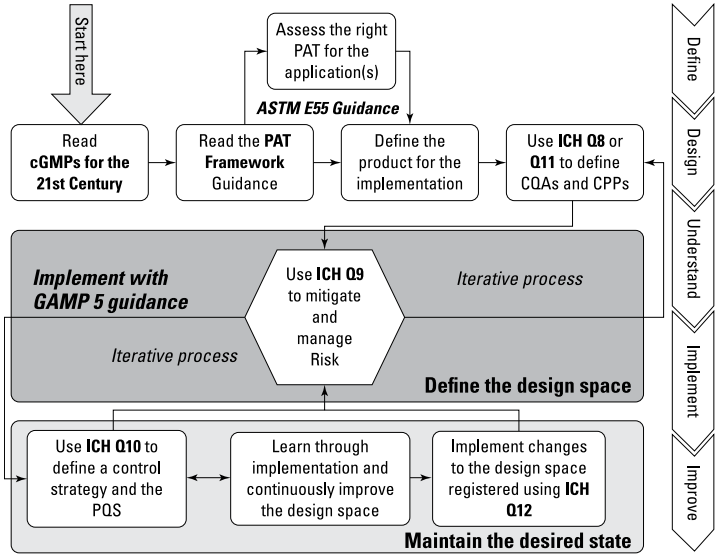


FIGURE 3-2: Mapping your way to a successful QbD/PAT implementation.

Here's a brief summary of the process:

1. Understand the premise and motivation for the QbD/PAT initiative before you start.
2. Use the right PAT tools for the application.
3. Define the drug substance/drug product formulation CQAs, and relate them to CPPs and material attributes.
4. Use ICH Q9 to prioritize the CQAs and CPPs.
5. Use ICH Q10 to define the control strategy. Qualify the integrated system using the principles of GAMP5.
6. Learn from the implementation.
7. Use ICH Q12 to implement changes to the design space, post-approval, using knowledge gained from the QbD/PAT implementation.

IN THIS CHAPTER

- Understanding the skill sets needed
- Starting a QbD/PAT project
- Planning project time and cost
- Estimating the return on investment (ROI)
- Implementing QbD without PAT
- Choosing the right tools
- Reviewing a roadmap

Chapter 4
Learning the QbD/PAT Process

How do you eat an elephant? One bite at a time. It's the same with any big and intimidating job, including implementing QbD and PAT. You have to start somewhere. In this chapter, we help you understand the process from start to finish. We explain how to gather your team, plan and estimate, and choose the right tools, and provide a roadmap that guides you through each step.

Understanding the QbD/PAT Skill Sets

For any project to succeed, in any industry, subject matter expertise is an absolute requirement. You need people who are thoroughly familiar with both the product and the process. That's true for a QbD/PAT project, of course, but the most important skill to acquire for QbD/PAT implementation is a paradigm shift in the way you approach the project. QbD/PAT does not necessitate any new rules or regulations outside of current GMP requirements. It is just a more efficient and enhanced way of doing things that avoids the pitfalls of the traditional approach.

REMEMBER

Regulatory agencies are not interested in change for change's sake. If your manufacturing processes were perfect in the first place, there would be no need to improve them. QbD/PAT is the current best practice for avoiding reoccurring process issues as set forth by the FDA and other regulatory agencies, as explained in Chapter 3. The QbD initiative is here to stay; manufacturers have to change accordingly or fall behind and no longer be competitive.

So what skills are needed to move to QbD/PAT? Here's a summary list of what's required for that paradigm shift, in terms of both managerial and scientific/engineering expertise:

- Persuasive and pragmatic leadership to change cultures and challenge the current way of doing things.
- A scientific/engineering approach to pharmaceutical development, rather than treating it as an art.
- A strong background in statistics, particularly multivariate statistics (chemometrics), design of experiments (DoE), and statistical process control (SPC).
- A solid understanding of process spectroscopy (and other sensor technology) and its implementation into process streams.
- A strong background in control systems and control script writing.
- High-level analytical and sampling expertise.
- A strong understanding of the regulatory framework put in place for the implementation of QbD/PAT.

TIP

These skill sets do not have to reside in one person. However, collectively the QbD/PAT team should have all these skills available, and preferably each individual should have expertise in two or more of the skill sets.

Starting a QbD/PAT Project

Ideally, QbD/PAT should start from Day 1 during drug development, formulation, and process development. But what if all of that is already going on? Where do you jump into the process stream with this new approach?

We suggest finding the most troublesome (and economically viable) process and starting a legacy QbD/PAT initiative on that process. Go for "low-hanging fruit" as the first project, the one that obviously needs to be improved. Don't start with the "glory" project, the biggest and brightest one, because if the attempt fails or stalls, senior management is more likely to scrutinize the attempt.

In our experience, most organizations implementing PAT start with the blending or mixing operations in solid dose manufacture. Biological systems PAT is still in its infancy, but already showing significant gains in upstream processing. Batch monitoring is the biggest area in which PAT starts for biologics. The reason blending is a favored first step (to the best of our understanding), is that such a PAT implementation is tangible, highly visible, may not require MVA modelling, and so provides a pathway that feels more comfortable.

Conceptually, quality is determined by how the selected process transforms raw materials into the desired state of the product. The final product quality is a function of how well the process adapts to changing raw and in-process material variability. This is not a linear function, but a function within a function:

$$Quality = f\left(Process\left(Materials\right)\right)$$

WARNING

As we point out in Chapters 1 and 2, ideally QbD/PAT starts with an understanding of raw materials. Raw material and in-process material variability determines the control strategy. Products are the result of raw/in-process materials transformed by a process. How the process adapts to minimize variability is dependent on the inherent variability of the materials. Understand raw and in-process material variability before trying to optimize the downstream processes.

Only when you have performed a complete study of raw material variability (lot-to-lot, season-to-season, and supplier-to-supplier) can the next phase begin, in which you consider operator-to-operator and shift-to-shift variability for in-process materials.

From there, unit operation design and understanding begins, with the overall goal of turning all unit operation understanding into a holistic PAT model. This approach is valid for both batch and continuous manufacturing approaches.

Estimating Project Time and Cost

The time required to implement PAT is dependent solely on the answer to one question: *Does your company's culture support the QbD/PAT approach with 100 percent commitment?*

If the answer to this question is no, then *stop*. Your organization is not ready, because you don't have the understanding and support of the key players. Trying to continue will only result in frustration.

If the answer is yes, then the time required to complete a simple implementation should be in the three-to-six-month range. For a complex, holistic PAT implementation, you're looking at 12 to 24 months. These are only rough estimates, of course, and do not take into account the unexpected.

The cost of implementation depends upon these factors:

- The new PAT infrastructure including sensors, IT and changes to legacy infrastructure
- Any new processing hardware requirements
- The cost of labor and raw materials
- Whether or not procrastination plays a part

As with schedule, the cost is affected by the corporate culture. For a successful implementation, there must be top-level commitment to see the project through, and the project team must have the resources it needs.

Estimating the ROI

It is difficult to get true ROI figures from the many companies that have successfully implemented PAT in their manufacturing processes. Companies can be cagey about sharing such financial data with the public. However, it is telling that most PAT adopters continue to expand its usage. That means they must be gaining tangible benefits.

The ROI figures for *your* process will depend on your process type, the value of the raw materials, the amount of wasted product from

a non-PAT enabled process, the scale-up time from laboratory to manufacturing, and many other variables that we can only touch on in this section. The following are a few high-level key points that can deliver a significant ROI.

Shorter scale-up time

Shortening the time in pilot plants and translating to a commercial processing line faster results in capitalization of critical production time before the patent expires. New patented products have the potential to deliver a huge annual value, so if you can bring a product to market even six months earlier, then the consumers/patients, your patent life, and your bottom line all benefit!

Material usage during scale-up and development

QbD/PAT can potentially reduce raw material usage during scale-up, for three reasons:

- Enhanced knowledge makes the scale-up phase faster, by utilizing the benefits of DoE compared to traditional methods.
- Using PAT in continuous manufacturing typically means there is no scale-up time or raw material waste during process development.
- Less downtime results in less labor and raw material requirements.

Material waste

As we discuss in Chapter 1, traditional manufacturing techniques "test quality into the product" after the manufacturing stage. In traditional manufacturing, waste is considered unavoidable and factored into the cost of manufacturing. This is where PAT has the capability to greatly reduce waste through non-destructive analysis.

QC testing to automated QA

Unnecessary quality control (QC) testing can account for a large part of a product's manufacturing cost. To perform such quality

analysis automatically in real time, and to adjust the process accordingly to minimize variability, lowers QC costs significantly, and this cost saving can potentially increase over time as continuous improvement is embraced.

Work in progress and productivity

Depending on the value of your product, work in progress (WIP) value and cost can be huge. By employing PAT, you can greatly reduce the level of WIP by an order of magnitude or more.


EXAMPLE

For example, consider a solid dose drug being manufactured in a batch process with an average processing time of around 30 hours. When physical samples require offline QC lab testing, the process is more like 30 days! By employing PAT, you can reduce the time from raw materials to finished goods to much nearer the target of 90 minutes (continuous) or 30 hours (batch). That puts the time to manufacture about 30-500 times faster, with a WIP at 0.2 percent of what it was!

That isn't an isolated example; results like that are typical. In addition, some processes show significant increases in yields, which not only improve productivity, but also manufacturing capacity. In the biotech industry, some PAT users are reporting threefold increases in productivity. This type of improvement will certainly translate across to other process industries.

Batch to continuous

As we mention briefly in the preceding section, PAT can potentially enable a move from batch manufacturing to continuous manufacturing that otherwise would not have been possible. This move can provide huge benefits in addition to the dramatic increase in productivity and reduction of WIP. Some companies have made improvements in floor space (up to 90 percent reductions have been reported) and energy usage (40 percent reductions reported). In addition, some chemical manufacturing processes have shown a lower cost for starting raw materials and a reduction in staffing — not only in the areas of QC/QA but in the overall process.

Each case is different; however, ROIs are usually achieved in a short timeframe, typically less than one year, because quality is being built into the product, not tested into it.

EXAMPLE

Here's another example to consider. A company implemented near infrared (NIR) spectroscopy into a fluid bed drier (FBD). This process change allowed the company to reduce product rework through enhanced process understanding. The product was consistently dried to its desired state, and moved to the next unit operation more quickly, enabling production of four extra batches of product per month through better overall equipment efficiency (OEE). The company's initial investment of $250,000 into PAT (including validation and regulatory submission) was recouped in only one month.

REMEMBER

Regulatory authorities don't care how much it costs you to make safe and efficacious products. Their only concern is public safety. If the only goal of implementing PAT is to save money, then your motivation is completely wrong. That said, PAT provides better product and process understanding, which enables you to continuously improve quality and reduce costs to a far greater degree than just cutting corners or staff.

Implementing QbD without PAT

It is theoretically possible to implement QbD without PAT, but we don't recommend it. Doing so would be very difficult for all but the simplest product/process combinations. Here's why.

Chapter 1 explains that the purpose of QbD is to establish a design space. As Chapter 3 shows, ICH Q8 defines a design space as:

The multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality.

Keeping in mind that regulatory agencies want to see continuous verification strategies, a QbD approach without PAT would require a *lot* of sampling (which would typically not be performed in a representative manner) to assure that the process remains within the design space. This traditional form of sampling and testing is reactive, not proactive.

ICH guidance and *cGMPs for the 21st Century* are clear in recommending that PAT be a part of any QbD initiative.

TIP

If you want to implement QbD but are scared of the technology, perhaps because you don't have the needed skill sets in your current workforce, you can easily contract with a company that will come in and do it for you.

Choosing the Right Tools

The old saying "Choose the right tool for the job" holds true for QbD/PAT implementations. Here's an overview of the common tools available to the PAT practitioner:

- The PAT knowledge manager (PAT KM), which we discuss in detail in Chapter 5
- Advanced statistical software for univariate, multivariate, and design of experiments (DoE) analyses
- Process vibrational spectroscopy, including
  - Near infrared (NIR) spectroscopy for solid dose blending, mid-low moisture formulation monitoring, and raw material characterization
  - Raman spectroscopy for bio-fermentation and chemical reactors, polymorphic monitoring, and some difficult-to-measure solid dose formulations
  - Mid-infrared (MIR) for chemical reaction monitoring and some biological applications
- In-line particle size distribution analyzers for milling operations critical to blending and drying
- Process ultraviolet and visible (UV-Vis) spectroscopy for chemical reaction monitoring or cleaning validation
- Univariate sensor combinations, including temperature, pH, CO_2, pO_2, conductivity, and other sensors used singly or in combination for enhanced process monitoring.

WARNING

Putting three NIR/Raman sensors (or any sensor) into a single vessel will not necessarily give you better information. They are all still considered "grab samples" and are not representative. Instead, put more time and effort into correct sampling practices. You will ultimately find that grouping different analyzer types at one point will provide more information and better correspondence with collected samples than multiple grab

sampling points. Refer to the Theory of Sampling (TOS) for more details (www.kheconsult.com/).

Your ability to successfully implement the correct PAT tools is dependent upon your subject matter experts' levels of skill. If you have a good working relationship with vendors who have hands-on expertise available in their organizations, you might be able to tap into their knowledge pool. Of course, as the GAMP 5 guidance suggests, you should leverage vendor expertise and documentation only if you can be sure that those you rely on have the relevant knowledge.

Reviewing a Roadmap

The following roadmap is intended to be a high-level overview of what a QbD/PAT implementation could look like for any generic process:

1. Decide that you want to go on a QbD/PAT journey, and get 100 percent buy-in from all critical decision-makers and influencers in your organization.
2. Decide on the first target process. Choose a relatively simple process that can provide product quality benefits and a reasonable ROI. Try to find a "low-hanging fruit" candidate product or process, and do not start with anything complex. Consider starting with raw materials.
3. Assemble all the skills necessary. They could all come from internal people, but if this is your first PAT project, consider using external SMEs to assist and provide you with "on the job" training. You may not need them the second time around!
4. Double-check that all team members are on board with your vision, and make the objectives and time frame clear. Ensure that your team includes at least one member who is practical and pragmatic with the necessary authority to drive the project forward.
5. Using the team members and possibly key vendors as well, select and install the fit for purpose tools including these:
   - PAT tools — spectroscopic and univariate
   - The PAT knowledge manager (PAT KM)

- The MVA and DoE packages
- One or more control systems with human machine interfaces (HMIs) for process output display
- The IT infrastructure that connects all this equipment together, and maybe to your corporate network

6. With everything in place, start your PAT journey by developing process models:
   a. Build models using your PAT KM, DoE, and MVA packages.
   b. Test, refine, and validate your models, as fit for purpose, *not* the ultimate models. Those will come later!
7. Through model utilization, gain better insights into the process.


TIP

Some PAT projects "rest" at the prediction phase for a while before moving on to closed-loop control.

8. Using the process and product knowledge, implement PAT-based process control.
9. When the system is being used in production utilize continuous improvement, and periodically improve the process in terms of prediction and control. Continue improving the process until there are no more gains to be made.
10. Celebrate! You now have the knowledge and skills to roll this technology out throughout your organization.

IN THIS CHAPTER

- Understanding what a PAT knowledge manager does
- Reviewing the data types that PAT systems manage
- Considering product tracking challenges
- Understanding the PAT process with a knowledge manager

Chapter 5
Why You Need a PAT Knowledge Manager

When you first embark on a PAT project, you might not immediately see the need for a PAT knowledge manager (KM) software package. You might be thinking you can save some money by either not using any KM at all, or by building a bespoke KM. Let's get this out of the way right now: *It's a terrible idea*. Trying to implement PAT without a KM is like asking your accounting department to do its work in paper ledgers rather than on computers, and creating a bespoke KM is like asking the same department to build and maintain its own accounting system. If you don't see that now, it will become more and more apparent each day as the project develops. In this chapter, we explain the role of knowledge management in the overall QbD/PAT process and show you why a high-quality KM system is a must.

Understanding What a PAT Knowledge Manager Does

Process Analytical Technology: *It's complicated*. And then some. PAT KM systems perform many important functions, including managing connectivity, enabling you to build and run

orchestrations, collecting data, turning data into knowledge, enabling you to control the process based on product quality, and facilitating continuous improvement. The following sections look at each of these in more detail.

Managing connectivity

One reason PAT gets so complicated is that it connects and affects many different systems that were previously separate, such as:

- Univariate data producers and consumers such as control systems and historians
- Spectral and multi-array instruments
- Multivariate analysis (MVA) software packages
- Prediction engines (associated with MVA packages)
- Laboratory information management systems (LIMS)

A PAT system typically has at least one spectral type instrument, but not always; it could function purely using multiple univariate data sources (such as temperature, pH, CO_2, agitator speed, and so on). However, a PAT system based purely on univariate data is rare.

The disparate systems associated with a process all consume and produce different data types and data sets in different ways, at different rates, and transfer it to the PAT KM using different communications methods and standards.

Then there are equipment differences because many different types of each technology exist. For example, many vendors offer instruments like near infrared (NIR), Raman, and UV-Vis. There are also many vendors of MVA packages, LIMS, control systems, historians, and so on, each with its own data and communication requirements. Often a PAT system will have many of these systems, and so the number of possible combinations of languages, data, technologies, and interfaces is nearly infinite.

For a PAT system to function effectively in a QbD environment, all of the systems must collaborate in a timely manner. The KM interprets each communication protocol, gathers all data, and makes the quality predictions. The PAT KM can then use process and control models to maintain the design space and desired state.

Building orchestrations

One of the most important functions of a PAT KM is to help set up PAT methods — often called *orchestrations*. These orchestrations control data flow, which consists of data collection, collation, and coordination, plus the required logic, math functions, quality predictions, and control actions to be executed within the orchestration. Orchestrations also dictate what and how data is output, either for process control, a third- party database, or local data storage. The PAT system must be able to run many of these orchestrations concurrently, in real time, and they must be simple to set up and easily maintained in a GMP manner (for more on that, refer to the section on ICH Q10 in Chapter 3).

REMEMBER

Simple setup is important because of the way PAT systems are developed. Scientists and engineers are intimately involved in the development of PAT systems, and the process is far more straightforward and maintainable if these orchestrations can be developed and maintained by these scientists, rather than having to call in software engineers whenever they need something changed.

Collecting data

Not all QbD/PAT implementations are subject to strict regulatory control, but many are, and those that aren't heavily regulated are still subject to ever-increasing quality assurance requirements. A PAT KM can provide traceability for all data gathered and derived, while maintaining full data integrity.

Even the smallest PAT system makes quality predictions. Most of the larger, holistic systems are completely controlled by PAT KMs, including their multiple quality and process control functions. By storing collected and derived process data in a structured environment, not only will you have better access to data for gaining product and process knowledge, but there will also be more confidence and less scrutiny when audited by regulatory authorities. Traceability, regulatory compliance, and data integrity are essential in a PAT KM. Some of the data storage requirements are:

- Identification of the instrumentation used to collect data
- Each instrument's calibration status and configuration

- Reference data from selected samples and the analysis method
- Identification of who generated reference data/models
- Data used to build and validate a model, including preprocessing methods and excluded samples
- All raw data
- All derived data
- What orchestrations, calibration, and control models were used
- All electronic signature and audit trail data
- All meta data

The auditor will likely want to see all the data gathered during the model building phase as well as during the production runs. Without the data, the provenance of the models cannot be determined.


TIP

Normally more data must be generated for regulatory and/or quality reasons than for process control reasons. The regulatory requirements can drive the design of the PAT system, and so you should engage the regulators early in the PAT design phase to avoid having to redesign later to gather more information.

Turning data into knowledge

So far, we have only talked about data collection. However, *knowledge management*, the conversion of data into information, is fundamental to a PAT system. This is a key function of a PAT KM. QbD/PAT systems are based on using representative data collection and sound, scientifically based knowledge. Together these provide confidence to regulatory authorities that you understand your process! (Refer to ICH Q8/11 and Q10, covered in Chapter 3.)

Empirical information generated during experimentation with your process, where the changes in CQAs as a result of perturbated CPPs, allows the knowledge management cycle to begin. This learning does not stop after the initial experimentation phase, but should continue during the manufacturing phase using continuous improvement strategies.

EXAMPLE

For example, in a fluidized bed dryer (FBD), your CQAs might be moisture content and particle size distribution (for more on this example, see Chapter 2). You might therefore conduct an experiment where you vary inlet temperature and airflow to understand the relationships between these input control variables (CPPs) and the output — the CQAs.

Of course, this assumes that you know your CQAs and your CPPs. These are often known, or at least *thought* to be known, but there will be occasions where more CQAs must be introduced into the process over time to get a full understanding. There might also be cases where a CQA or CPP turns out to *not* be critical and can be removed using a quality risk management approach.

So, back to our FBD. You might develop what you believe to be a full understanding of all the variables, but perhaps later in the year the control actions no longer seem to produce as good a quality product as they previously did. By reviewing the historical data stored in your PAT KM, you might notice that another variable (such as inlet humidity, which may vary with season) also has a significant effect on the final product quality. At that point, you would need to extend the design space to incorporate this new CPP.

REMEMBER

Keep in mind that extending existing design spaces after they have been submitted for regulatory approval is covered under the new ICH Q12 guidance on lifecycle management. For more information, turn to Chapter 3.

TIP

Use your PAT KM to store *all* data. Data storage is inexpensive compared to the cost of time and raw materials required to repeat an experiment. If you discover that another CQA or CPP is required in your process, then you might be able to develop the necessary knowledge and new model using historical data and key associated functionality in your PAT KM.

For such experiments to be possible, you need three fundamental software systems:

- A DoE package for effective experimental design strategy
- A multivariate modeling software package that calibrates your spectral instruments
- A PAT KM for enabling the building of knowledge, and subsequently putting this knowledge and the models into practice

You need all three if you are to establish an effective QbD/PAT system.

Enhancing control

A key difference between a traditional control regime and an enhanced PAT-based control regime (ICH Q10) is that with a PAT based system you proactively control the process in a timely manner using risk-based, scientifically valid methods, and only using information that is known to be important. Although both approaches *may* control the same process parameters, the *way* in which you control them is different. Think of an orchestra's instruments all playing notes at random, versus the same orchestra working as one to play a beautiful piece of classical music. In both examples, the orchestra is playing the same notes. The difference is that in the second example they are being played with coordination and strategy.

REMEMBER

The PAT KM in your process is the "conductor" of your beautiful PAT orchestrations!

In traditional approaches, manufacturers have controlled the process parameters based on a fixed recipe with process parameter setpoints. In a PAT process, we still have a recipe, but the process parameters can be modified within controlled boundaries by the PAT KM for the duration of the process.

Figures 5-1 and 5-2 compare the traditional fixed-setpoint approach, which is limited and does not consider the effects of other process variables, to the enhanced QbD/PAT approach, which takes all effects and interactions into account in accordance with the definition of design space in ICH Q8.

If your system is using the enhanced PAT-based control, then you might adjust the starting process setpoints slightly in relation to the quality of the input materials. The process then starts. The product quality is continuously measured and the process parameters adjusted to either maintain the desired state as a constant (continuous process) or to move toward an ideal profile (batch process), so that the finished product quality is exactly as required.

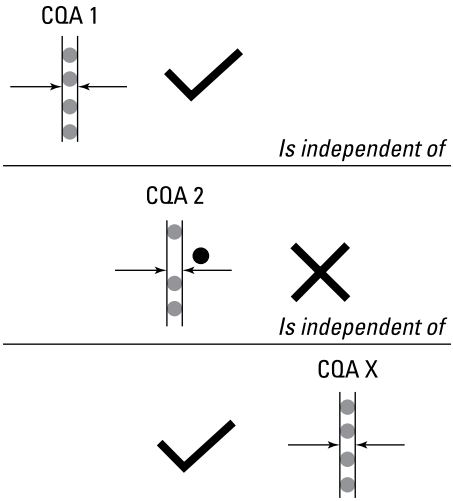


FIGURE 5-1: The traditional approach: one variable at a time (OVAT).

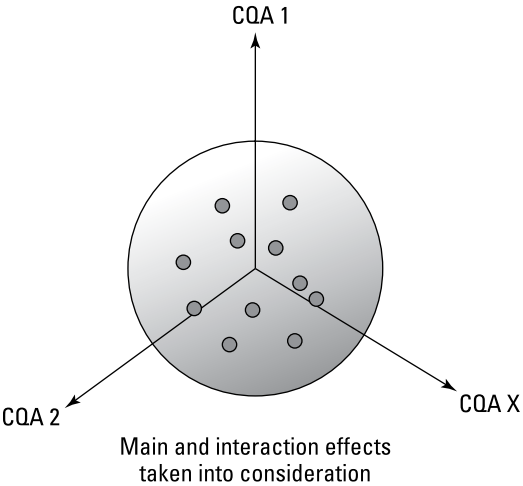


FIGURE 5-2: The enhanced approach: multivariate design space.

No matter whether you are looking at a batch or continuous process, and no matter whether you are using PAT-based true automated control or PAT control using a human operator, it isn't possible to develop the necessary control algorithms without developing the process knowledge we just described. If you understand the process mechanisms, you can develop control algorithms that specify the CPP changes necessary to either

maintain CQA values at their desired state, or move the quality value toward a desired time-based profile.

In some systems, the full control may be embedded within your PAT KM. However, it's more common for the control to be a math function embedded within the PAT KM that requests that setpoint changes be made. The required process changes could then be made either by the automated system or, in the case of a manual system, by an operator. However, in both cases a PAT KM is a fundamental tool for enabling PAT.

Summing it up

We've thrown a lot of information at you in the last few pages, so let's do a quick review. A PAT KM is a software package that can

- Communicate with multiple univariate and multivariate data sources and consumers in real time.
- Streamline MVA calibration model building.
- Make the necessary number of quality predictions in real time.
- Provide users with all the information they need to develop process knowledge.
- Provide a simple way to create orchestrations (PAT methods).
- Store all data in a secure and regulatory compliant way.
- Enable PAT-based process control.
- Facilitate continuous improvement.

Reviewing the Data Types that PAT Systems Manage

At the beginning of this chapter we mention that PAT systems handle a lot of data, from multiple sources. The following sections examine several types of data in greater detail and explain how the PAT KM works with it.

Receiving data input

Data management in a PAT KM is a big issue because potentially large amounts of data are brought into the system at different rates and from different sources. The system must store all this

raw data, without loss, not only for immediate use, but also for future reporting. Data reports might be needed at any time for regulatory, quality, development, or process improvement reasons.

Data input can come from virtually any source, as summarized in Figure 5-3.

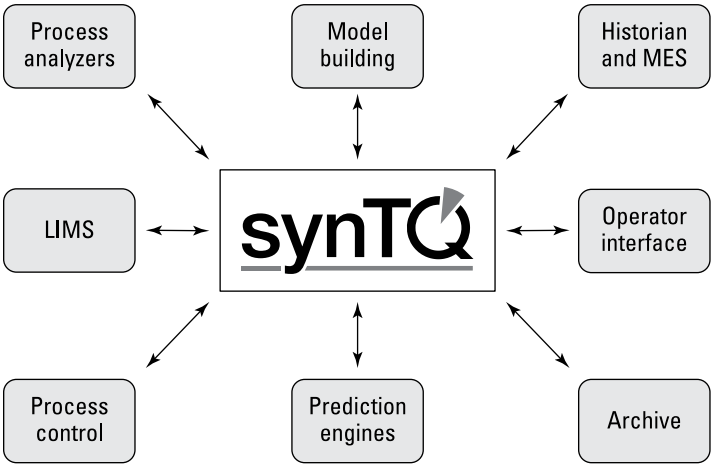


FIGURE 5-3: The PAT KM connection requirements.

All this data must be timestamped, which raises an additional set of issues. While most data are acquired in real time and time stamped accordingly, a system might sometimes receive time-shifted data, and it must understand how to store and process it. With time-shifted data, the data acquisition took place at some earlier time, such as information from a gas chromatograph (GC), high pressure liquid chromatograph (HPLC), laboratory information system (LIMS) and possibly a third-party database.

Generating and managing derived data

Derived data is generated from inside your PAT KM by performing calculations using math scripts or multivariate models. Predictions can come from single inputs or the complex combination of multiple spectral and univariate instruments feeding into one model. A single model may output one or multiple quality predictions.

In addition to quality predictions, there are many other important derived data values to be generated and stored, depending on your application.

Examples include:

- Aggregated and averaged data sets (such as per unit dose, or in the case of continuous processes, mass identifiers (MIDs)). See the section "Considering product tracking challenges" later in this chapter for more on MIDs.
- Predicted values based on a compounding function of other predicted values (such as dissolution).
- Tracking and residence time distribution (RTD) functions (in a tracked application).
- Instrument-specific quality data (such as when to calibrate/re-reference).
- Quality based process setpoint changes or process control values.

There will also be alarm and event data, audit trail data, and all of the associated metadata. That's a lot of derived data! And all of it must be stored, without loss, in a compliant way that maintains data integrity.

Exporting and reporting on data

There are two principal types of data output from a PAT KM: real-time data that is written out of the system during runtime, and transactional data that is written out after its storage, as part of a data query. Both types of data output may be univariate, multivariate, or string.

In addition to the process and product data gathered and generated within the system, there are also all the associated alarms and events, audit trails, and meta data. It must be possible to output and report on all this data.

When the data is output, where does it go? Some of it might get printed, but it may also need to go to any number of places, including into third-party systems. Consequently, a PAT KM must be able to convert the output into file formats suitable for use in a wide variety of external systems. Having options is essential.

Considering product tracking challenges

Continuous processing technology offers many advantages over batch technology, not the least of which is the potential for significantly increased profitability. However, continuous processing technology brings with it a new requirement: product tracking.

From a regulatory and quality perspective, product tracking is essential. You absolutely *must* know the composition of each sub-batch in relation to the starting raw material lots, at any given timepoint. Additionally, each sub-batch must have a full and detailed data set associated with it. Such extensive data can only be gathered via product tracking.

Using sub-batches

Notice in the preceding section that we mention *sub-batches*. Your continuous process will likely run for many hours, if not many days, so the output will probably be broken into sub-batches. You can tailor the size of each sub-batch to suit your process and requirements, provided it complies with the regulator's requirements. For example, the requirements might dictate *"a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits."* Even if your process does not have to comply with regulatory requirements, you will still want to track the product for the same reasons regulators do. Tracking will also enable you to better manage any product recall events if issues are found with the raw materials after production.

Using mass identifiers (MIDs)

Product tracking in a continuous process can be complex and difficult to understand because the product is usually in a state of dynamic flux. An amount of inter-mixing often occurs during the processing. Unless you have true, total plug flow (where one "micro batch" never comes in contact with another "micro batch"), all tracking is based on probability. You are attempting to track product through the process to the highest level of probability you can achieve. Therefore, all tracking must be based on formulas that come from experiments conducted on the actual equipment being used, with the actual product that is being processed. (This is known as *empirical modeling.*) You may find that

one product flows through the process in a similar way to another, but similar is not good enough. To be sure, you need to use the actual target product.

One way of tracking the product is to break the material flow down into small chunks, often called *mass identifiers (MIDs)*. These MIDs can be quite large (for example, three minutes of production), and can be measured in terms of either time or mass. However, for productivity, it could be advantageous to limit the size of MIDs to a handful of seconds of production. By reducing the size of an MID, you reject less in the event of a short quality deviation.

At a theoretical level, MIDs must move through the process in a steady state, right? After all, this is a continuous process. However, when you examine them on a unit operation basis, you find that the flow rates are not necessarily constant.


EXAMPLE

For example, the flow rate through a screw blender might be constant at any given rotary speed with a constant feed input, but this same mass flow is anything but constant when it is handled by, for example, a semi-continuous fluidized bed dryer. In the drying process, multiple MIDs can become mixed and can exit the dryer at a different rate than they entered. As a result, your tracking system must take into account the flow rate through each unit operation. It might be necessary to break unit operations into sub-sections and track the movement through each.

Being aware of mixing

Unless the process is plug flow, the rate of intermixing between MIDs depends on the unit operation type and the residence time distribution (RTD). The movement and RTD functions can be determined only through empirical studies, and the tracking system must use a model generated from this empirical data. The RTD models will then predict the amount of intermixing between the MIDs.

You must know the rate and level of mixing for several reasons:

- Product rejection
- The percentage of raw material lots in finished sub-batches
- Re-calculation of CQA values

If you ever need to reject some product from the system, you must track the associated MID from the detection point to the rejection point so that it is removed from the system. MIDs on either side of the originally rejected MID might also have to be rejected, the number of MIDs being dependent on the level of intermixing.

As we've explained here, tracking product in a continuous process is essential, no matter what the industry sector is (for example, pharmaceutical, chemical, or food). Tracking product is complex to achieve and is dependent on the capabilities of the PAT KM, but, more importantly, it is dependent on client-executed experiments that provide the key algorithms for flow rates and RTD used in the tracking system.

Understanding the PAT Journey with a PAT KM

The work that a PAT knowledge manager assists you with can be summarized neatly in three words:

- *Measure*: Representative data collection, analysis, and modeling
- *Understand:* Through the implementation of developed models
- *Control*: Model utilization to maintain the desired state

A PAT KM makes this three-step process possible — to execute all three steps manually would be virtually impossible!

The following sections outline a general procedure for achieving a QbD/PAT QMS.

Step 1 – Build calibration models

The first step is to collect the data you need. This data will be used to generate the quality prediction models for the PAT system. These models are often referred to as *calibration models* because they effectively calibrate the spectral and/or other data types to give you real-time quality predictions. They are also sometimes called *process models*.

Using the correct technology and performing representative sampling should result in effective calibration models. If either of those factors is lacking, the resulting models will be unreliable.

Placing a sensor (univariate or multivariate) into a process does not guarantee that the data generated will contain useful information. You should follow the methodology outlined in the Theory of Sampling (TOS), which will help you determine the best locations for PAT sensors and explain how to evaluate the extent to which the data the PAT sensors generate is representative. TOS is outside of the scope of this book, but you will want to explore it on your own. One good resource to get you started is `www.kheconsult.com/`.

Model development can begin once the following have been implemented:

- The right PAT tools have been chosen for the application and all sampling issues have been addressed and understood.
- Using risk-assessment, the initial CPPs and CQAs have been defined.
- Your PAT-KM is installed into your test or manufacturing environment.
- You have the necessary data analysis tools and staff available to develop models and implement them into the PAT KM.

Reliable predictive models are the result of representative data collection and valid reference analyses. If one is lacking, the model is not robust. A great deal of upfront effort is required at this stage.

When you have completed all those prerequisite steps, you're ready to begin modeling. DoE can be employed to design a set of experiments that span the largest space of the process conditions, within the expected boundaries of failure. The objective is to maximize the amount of information gathered from the minimum number of experiments. You need sufficient data points to enable not only model building, but also model validation.

During the running of the experimental trials, use your PAT KM to trigger and track product samples as close as physically possible to the data acquisition point. Both quantitative (predictive) and

qualitative (class) models can be developed to predict the composition or state of the product as it exists in the process.

WARNING

The correct alignment of process data and reference analysis is essential. If the database location is wrong, then the prediction results will be based on incorrect data and will be meaningless.

With the reference results added back into your PAT KM, the database now contains all of the data gathered during the experiments, along with the laboratory quality results. The chemometrician now selects which data set is required for model building, and which set is going to be used for model validation. The data sets can be collated extremely quickly using your PAT KM — in minutes, rather than the hours it would take if done manually. Export these data sets to the MVA package of choice, where the chemometrician will build the calibration models. If the selections and installation were correct, correlations between the data inputs and the CQAs should be apparent (if there is no correlation, suspect data entry mistakes or incorrectly chosen or positioned instruments).

The chemometrician may produce one or more models for any one prediction task. You can validate these models either using your MVA package or within your PAT KM. If you use your PAT KM, it might be possible to test more than one model at a time with the same validation data, so that you can instantly compare their performance. When a model provides the required quality predictions at a suitably high level of accuracy, and is interpretable, you can move on to the implementation phase. If necessary, run more experiments, gather more data, and refine your model. However, don't keep adding data to a poorly performing model! It may be that you have a sampling issue that requires urgent attention.

REMEMBER

You are trying to build a model that is fit for purpose, can be validated, and is interpretable. This likely won't happen on Day 1, when you have a limited number of data points. Your initial model might not be the best that it can be, but as soon as it is good enough, use it! After you have run many more batches in R&D or production, you will be much more data-rich. You can then use selected additional data to refine your model over a period of weeks, months, or even years. PAT embraces continuous improvement!

Finally, remember that models are product-specific. If you have multiple products, you need to build multiple models.

Step 2 – Process understanding

At this point, you have your calibration models, and you can predict product quality in real time to an acceptable level. The next phase is to gain *process and product understanding*, which is the turning of information into knowledge. In the process understanding phase, you gain knowledge about your process and product mechanistics, as well as define the relationship between your CQAs and CPPs. These CPPs may be variations in the raw materials themselves, variations in processing parameters, or both. Without mining your process information and developing better understanding, it is not possible to control the process based on sound, scientific knowledge.

You may have two choices of how to gain understanding. Option 1 is to use your recently acquired "historic data" to study how product quality varied over time with changing CPPs, and use that data to deduce the process and product mechanistics. This is likely to be the data gathered during your model building phase.

If you have insufficient data to draw these conclusions, you can fall back to Option 2, which is to once again run experiments. These experiments typically use DoE (or evolving operations), which vary the CPPs, and measure the resultant change in the CQAs. Ensure that all data is recorded within your PAT KM (including raw material and/or process parameter data that is not considered to be a CPP, but could conceivably be a CPP). After you complete the experiments, you can analyze the data, so that the process scientist can deduce further how CPPs affect the CQAs.

Process understanding is a technically difficult step. The process scientist must have extremely good process and product knowledge in order to make the necessary deductions. You will also likely have to replicate experiments to confirm the deduced interrelationships.

The difficulties of these first two steps are further compounded in that there may well be undiscovered CPPs that vary only when a rare event happens. For example, when you change raw material suppliers, a quality attribute that was stable in your previous supplier's product is now different in this new product, and your CQAs will respond accordingly. Thus, your deductions (and model) might not perform well after the raw material change is made. Seasonal changes might also affect quality. You have a great deal to consider when building the model and gaining process and product understanding.

Step 3 – PAT-based control

With the process understanding in place, the next step is to develop the control system algorithms that will maintain the desired state and control the process within its design space. Normally these algorithms are based on how the CPPs that can be changed are adapted to minimize and control product variability. The PAT KM then writes the setpoint changes out to the control systems, which in turn control the process to minimize variability. When running, the PAT KM continuously monitors the process in a feed forward/feedback manner so that the quality is always maintained at its desired state. It is not a one-shot event.

With these control algorithms in place, the PAT system is ready to run. As mentioned in the previous section, as more and more batches are run, you will collect more data, and you can use some of it to improve your calibration models, process understanding, and process control algorithms.

REMEMBER

PAT embraces continuous improvement.

Step 4 – Continuous improvement

A key theme in the QbD/PAT approach is that PAT embraces continuous improvement. This theme is often overlooked, probably because it is an alien concept when compared to traditional processing techniques. Traditional approaches are based on running the process rigidly to a recipe that was developed perhaps years ago. Changing this fixed process would be unthinkable. PAT turns this concept on its head because it actively encourages continuous improvement. You continuously seek to improve the process to further improve product quality, yields, and productivity, and perhaps to increase the opportunity for lower-cost raw materials.

The concept of continuous improvement is simple. On Day 1 of production, you will be using models and orchestrations that are fit for your purpose, but are based on an adequate but not exhaustive number of experimental points. It is done this way by design. Generating more experimental points means more time expended and more raw material used, and neither of those are desirable. However, once you are running the process in an R&D or production environment, you quickly gather much more data and become "data rich."

You can use your PAT KM to identify data points that are a suitable distance from those used during the model building phase (called

inliers), and then use these together with the reference method results and sample data to improve your models. You can use a good PAT KM to run these new models alongside your existing ones to "validate" them prior to them being used in production.

Furthermore, as you gain running experience you may find that you have missing CQAs or CPPs that must be added into your system. You might also need to introduce new orchestration functionality to further enhance your PAT system's performance. While this is all actively encouraged, you do, of course, have to back up all changes with sound science and validated processes (and models). However, this need not be overly onerous, and is absolutely worth the effort, particularly in light of the new ICH Q12 guidance on life cycle management.

CAN I HAVE A PAT SYSTEM WITHOUT A PAT KNOWLEDGE MANAGER?

Technically, maybe, but why in the world would you want to? As we stress in this chapter, a true PAT process has many interconnections and interactions, as well as math and logic functions that must be taken into consideration. You must be able to configure those functions in a simple and flexible way. The data must be stored in a robust manner that complies with data integrity requirements, together with full GMP and regulatory compliance.

So, you definitely need a PAT KM. The only real decision is whether you will use an off-the-shelf product or design and develop your own custom software for the task.

All of this functionality can, of course, be achieved by developing a custom PAT KM software package tailored for your exact use. However, such software development represents a significant undertaking. Not only must you hire developers to create the initial application, but you must keep them available to do testing, validation, maintenance, and upgrades. Most companies find an off-the-shelf solution to be the best value. There's no need to reinvent the wheel when some other company has already done the hard work of programming a PAT KM tool and continues to release updates and improvements for it. In the long run (and often in the short run too), an off-the-shelf product is the most economical choice for most businesses.

IN THIS CHAPTER

- Implementing PAT in pharmaceutical systems
- Considering PAT in non-pharmaceutical applications
- Using PAT in a lab
- Deploying PAT in pilot plants
- Applying PAT to batch and continuous manufacturing

Chapter 6
Practical PAT Applications

PAT has many practical applications, both in pharmaceutical systems and elsewhere. This chapter presents several ways you can put PAT to work in your organization.

Implementing PAT in Pharmaceutical Quality Systems

A good-quality PAT KM system, installed and configured correctly, goes a long way toward realizing the Pharmaceutical Quality System (PQS) as defined in the ICH Q10 guidance. ICH Q10 lays out suggested quality system requirements for the life cycle of a product. Here's the full list of technical areas where PAT can fit in a product's life cycle:

- **Pharmaceutical development:** Improved understanding of drug substance, formulation, process interactions, and the analytical methods used to assess quality from Day 1.

- **Technology transfer:** Reduced time and effort when transferring new and legacy products within or between sites.
- **Commercial manufacturing:** Better control in relation to raw material variability, which enables process adaptation to reduce variability, costs, energy, and scrap, while maintaining the highest possible quality.
- **Product discontinuation:** Electronic record retention, managed for data integrity using the PAT KM.

To achieve the greatest benefits, QbD/PAT should start at product conception and work its way systematically through the product's entire life cycle.

Remember, products are the result of raw materials transformed by the process in a manner that maintains the desired state. Therefore, the best place to start a PAT initiative is with raw material understanding. This point bears repeating because it's such an essential concept. Understanding the raw materials helps you understand how to control the process, and that's where the PAT KM becomes indispensable.


TIP

A good PAT KM allows you to gather data in a regulatory compliant way, yet be configurable to minimize the number of operator interactions necessary to ensure that the data is GMP compliant.

Even with legacy products, revisiting raw material variability and adopting the QbD/PAT approach results in process improvements and reduces problems associated with traditional approaches. Of course, with legacy products, the time and cost penalties associated with development and scaling up using a traditional approach have already been "paid," so it can be difficult to justify new expenses for those products. Therefore, by adopting a PAT approach as early as possible in a new product's life cycle, you can maximize the benefits in terms of time, cost, and quality.

For new products, PAT might begin at the laboratory, where the first stages of process development and control begin. Process orchestration and model building on a small-scale lead to mechanistic understandings that will be invaluable during scale-up and later in the product's life cycle.

WARNING

Many a good PAT project has crashed and burned as a result of the PAT team trying to get stellar results at the early stages. PAT system deployments involve highly qualified personnel, often with PhDs, who tend to focus much more on the science and technology than on the financial return. Although these folks are brilliant at the scientific tasks in hand, they are not always focused on timely profitability. There is a real risk of a PAT project, which must deliver a return on investment (ROI) in a sensible timeframe, taking too long to come to fruition. Ensure that your PAT team includes practical pragmatists with leadership authority, so that they can help steer the team through the complex process in a timely but compliant way.

REMEMBER

PAT embraces continuous improvement! Adopt an iterative, learning mindset, and let the data gathered over time continue to improve predictions.

A quickly executed, successful, small, focused PAT project with even just a small ROI will shed a positive light onto PAT within your organization and facilitate funding for follow-up projects. We have seen many successful projects develop in this way.

Considering PAT in Non-Pharmaceutical Applications

PAT has the potential to provide huge benefits to industries outside of the pharmaceutical industry. A holistic, end-to-end approach that supports regulatory and/or quality system requirements can bring increased efficiency and profitability to almost any manufacturing process.

Although the official structure and terminology of PAT originated in the pharmaceutical industry, other industries have been employing some of its concepts for years. The main difference is in the integration (or lack thereof). In most cases the approaches that non-pharmaceutical companies have taken have not been holistic, either in terms of process or product lifecycle. For example, they might have installed isolated "islands of PAT," where a NIR or Raman instrument is used on a stand-alone basis with little to no documentary control or traceability. Such isolated uses might have been acceptable in years gone by, but they are

becoming increasingly unacceptable from a quality (and perhaps a regulatory) standpoint.

REMEMBER

PAT is not just for the pharmaceutical industry. All industries can benefit from improved quality, reduced time to market, reduced manufacturing times, and reduced costs.

As was the case for pharmaceutical development, PAT can help non-pharmaceutical companies with product development, technology transfer, commercial manufacturing, and product discontinuation. The opportunities for a rapid ROI in the non-life science industries should be even faster than for the life science industries, because there are normally not the same regulatory constraints.

Next up, here are some specific areas in which PAT can benefit the manufacturing lifecycle.

Using PAT in a Laboratory

You might use a PAT system in a laboratory for many reasons, such as:

- Centralized instrument and analytical method deployment to local and global facilities
- First-stage process modelling and early-stage process control
- Feasibility studies that can be expanded to pilot and commercial scale manufacture
- Timely at-line quality measurements

TIP

If you intend to implement PAT in your production plant, we recommend that you establish a PAT infrastructure in your laboratory if at all possible. Doing so creates the most cost-and time-effective route to implementing PAT in manufacturing, especially with new products.

Figure 6-1 shows an example of a PAT lab infrastructure. Such an architecture enables you to build small-scale process models

in a GMP/quality-compliant way. Understanding the critical process parameters (CPPs) associated with critical quality attributes (CQAs) allows the first definition of the design space for the process (as per ICHQ8), as well as the first control strategy for your process.

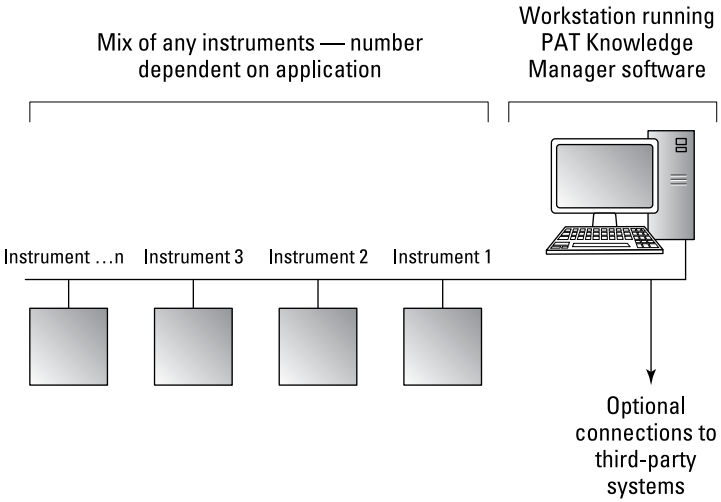


FIGURE 6-1: A typical PAT laboratory infrastructure.

REMEMBER

All savings in scale-up time are effectively an extension in your new product's patent life. You will have your product on the market sooner, which is of huge benefit to both your company and the consumer or patient.

You can also use an automated, PAT-driven, laboratory-based method to deliver near-real-time, at-line quality analysis for manufacturing. The point is not to bring the lab to the process, but to gain information in a timeframe that enables you to make proactive changes to the process (within the design space) so that the desired state is always maintained.

Figure 6-2 shows what an at-line PAT installation might look like.

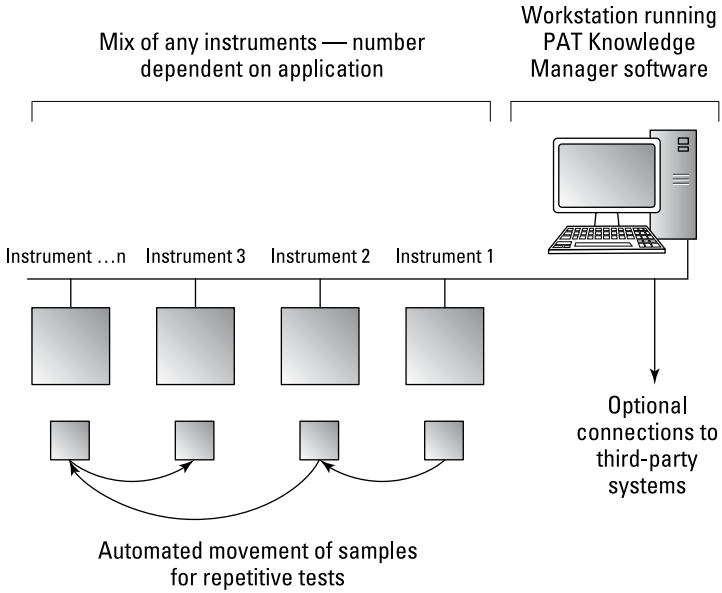


FIGURE 6-2: An at-line PAT installation example.

Deploying PAT in Pilot Plants

From a macro viewpoint, the PAT infrastructure required for a pilot plant is the same as for a laboratory. The main differences are that the system might need more users involved and might need to communicate with a third-party control system. The basics, however, are the same, and the fundamental tenet still holds: "Understand your process and reduce variability."

A pilot plant deployment might consist of a scaled-up version of the laboratory equipment. On the other hand, it might be a full-size portion of the final manufacturing plant, especially in the case of continuous manufacturing. We talk more about the demands of continuous manufacturing later in this chapter.

Figure 6-3 shows what a pilot scale PAT installation might look like.

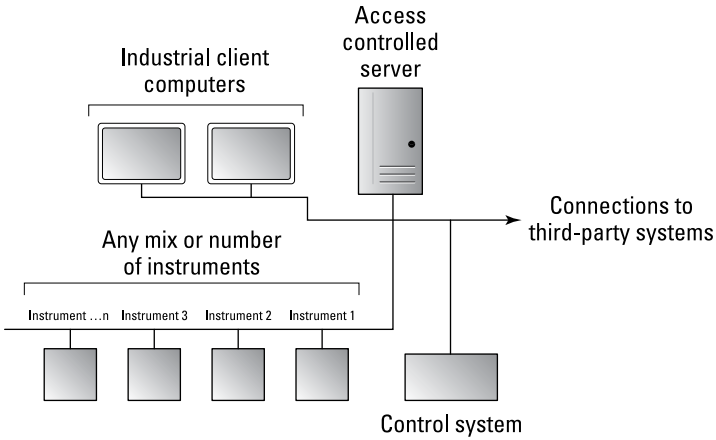


FIGURE 6-3: An example PAT pilot scale installation.

Deploying PAT in Manufacturing

To put it bluntly, if you don't move PAT into manufacturing, then you have wasted your time and money. Every previous step in your PAT implementation leads toward the ultimate manufacturing goal: to manufacture product at a higher quality standard in a faster, more cost-effective way than you can do without PAT.

WARNING

Excessive testing and trials in a laboratory or pilot plant is a sign that an organization may not be ready for PAT. Only when PAT is implemented in a manufacturing environment can real knowledge and improvements be realized.

No matter what you are manufacturing, your process is likely to fall into one of these categories: batch, continuous, or discrete. As of this writing, PAT has been widely applied only to batch and continuous processes, so these are the two categories we focus on in the following sections.

Applying PAT to Batch Manufacturing

Batch manufacturing has been a fundamental process manufacturing approach for centuries. It is a well-contained processing method that enables manufacturers to verify the quality of the product at the end of each unit operation.

Traditional batch manufacturing checks quality only when the product is finished. As is often said, "Quality is tested into the product." Only at the end of a manufacturing step are products evaluated as good, scrap, or needing rework with no quality information in between. This QC approach makes production slow and inefficient, with large amounts of scrap, rework, and work-in-progress (WIP). The variable processing time and scrap rate means that just-in-time (JIT) manufacturing is not possible.

These inefficiencies can be corrected with the application of PAT. By inserting suitable measurement instruments into the process, you can begin to establish process signatures and predict product quality in real time. That means you can control the process as it is happening.

In active pharmaceutical ingredient (API) or biological fermentation systems, batch manufacturing is currently the predominant approach (although continuous manufacturing is becoming increasingly popular). In well-defined systems, you can establish a process signature (that is, a consistent profile) for a particular process. This profile is often referred to as the "Golden Batch." Be careful, though, in establishing the criteria for what makes any specific batch a "Golden Batch."

Figure 6-4 shows what a batch reactor/bio-fermentation PAT installation might look like.

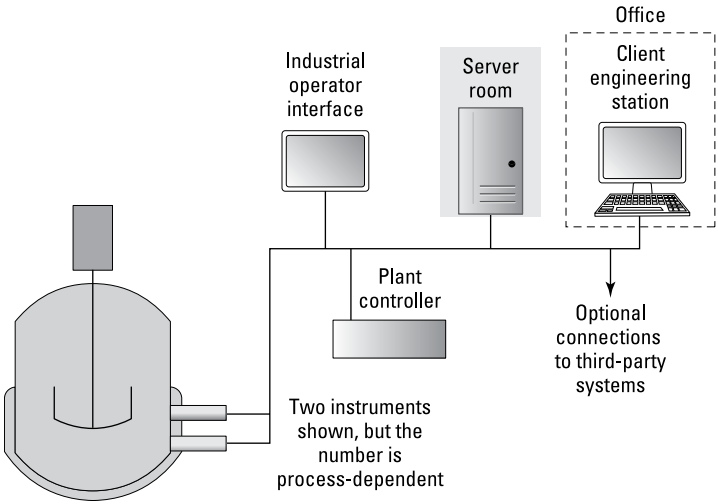


FIGURE 6-4: A batch reactor/bio-fermentation PAT installation.

Applying PAT to Continuous Manufacturing

Many industries outside of the pharmaceutical industry, such as the petrochemical industry, have used continuous manufacturing processes for many years.

Some continuous processes are stable, robust, and well understood. For such rare cases, it may be possible to manufacture without PAT, based on well-controlled raw material sourcing, controlling critical process parameters to a recipe, and accepting the product into final QC testing based on a business risk decision. If the product is not of suitable quality, it all must be scrapped. You can easily see why such a system is applicable only to very stable processes!

PAT-enabled continuous manufacturing systems collect considerable volumes of data per second from many disparate systems working together. The data generated is not typically synchronized to a single heartbeat, so it can be a complicated matter to time-match data in order to create a unified picture. This is where a PAT KM system really shines.

A PAT system for a continuous process typically employs multiple PAT tools and multiple critical process parameters. Data fusion requirements are a given, and quality based control is enabled for the whole process. The materials move through the process, from unit operation to unit operation, with the PAT system providing real-time quality assurance and potentially holistic, real-time release testing (RtRT). Additionally, product tracking is essential because:

- You must track the product to know the identity of raw material lots contained within every sub-batch.
- Tracking is required to remove out-of-specification material from the process. You must also know the composition of the rejected material.
- Tracking is occasionally required for samples that need extraction from the line for laboratory analysis.
- Irrespective of whether you have a plug or mixed flow process, tracking is required. There must be the additional capability for calculating residence time distributions.

A good PAT KM helps you track the product and its composition through the process to the best level of probability possible, based on the input flow data and the statistical nature of sampling. The system uses mixing algorithms, with the movement and intermixing precision being based on experimental studies that need to have been previously performed.

Figure 6-5 shows what a continuous manufacturing PAT installation might look like.

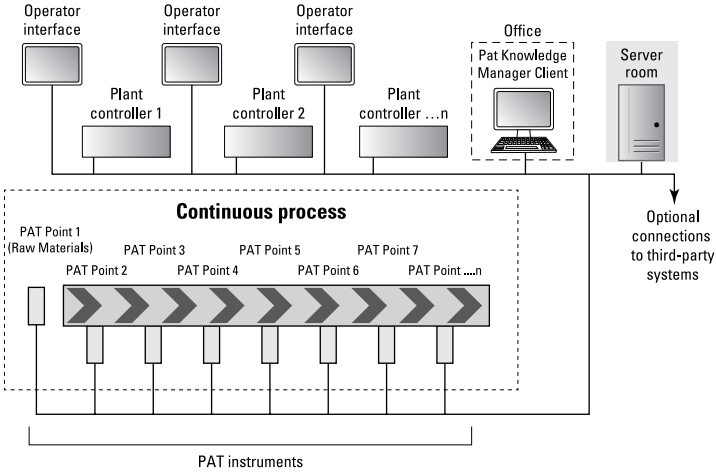


FIGURE 6-5: An example of a continuous manufacturing PAT installation.

IN THIS CHAPTER

- Thinking about quality in a new way
- Building in quality by design, not by testing
- Championing QbD/PAT and working with regulators

Chapter 7
Ten Key Points about QbD and PAT

This is an information-packed book with lots of detail about QbD and PAT. Don't worry — you don't have to remember all of it! There's no final exam. Instead, here's a list of the ten most important points we hope you will take away:

- **QbD does not carry baggage from the past**

  The traditional ways of manufacturing served the industry well in the past, but are too restrictive when it comes to implementing change. QbD provides an opportunity to implement process and product knowledge in a regulatory framework that is completely different from the past.

- **PAT is about process and product understanding**

  The main reason to implement PAT is to gain timely information about product quality and how a process works, in order to optimize quality (plus time and cost), and then facilitate continuous improvement. If PAT is nothing more than bringing the QC lab to the process for post-process analysis, then we are not performing Quality by Design — we are endorsing Quality by Testing!

- **Continuous improvement needs knowledge management**

  QbD and PAT are successful only when implemented into commercial manufacturing. Knowledge gained in development and on real manufacturing processes enables you to define the design space for that process. Continuous improvement should be embraced, and can be performed within the proposed design space without regulatory oversight.

- **PAT is not just expensive analyzers**

  Contrary to popular belief, PAT is not focused on expensive process spectrometers. Those devices are desirable in many situations, but PAT is about knowledge management and implementation. Any sensor that can provide timely information about quality and its relationship to critical process parameters is considered PAT, regardless of its cost or complexity.

- **Orchestration is the key**

  A piano with one key can provide a simple tune, but having 88 keys provides color and depth. Combine the piano with other instruments and a conductor, and an orchestration becomes possible. The same principles apply to QbD/PAT. One analyzer/sensor may be okay, as long as it is directed by some type of control and management system. When a number of sensors are being used, however, a PAT knowledge manager is absolutely essential for orchestrating the whole process.

- **Work with regulators**

  An effective PAT project is very much a teamwork event, and we strongly encourage you to include your regional regulatory agency in the team at an early stage. Regulators are eager to learn, and by giving them access and some sort of ownership of the process, you might be more likely to gain regulatory approval for your design space in a shorter timeframe.

- **Persevere to the end, and then start again**

  The first QbD/PAT implementation is often the most difficult and time consuming. You might feel like giving up because of the technical issues and pushback from those who don't understand what you are trying to achieve. Persevere to the

end, and then start the next project. The process becomes much easier with experience, and the benefits to your organization will be worth the effort.

- **Start small, think big**

  We strongly suggest that you don't try to take on the company's most prized and valuable "glory project" as your first QbD/PAT initiative. Ideally start by better characterizing raw and in-process materials. If this is not possible, then choose a modest project that is not too complex. The demonstration of a quick success with the first project is more important than a massive ROI. From this success, bigger and more complex projects will follow.

- **Be the champion**

  Full commitment is required when embarking on a PAT journey. Without dedicated staff and resources, the project will be slow at best, or may stall. However, if an organization makes a commitment where a full-time QbD/PAT champion with appropriate resources is appointed, then timely success is far more likely. The QbD/PAT champion should understand the new regulatory guidance and PAT technologies, explain these to all levels of staff and coordinate the various departments to ensure a smooth implementation. In addition to being technically competent, the PAT champion should also be practical and pragmatic!

- **QbD is not only DoE**

  QbD is much more than just DoE, although you might see them conflated in some literature. Make sure the focus is on data and knowledge management systems that allow optimized usage of DoE, MVA, and SPC, rather than zooming in on DoE in particular. Use the right tools for the job at hand, and your QbD/PAT approach will have a greater likelihood of success.

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Quality by Design (QbD) and Process Analytical Technology (PAT) are innovative approaches to improving manufacturing efficiency and quality. QbD stresses designing quality into manufacturing, rather than testing for quality after the event. To enable QbD in manufacturing, PAT enables real-time, quality-based adjustments to your process. QbD and PAT are here to stay, not only for the life science industries but for many other processing industries. This book gives you a better feel for the principles behind the initiative.

Inside...

- Learn the basics of QbD and PAT
- Improve quality
- Reduce cost and manufacturing time
- Understand regulatory approaches
- Implement QbD/PAT in your organization
- Learn what a PAT knowledge manager does
- Explore practical applications of PAT

Brad Swarbrick is a world-recognized expert in the implementation and application of QbD/PAT across a number of industrial sectors. **Martin Gadsby** is a co-owner of the Optimal Group with more than 30 years' experience in the industry and 17 years with PAT knowledge management. **Faithe Wempen** is a veteran Dummies author with many books to her credit.

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ISBN: 978-1-119-46633-8

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