SIPAT
the software heart of PAT

White paper
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTRODUCTION</td>
<td>3</td>
</tr>
<tr>
<td>EXECUTIVE SUMMARY</td>
<td>4</td>
</tr>
<tr>
<td>1. PAT – WHAT, WHY AND HOW?</td>
<td>6</td>
</tr>
<tr>
<td>1.1. What is PAT?</td>
<td>6</td>
</tr>
<tr>
<td>1.2. The regulatory impetus for PAT in the pharmaceutical sector</td>
<td>7</td>
</tr>
<tr>
<td>1.3. Why is PAT beneficial for pharmaceutical manufacturers?</td>
<td>8</td>
</tr>
<tr>
<td>1.4. How can companies best evaluate PAT implementation?</td>
<td>9</td>
</tr>
<tr>
<td>1.5. What needs to be in the PAT toolbox?</td>
<td>10</td>
</tr>
<tr>
<td>1.6. What about wider people and organisational change issues?</td>
<td>11</td>
</tr>
<tr>
<td>2. SIPAT DESCRIPTION</td>
<td>13</td>
</tr>
<tr>
<td>2.1. INTRODUCTION</td>
<td>13</td>
</tr>
<tr>
<td>2.2. SIPAT Description</td>
<td>14</td>
</tr>
<tr>
<td>2.3. SIPAT functionality and structure</td>
<td>15</td>
</tr>
<tr>
<td>2.4. SIPAT Instances</td>
<td>16</td>
</tr>
<tr>
<td>2.5. SIPAT Features</td>
<td>17</td>
</tr>
<tr>
<td>2.5.1. Control of the PAT Instruments</td>
<td>17</td>
</tr>
<tr>
<td>2.5.2. Measurements via the Process Control System</td>
<td>18</td>
</tr>
<tr>
<td>2.5.3. Input from MES and LIMS</td>
<td>18</td>
</tr>
<tr>
<td>2.5.4. Chemometrics / MVDA</td>
<td>18</td>
</tr>
<tr>
<td>2.5.5. Integrating SIPAT in the Control loop</td>
<td>18</td>
</tr>
<tr>
<td>2.5.6. Output to MES and LIMS: Real Time Product Release</td>
<td>18</td>
</tr>
<tr>
<td>2.5.7. SIPAT Graphical User Interface</td>
<td>19</td>
</tr>
<tr>
<td>2.5.8. Process Analyzer Suitability and Performance tests</td>
<td>19</td>
</tr>
<tr>
<td>2.5.9. Version management, Access Rights and 21CFR11</td>
<td>19</td>
</tr>
<tr>
<td>2.5.10. SIPAT Archive and Knowledge Management</td>
<td>20</td>
</tr>
<tr>
<td>2.5.11. Customer-specific requirements</td>
<td>20</td>
</tr>
<tr>
<td>2.6. SIPAT interfaces</td>
<td>20</td>
</tr>
<tr>
<td>2.7. SIPAT models</td>
<td>21</td>
</tr>
<tr>
<td>2.8. SIPAT IT Architecture</td>
<td>22</td>
</tr>
<tr>
<td>2.9. SIPAT and MES</td>
<td>26</td>
</tr>
<tr>
<td>2.10. PAT for development and manufacturing</td>
<td>26</td>
</tr>
<tr>
<td>2.11. SIPAT Stepwise PAT implementation</td>
<td>27</td>
</tr>
<tr>
<td>3. FURTHER INFORMATION</td>
<td>29</td>
</tr>
</tbody>
</table>
INTRODUCTION

Regulatory agencies and patients, science and technology are forcing rapid change on pharmaceutical manufacturing. Manufacturing efficiency and innovation are high on the agenda of the big pharma and will be secured by those companies that innovate successfully. The US Food and Drug Administration (FDA) made the point vividly when it observed: “a recent estimate\(^1\) of potential world-wide cost-savings from efficiency improvement is suggested to be as high as US $ 90 billon. This would be equivalent to the current cost of developing 80-90 new drugs every year”\(^2\).

Change will occur in many aspects of pharmaceutical manufacturing. Process Analytical Technology (PAT) is only one aspect but it is of major significance for the industry. PAT fits nicely in the FDA’s more general view of how to improve pharmaceutical manufacturing, described in the ‘good manufacturing practices (cGMP) for the 21\(^{st}\) century’ initiative. The cGMP initiative stimulates process know-how and understanding and puts PAT forward as the enabler to reach this understanding. PAT offers companies in bio-API, chemical-API and secondary manufacturing the possibility to gain better control of their processes, to design quality into the production process and eventually to move to real-time product release. It brings major benefits in terms of product quality, reduced time to market, and tighter and more responsive supply chains.

Today, Process Analytical Technology (PAT) has become a buzz word in the pharmaceutical manufacturing world. However, it should not be considered as a trend, but regarded as a new technology that is here to stay. Some (larger) pharma companies are already further down the PAT learning curve, while others are struggling to appreciate the full potential of PAT - seeing it only as a way to replacing the current off line tests with on line analyzers. All are challenged to find the most optimal way to introduce PAT and to select the right tools and infrastructure to match future manufacturing needs.

In this White Paper, we review what PAT is, why pharmaceutical companies should implement PAT and the factors that will determine its successful development. We look at the tools companies will need and consider the organisational development of PAT implementation as well as the technological aspects. We also provide an overview of Siemens’ new SIPAT™ solution. It links those tools necessary for a PAT system architecture and is designed to meet the specific requirements of the pharmaceutical industry.

\(^1\) R. S. Benson and D. J. MacCabe. From Good Manufacturing Practice to Good Manufacturing Performance. Pharmaceutical Engineering. July/August 2004

\(^2\) US Food and Drug Administration, Innovation and Continuous Improvement in Pharmaceutical Manufacturing Pharmaceutical CGMPs for the 21st Century, September 2004
EXECUTIVE SUMMARY

The introduction of Process Analytical Technology in the pharmaceutical industry comes at a time when the risk-reward context for pharmaceutical manufacturing is changing. Companies are becoming exposed to more powerful, wider market forces. The pharmaceutical industry is at a key turning point in many respects. Indeed, PAT coincides with the FDA’s bold ‘innovate or stagnate’ call to the industry.

Although the FDA published its first Guidelines on PAT (Guidance for Industry: PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance) in September of 2004, still companies vary enormously in both their stage of PAT implementation and their ambition for its use. Process understanding lies at the heart of PAT. A process is well understood when all critical sources of variability are identified and explained; when variability in the process is managed by process controls that deliver a consistent process output; and when product quality attributes can be accurately and reliably predicted.

With PAT, quality becomes something that is designed into the process rather than checked afterwards. Introducing PAT, thus, has a considerable positive impact on reducing production costs. PAT speeds up decisions on the unit operation level and improves quality/efficiency of process steps. This leads to shorter batch runs and increased quality consistency which then can lead to eventual real-time product release.

A clear understanding of the business goals a company wants to achieve when implementing PAT is the vital starting point for a PAT investment. Each company will find itself in a different situation and judgements on the focus and pace of PAT implementation will vary according to the return on investment (ROI) analysis of the different options open to them.

The migration to PAT is much more than just a technological one. Companies that view it in narrow technical or manufacturing process terms are, at best, unlikely to capture its full potential and, at worst, run into major implementation failures. While innovation in technology lies at the heart of PAT, its successful application relies on full integration of the company’s multidisciplinary PAT team, knowledge systems and risk management.

PAT is already far advanced in other industries. Siemens’ involvement with the FDA, together with our cross-industry experience and know-how, has permitted us to develop a PAT implementation methodology for pharmaceutical manufacturing. Pharmaceutical companies implementing PAT can make use of the steps outlined in the “Siemens PAT method implementation Roadmap”. This follows eight steps, moving from off-line to on-line activity, which allows the user controlled quality growth of their PAT initiative as they move towards a real-time release solution.
Siemens has decided to develop its PAT solution around a deployable product (Configurable Off The Shelf) called SIPAT™. Siemens is unique in its ability to utilize its globally recognized and accepted Product Lifecycle Management (PLM) program for SIPAT. We expect that the pharmaceutical industry will achieve maximum lasting gain in minimum time from SIPAT. SIPAT represents an integrated PAT software solution, fully in line with the industry requirements, improved thanks to our strategic partnerships and and revolutionary because of our control loop strategy.

SIPAT includes capture of analytical and process measurements, model creation and validation, online prediction and analysis, feedback to process control and finally real-time product release. SIPAT enables process understanding and continuous process improvement in both manufacturing and development.

The tools for supporting the PAT principles are:
- Process analyzers
- Process control tools
- Data analysis & mining tools (Multivariate Data Analysis, …)
- Data collection, storage and retrieval tools
- Reporting tools
- Continuous improvement & knowledge management tools.

SIPAT includes or links all PAT tools mentioned above into one PAT system architecture, easy to integrate into an existing manufacturing architecture, allowing full transparency on quality aspects from unit operation up to MES or even ERP. SIPAT is built so that it can be used in two ways on two different levels:
- SIPAT Base Station - focuses on specific Unit Operations and enables (Advanced) Process Control.
- SIPAT High Level - covers total manufacturing line batch quality to enable Real-time Product Release.

In conclusion, SIPAT gives pharmaceutical companies the opportunity to deliver a scalable PAT roll-out and deployment. It moves from off-line model building to on-line use. The solution integrates with a process control / automation infrastructure, for feedback and feed-forward controls, batch-to-batch comparison, real-time product release, ongoing process optimization and fine-tuning. In combination with MES and ERP systems it forms a true Quality Management System.
1. PAT – WHAT, WHY AND HOW?

1.1. What is PAT?

In accordance with the FDA’s guidelines on PAT for the pharmaceutical industry\(^3\), Process Analytical Technology is defined as:

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.

Process understanding lies at the heart of PAT. A process is well understood when all critical sources of variability are identified and explained; when variability in the process is managed by process controls that deliver a consistent process output; and when product quality attributes can be accurately and reliably predicted. New production methods and the demand for shorter time-to-market create a need for a faster and more complete understanding of processes. An increased emphasis on production efficiency also requires increased real-time process information.

Stricter control of operational conditions throughout the process is achieved through new advanced sensor technologies and new techniques that handle a wider range of process parameters. These are typically linked into overall plant automation which is now reaching a level where all processes can be operated centrally.

It is important to note that the term analytical in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner. Many companies, however, make the mistake of seeing PAT too narrowly. They think of PAT in terms of current validation and quality control processes. The focus is often just on the sensor and what it can measure rather than the wider quest for process understanding that should be determining the choice of technology and the design of the system.

Some companies, thus, get stuck at a point where they just replace the measurement of current parameters with a technology that gives them a quicker result without seeing beyond that. No wonder Dr Ajaz S. Hussain, who at the time of being quoted was Deputy Director at the Office of Pharmaceutical Science CDER at the FDA, reminded companies: “you’ve got to remember that PAT is not about just throwing in-line sensors at a production line. It is more about understanding the sources of product variability during production and controlling your processes in a flexible way to allow you always to produce a quality product”\(^4\).

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\(^4\) Quality manufacturing: a blockbuster opportunity for pharmaceuticals, Economist Intelligence Unit, 2005
1.2. The regulatory impetus for PAT in the pharmaceutical sector

Much of the start for PAT comes from the initiative the US Food and Drug Administration (FDA) took in September 2004. Also the European Medicines Evaluation Agency (EMEA) started around that time an EU PAT team, working in close cooperation with its US counterpart on the PAT topic. The FDA wants the industry to place its focus on the science of manufacturing and recognizes that significant regulatory barriers have inhibited pharmaceutical manufacturers from adopting state-of-the-art manufacturing practices within the pharmaceutical industry in the past. The FDA’s PAT framework and its new risk-based approach for Current Good Manufacturing Practices (cCMPs) for the 21st century seek to address the problem by modernizing the regulations of pharmaceutical manufacturing, to enhance product quality and allow manufacturers to implement continuous improvement, leading to lower production costs.

The FDA talks about a ‘desired state’ of manufacturing with:

- Product quality and performance are ensured through the design of effective and efficient manufacturing processes
- Product specifications based on mechanistic understanding of how formulation and process factors impact product performance
- An ability to affect continuous improvement and continuous “real time” assurance of quality

The final report of the FDA’s cGMP’s for the 21st Century Initiative highlights the choices that pharmaceutical companies face:

“At the end of the cGMP Initiative the pharmaceutical community has arrived at a cross-road; 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 community will choose to move towards the desired state.”

This new regulatory approach presents companies with the possibility of more attractive regulatory framework. The initiative’s premise is that, if manufacturers demonstrate that they understand their processes, they will reduce the risk of producing poor quality products. They can then implement improvements within the boundaries of their knowledge without the need for regulatory review and will become a low priority for inspections.

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1.3. Why is PAT beneficial for pharmaceutical manufacturers?

The prospect of a ‘lighter touch’ risk-based regulatory framework is a considerable benefit for companies. However, while regulation may be the catalyst, it is competitive advantage that is the compelling prize. Typically, therapeutic drug performance analysis cannot be evaluated online. This limits the possibility of controlling and optimizing processes due to the relatively long times required for laboratory analysis. PAT closes this information gap: in-process data and data analysis tools improve process understanding and control. This ensures quality and reduces the risk of bringing non-compliant products to the market. Built-in process optimization and quality assurance thus ensures right-first-time (RFT) quality.

PAT speeds up decisions on the unit operation level and improves quality/efficiency of process steps. This leads to shorter batch runs and increased quality consistency. Consistency in quality is a critical component to enable real-time product release.

Early adopters can secure cost and competitive advantage gains. For an existing production process, PAT adoption and implementation tends to be seen in terms of reduced cost, lower inventory levels and a move towards ‘just in time’ production and supply. For new processes, the benefit of PAT is the ability to quickly develop the manufacturing process, upscale to a robust process and perform validation more easily. These are tremendously important but the full competitive advantage potential also needs to be seen in the context of the end consumer or patient.

The ‘process understanding’ that lies at the heart of PAT also means that manufacturers can gain improved knowledge and production capability to create products to match the quality and therapeutic expectations of patients. Bio-availability is a critical patient variable but it is not a current production variable. PAT enables manufacturers to gain improved control of their product quality but it also enhances a company’s ability to better match different patient needs. This is significant because bio-availability differences are, of course, important for drugs with a relatively narrow therapeutic index and also because of the potential of PAT to deliver competitive advantage as companies move towards a future era of more personalised medicines.
1.4. How can companies best evaluate PAT implementation?

PAT comes at a time when the risk-reward context for pharmaceutical manufacturing is changing. The pharmaceutical industry is at a key turning point in many respects. Historical ways of delivering value will not be sustainable on their own in the future. The industry’s whole business model is in transformation – drug development pipelines are drying out, pricing is under pressure and generic competition is more intense. Cost containment is the name of the game both for the government customer bodies that play a lead role in the pharmaceutical market around the world and the private insurance customers in markets such as the US. Double-digit sales and income growth has come to an end under pressure from patent expirations, generic competition and over the counter (OTC) switches.

However, the prize of longer term PAT gain comes at significant short term hazard and cost. Introducing PAT investment and change in a well-judged and timely manner is crucial. How can companies feel more confident and certain about their PAT journey? A clear understanding of the business goals of PAT implementation is a vital starting point. There are many and their exact fit with a particular company will be dependent on the company’s current manufacturing base and its future strategy. PAT can fix or improve existing processes, speed new product development, reduce site to site transfer risk and times, reduce validation costs and, through quality reliability, enhance a company’s image. At the end of a drug’s life cycle, PAT can help prolong patent life through the development of new formulations.

Most companies will want to realise a blend of these business benefits but, at the same time, they will also want to take a view on which one is their most important priority. This will be determined by the current state of play of its manufacturing and wider market activities. In turn, a company’s decision on which business benefit to prioritise will determine the focus and pace of PAT investment.

A company’s view on the business benefits it wants to prioritise will be the lens through which it evaluates its return on investment (ROI) in PAT. For example, a company may want to focus on improvements in existing processes. Some companies choose an easy and stable production process for PAT introduction. However, this may not be the choice that will yield the quickest benefits. An alternative focus might be on a troublesome process where the gains of better process understanding and control will be far higher. Other companies may be at a stage in their product portfolio where they may want to make new drug development the focus of their PAT investment. For these companies, the potential gains in revenue of using PAT to speed the time to market of drugs in the development pipeline may be greater than prioritising the application of PAT to the manufacture of existing drugs.
Each company’s situation will be different and judgements on the focus and pace of PAT implementation will vary according to the ROI analysis of the different options open to them. Companies will need to carry out ROI analysis of all options to validate their prior assumptions about the lead business benefits. In some cases, they may decide that these prior assumptions need to be adjusted with some options, on examination, emerging as better contenders than previously expected. Such an examination of priorities is crucial since one of the key issues for companies is where and how best to start implementing PAT.

1.5. What needs to be in the PAT toolbox?

In order to identify sources of process variability, companies need to be able to integrate information ranging from raw material and intermediate measurements to processing and environmental data. There is often a mix of real-time measurements, both univariate (temperature, pressure, pH) and multivariate (NIR or other spectroscopic methods), sampled during processing, as well as static data sampled from raw materials, intermediates and finished product. The greatest hurdle involved in almost any analysis is generation, integration and organization of data. A great deal of effort is required to assemble meaningful datasets. Integrating, synchronizing and aligning data from all relevant sources is therefore a prerequisite before analysis can begin.

The objective of PAT is to develop process understanding. PAT encourages translation from defining critical product specifications (usually tested afterwards in the laboratory) into creating critical process specifications that define the parameters to keep the process under control. But also the development of a release philosophy with quality built into the control system.

PAT can be realized using an appropriate combination of the following tools:

**Multivariate tools**

Both the product and the production processes are complex multifactorial systems. Insight in the production process and the interaction with the product requires complete multidimensional experiment data: modifying one factor at a time around the normal operation conditions is not sufficient. The Design of Experiments (DoE) Theory is used to gather complete data sets allowing to unveil the underlying models. Consecutively modeling software like Umetrics, Matlab, Camo… allows to derive a mathematical of the experiment data which simulates the system behaviour. These models can be MVDA (Multivariate data analysis) or other (e.g. Bayesian Networks). Once models are made, the same tools need to be used to evaluate the model and validate it with separate data sets.
Process analyzers
Typical analyzers that will deliver input to allow online monitoring are e.g. NIR, Raman, Process GC analyzers. Process parameters, such as temperature, pH, pressure, flow which can easily be measured online, will be used as well. In addition, we will also use characteristics of raw materials which were measured offline. A combination of scientific insight and experimental/modelling allows decisions to be made on the relevance and reliability of the mathematical relationships.

Process control tools
Process insight delivers relevant process/product attributes. Online monitoring of these attributes should allow early detection of abnormal behaviour. These attributes can be used to feed a classic or Advanced Process Control loop.

Continuous improvement and knowledge management tools
Gaining process insight can allow the improvement of the process as well as improvement of the control strategies. Data and metadata (conclusions, observations etc.) gathered during the use of PAT should be archived to allow later reuse, e.g. during a future improvement cycle.

1.6. What about wider people and organisational change issues?

The critical thing for companies will be to make the move to PAT effectively. The migration is much more than just a technological one. Companies that view the migration in narrow technical or manufacturing process terms are, at best, unlikely to capture its full potential and, at worst, run into major implementation failures. While innovation in technology lies at the heart of PAT, its successful application relies on full integration with a company’s people, knowledge systems and risk management.

From the outset, clear and appropriate leadership needs to be established for the migration to PAT. A variety of approaches is been taken on board by pharmaceutical companies to project leadership. Some companies have appointed a vice president to co-ordinate the PAT initiative, in other companies it is the production/engineering or quality manager that takes the initiative and is trying to convince and ‘educate’ top management. The vital point is that companies need to be sure that their project leadership is empowered to make all the changes across the company that will be necessary for project success. For the same reason, it will be important to select carefully the potential technology providers, rigorously investigate their understanding of the pharmaceutical sector and consider how well-suited they are to play a part in the wider organisational-change journey.

A move on the scale of introducing PAT represents a significant people change. Quality control, for example, moves from the laboratory to the production floor with an attendant shift in responsibility and need for both procedural change and people change. A cascade of reactions has to happen for implementation to be successful. Skill-set requirements will change significantly. For example, instrumentation and electrical
engineering skills will play a key role. Enterprise-wide data management, retrieval and querying will be vital. Pharmaceutical scientific skills will need to extend into understanding the supportive database structure and be capable of managing knowledge retrieval systems in an efficient, usable and timely manner. Against a background of possible job uncertainty, people need to be guided through the change.

Often, however, PAT remains the responsibility of a relatively narrow team of people. Implementation projects often lack a multi-disciplinary approach with the result that companies run the danger of simply reinforcing existing approaches rather than open-mindedly questioning the current quality principles and methods and exploiting the full potential of PAT. This is a significant problem because effective PAT implementation needs to cross traditional boundaries. The experience of Astra Zeneca in Sweden is helpful here to explain this challenge. In an article Ulrika Henningsson, manager Process Analytical Chemistry team, reports on the experience she had over a ten year period of implementing PAT: “the greatest challenge though, has been to convince the organization and train the people to understand the point of PAC/PAT. The technology in itself has shown to be the tip of the iceberg - people are the foundation!”

2. SIPAT DESCRIPTION

2.1. INTRODUCTION

Maximum benefit of PAT or Process Analytical Technology can be achieved when a broad PAT definition is applied. This means looking at the opportunities of PAT, as outlined in the FDA PAT Guidance (A framework for innovative Pharmaceutical Manufacturing and Quality Assurance, September 2004), is offering e.g. real-time product release, manufacturing performance improvement, quality consistency improvement and regulatory flexibility. This approach prevails on a “narrow PAT” approach only based on the implementation of process analyzers only.

PAT is all about process understanding, being able to control Critical to Quality (CTQ) parameters in an automated way (based on mathematical models, including parameters influencing the process and ultimate quality) and hence obtain a predictable process and pre-defined product quality. Only when this condition is met real-time product release can be achieved and consequently manufacturing costs (reduction of personnel, shortening of cycle time, quality costs reduction, reduction of waste and rework, reduction of work in process costs), inventory cost, regulatory & validation costs, can be dramatically reduced.

On top, PAT is a multidisciplinary topic. It has to be interfaced with various other manufacturing related systems, like process automation system (control and SCADA), industrial IT systems (like MES, LIMS, and EBR), data storage (historians), data portals and management systems, etc. This means that PAT implementation projects have a lot of interactions with other systems.

The Challenge

In order to identify sources of process variability, you need to be able to integrate information ranging from raw material and intermediate measurements to processing and environmental data. There is often a mix of real-time measurements, both univariate (temperature, pressure, pH) and multivariate (NIR or other spectroscopic method), sampled during processing, as well as static data sampled from raw materials, intermediates and finished product. The greatest hurdle involved in almost any analysis is generation, integration and organization of data. A great deal of effort is required to assemble meaningful datasets. Integrating, synchronizing and aligning data from all relevant sources is therefore a prerequisite before data analysis can begin.

The objective of PAT is to develop process understanding. PAT encourages translation from defining critical product specifications (usually tested afterwards in the lab) to creating critical process specifications that define the parameters to keep the process under control. But also the development of a release philosophy with quality built in into the process control system.
The Solution
Siemens has developed an Information Technology and control infrastructure to support PAT systems. Our PAT solution, SIPAT, is characterized by its inherent modularity. It allows the user a scalable solution from off line to plant-wide use, starting with identification and monitoring of Critical to Quality Attributes (CQA) (phase 1), followed by control (phase 2) and finally optimization (phase 3). SIPAT offers a common interface for all PAT tools (process analyzers, data mining tools…). It assures user friendliness and ease of operation. The modularity allows an easy and fast validation.

2.2. SIPAT Description

As there is a growing industry commitment towards PAT, Siemens decided to develop the PAT solution into a deployable product suitable for Configurable Off The Shelf (COTS) implementation, called ‘SIPAT’. Siemens is unique in its ability to utilize its globally recognized and accepted Product Lifecycle Management (PLM) program for SIPAT. We expect that the pharmaceutical industry will achieve maximum lasting gain in minimum time out of the numerous PAT initiatives that are currently being defined by using Siemens. SIPAT consolidates several of these initiatives into integrated software fully in line with the industry requirements, strategic partnerships and the overall Siemens MES and control strategy.

To be able to develop processes by making use of the PAT approach and control quality in manufacturing, SIEMENS has developed a standardized and modular PAT software solution, called SIPAT, allowing to:
- gather process understanding
- strive for continuous process improvement
- perform real-time product release
- develop processes based on Quality by Design principles
- manufacture Right-first-time

The tools for supporting the PAT principles are:
- Process Analyzers
- Process Control tools
- Data analysis & mining tools
  (Multivariate Data Analysis, …)
- Data collection, storage and retrieval tools
- Reporting tools
- Continuous improvement & knowledge management tools

SIPAT links all PAT tools mentioned above into one PAT system architecture, easy to integrate into an existing manufacturing architecture, allowing full transparency on quality aspects from unit operation level up to MES and LIMS. SIPAT offers a common interface for all PAT tools (process analyzers, data mining tools…) and assures user friendliness and ease of operation.
SIPAT includes capture of analytical and process measurements, model creation and validation, online prediction and analysis, feedback to process control and finally real-time product release. SIPAT enables real-time PAT use for process understanding and continuous process improvement in both manufacturing and development.

SIPAT consists of 4 main modules reflecting the four main functions. PAT allows a scalable PAT roll-out and deployment, from off-line model building to on-line use, integrated into a process control / automation infrastructure, for feedback and feed-forward controls, batch-to-batch comparison, real-time product release and ongoing process optimization and fine-tuning.

This modular approach offers the flexibility to:
- stage the implementation and roll-out
- commission and validate independently as it is operated independently
- have a higher availability (changes on one unit have no impact on other units)

SIPAT can be interfaced to:
- various analyzer types, for data collection
- various chemometrics and/or data mining packages
- various process control systems (various process machines)
- various process automation systems (DCS, SCADA)

### 2.3. SIPAT functionality and structure

SIPAT has the following structure:

The functionality of the main SIPAT modules are:

- **Configuration module**
  Makes it possible to create the configuration of data, measurement and method types containing all necessary settings to start a runtime monitoring. This includes setting up PAT Methods, interfaces, set-up of the instruments, access rights, charts, ...
• **Model Builder**
  Enables to gather historical data to feed the MVDA routines resulting in a MVDA model against which the process will be checked. This module also allows model validation and optimization, typically used off-line.

• **Execution module**
  Fulfills the runtime functionalities using an approved configuration:
  - Read continuously data from process control system and/or process analyzers and stores it into the SIPAT Archive.
  - Synchronize data and send it to chemometric routines using previously developed chemometric models to predict or analyze data online. Predictions and analysis results can be visualized within SIPAT itself or within SCADA, PCS or MES.
  - Store and visualize the results from the chemometric routines.
  - Pass information to process control system (alarms, updated setpoints,…).

• **Data Archive**
  Makes it possible to store and retrieve all relevant data from the historical run-time PAT data and from the PAT configuration data. Captured raw data, pre-treated data and predictions are stored in the SIPAT Archive together with their **Batch context** (information about the batch being produced, the operation being executed,…).
  Data summaries can also be sent to advanced Process Historians.

The process insight gathered during the use of SIPAT is stored in the SIPAT Archive from where it can be queried using reporting tools.

### 2.4. SIPAT Instances

SIPAT is build as such that it can be used in two ways on two different levels:

• **SIPAT Base Station** focuses on specific Unit operations and enables eventually (Advanced) Process Control.

• **SIPAT High Level** covers total manufacturing line batch quality to enable overall batch quality monitoring and eventually Real-time Product Release.

**SIPAT Base Station**

SIPAT Base Station is the **PAT solution to control one specific Unit Operation**. Input from one or more analytical instruments and process variables is used to predict Critical to Quality parameters or determine a qualitative process fingerprint (based e.g. on principal components). This resulting real-time information can be used to improve process understanding, improve online process follow-up or the control of specific critical to quality parameters for one specific Unit Operation or for optimization of the unit operation process.

**Visualization** of the predictions or principal components can happen through the specific SIPAT visualization graphical user interface (GUI) or via the Process Control System / HMI of the process equipment.

**SIPAT High Level**

SIPAT High Level enables **optimization of the complete process** across different Unit Operations. It gathers data from all Unit Operations via SIPAT Base Station systems. It
allows you to follow up the progress of the **total batch quality** throughout the manufacturing process and compare it to your process and quality specifications. SIPAT High Level enables **Real Time Product Release**. The actual Release can be communicated through the MES, LIMS or PCS system.

An example of a possible PAT architecture for a secondary manufacturing is illustrated hereunder:

In this case a SIPAT Base Station is used on the unit level for one unit operation. A similar solution is set up on the upper level where several unit operations can be combined and consolidated by a SIPAT High level instance. Each SIPAT has its own local data store with the capability of storing the raw data on a temporary basis before being passed to the central PAT Historian for long term archiving.

### 2.5. SIPAT Features

This paragraph describes the various SIPAT features in more detail.

#### 2.5.1. Control of the PAT Instruments

SIPAT offers integration to a series of supported analytical instruments. Each analytical instrument interface is a combination of the SIPAT Common Instrument Interface and an instrument specific part.

The SIPAT **Common Instrument Interface** includes a series of standard measurement functions like: initialize, start, stop, calibrate, log … This common part ensures the synchronisation and registration of measurements and validation programs as well as error handling. The instrument specific drivers translate these functions towards the specific instrument.
SIPAT can offer the advantage of having only one common user interface for different types of analyzers; obviously this facilitates use, training...

2.5.2. Measurements via the Process Control System

SIPAT uses industry standard open techniques for interfacing with 3rd party packages such as the Process Control System. If measured process parameters like e.g. pH, temperatures, pressure … are used within a PAT method, SIPAT can read these through OPC.

The same OPC communication can also be used to inform SIPAT about the start and finish of a batch, operation or phase.

2.5.3. Input from MES and LIMS

Besides online measurements from Analytical Instruments and Process Control, SIPAT can also use quality parameters from a LIMS system (e.g. raw material analysis results) like SIMATIC IT Unilab or an MES system like SIMATIC IT Production Suite.

2.5.4. Chemometrics / MVDA

In the Model builder (offline), you use SIPAT to gather measurement data and pre-treat them, consecutively you start analyzing the data and building and validating models. The models are stored in the SIPAT Archive with version information and status.

At runtime (online), SIPAT will collect data, do pre-treatment and use the model in background to make predictions. SIPAT will visualize and/or distribute the model results.

SIPAT does not force you to combine all predictions for a PAT Method in a single model: one Method can contain multiple models and can reuse the same measurements. To allow this, SIPAT foresees a common layer channeling and optimizing all model prediction requests.

2.5.5. Integrating SIPAT in the Control loop

To integrate PAT in the control loop, you feed the PAT predictions to the Control System. SIPAT can send predictions and principal components online to the Control System via OPC. These can consecutively be used in traditional PID controllers or Advanced Process Control (APC) techniques.

2.5.6. Output to MES and LIMS: Real Time Product Release

The LIMS and MES systems can also be integrated as outputs. A typical example would be to inform MES or LIMS about one or more Critical to Quality parameters to release a batch after a specific Unit Operation (Base Station SIPAT).

Alternatively, the High Level SIPAT system can inform MES or LIMS about the total batch quality allowing Real Time Product Release.
2.5.7. SIPAT Graphical User Interface

The SIPAT Graphical User Interface (GUI) can be used interactively to gather data according to a Design of Experiments (DOE), setup a new PAT Method or lookup extra information about actual or previous production batches. The setup of your configuration and interactive data gathering is flexible, but with full audit trail as discussed in the section on 21CFR Part 11 later in this document.

SIPAT can also be used in background (without GUI) based on specific settings: you can configure the system to start certain methods (and interfaces) automatically on specific computer systems. This way of working can be used to start SIPAT automatically in day-to-day business according to validated procedures without using the SIPAT GUI.

2.5.8. Process Analyzer Suitability and Performance tests

Typically instruments can not be used “as is” without first checking the performance. Therefore SIPAT foresees workflow execution to trigger calibration or a System Suitability Test (SST) using e.g. internal and external standards. In case of external standards, a typical way of implementing user interaction would be through the Process Control System integration: SIPAT triggers the PCS system to request user interaction; PCS should inform SIPAT about the successful execution of the proposed actions.

Different types of validation functions provided by the instruments can be used to determine the validity of measurements or to obtain calibration data which are used to correct measured raw data. This correction can be done either by the instrument itself or by SIPAT. If required, SIPAT can also execute other calculations on measured data or predictions (e.g. calculate the average of certain measurements, background subtraction…).

2.5.9. Version management, Access Rights and 21CFR11

SIPAT Configuration objects (methods, models …) have a specific status and version, to allow a clear differentiation between objects in development or testing phase, objects validated for operations and obsolete objects.

SIPAT Configuration allows you to define certain User Profiles. Each user has its own unique User identification and Password; every user is linked to one (or more) User Profiles. Access Rights are assigned to Users through these User Profiles; some examples of possible User Profiles are:

- visualize data only
- system administration only
- run validated Methods / Models only
- all configuration & operational activities (but no system administration)

Configurational changes and relevant operational actions are registered in detail in the Audit Trail (containing time-stamp, user identification, comments…).

SIPAT also supports other 21CFR Part 11 requirements like record reproducibility, Record Protection and Retention and Electronic Signature. The development of SIPAT happens according to a formal life cycle approach.
2.5.10. SIPAT Archive and Knowledge Management

All configuration data, captured operational data and Audit Trail data are stored in a relational database (the SIPAT Archive).

SIPAT data (measurements, predictions, batches) can be tagged by the user with comments which can be reviewed or analyzed later on.

The SIPAT Archive is an open database structure. Users with the required Access Rights can access the database (read-only) to retrieve data via reporting tools like Business Objects or Microsoft Reporting Services. It is also possible to extract certain data for further analysis in other tools (statistical tools, Microsoft Office …). These tools can be used to review, compare and analyze data.

2.5.11. Customer-specific requirements

The SIPAT software product offers a lot of standard functionalities; these can be configured by the trained key users using the SIPAT configuration graphical user interface. On top of this, the SIPAT standard software also offers possibilities to customize system behavior according to customer specific requirements.

Possible customer specific extensions are e.g. adding extra preprocessing and post processing logic to certain SIPAT functionalities or adding a non-standard interface driver (by extending standard interface logic with instrument or system specific logic).

Adding customer specific extensions includes good requirements definition, functional and technical design, programming, systematic testing and validation. Obviously Siemens can either support you in the creation of these extensions or realize them for you. See also chapter 4 on the implementation approach.

2.6. SIPAT interfaces

SIPAT interfaces are able to handle various systems:

- **Interfacing to process analyzers**
  SIPAT is able to connect with different types of analyzers. It provides full instrument configuration and control (limited only by the facilities provided by the instrument manufacturer). Via drivers for each instrument individually capabilities will be maximized. It also provides data collection and storage and analyzer performance tests (analyzer diagnosis, result storage and comparison, alarming). (Limited to the facilities provided by the instrument manufacturer.)
  Various interfaces are possible for the Analyzer to SIPAT connection: file communication, serial communication, OPC, proprietary interface (DLL) …
  Like with our Siemens LIMS system, SIMATIC IT Unilab, we have a long experience in interfacing various types of analyzers from different vendors.

- **Interface to data mining tools**
  SIPAT is able to connect with different types of Data Mining or MVDA software packages. New interfaces can be created for various required third party / external
packages. By this modular approach, impact of changes (and corresponding validation efforts) on the system is limited.

Chemometrics software tools are integrated and embedded in SIPAT and allow to deal with on-line (uni- and multivariate) monitoring.

The Umetrics software modules all are “off-the-shelf”, and are 21CFRpart11 compliant. (Software audits have been made by AstraZeneca twice, GSK, and Beiersdorf.)

- Simca-P and Simca-P+ (v.11.0) for multivariate data analysis, trouble shooting, multivariate calibration, multivariate batch and continuous process model building. A general chemometrics multivariate software for calibration, classification, pattern recognition, quantitative relationships (PLS), time series process modeling (continuous and batch), etc., with extensive diagnostics and graphics.

- Modde (v.7.0) for DoE and experimental optimization in the process development stage. Has all classical screening and RSM designs, mixtures, mixture and process designs, and Onion designs for complex situations. Multiple regression and PLS for the data analysis, extensive graphics, sweet spot plots, optimizer plots, and more tools for predictions.

- Simca QP+ for on-line predictions is standardly embedded as prediction engine for SIPAT.

The CAMO software Unscrambler® is a complete Multivariate Analysis and Experimental Design software solution, equipped with powerful methods including PCA, Multivariate Curve Resolution (MCR), PLS Regression, 3-Way PLS Regression, Clustering (K-Means), SIMCA and PLSDA Classification.

- Unscrabler Classifier (v9.8) performs real-time classification of raw data obtained from laboratories or process equipment. It supports SIMCA classification, automatic data preprocessing and PCA models.

- Unscrambler Predictor (v9.8) performs real time predictions from data obtained from laboratory or process equipment. It supports automatic data preprocessing, MLR, PCR and PLS-R models.

MATLAB® version R2007B is a high-level technical computing language and interactive environment for algorithm development, data visualization, data analysis, and numeric computation.

2.7. SIPAT models

SIPAT can be used for building and using models on various levels:

- Analyzer model
  Model based on data collected on a particular analyzer (e.g. NIR for creating an analyzer model, prediction of a certain parameter or the creation of PCA trend plots)
• **Unit Operation model**
  Model based on data collected on one particular unit operation (data from sensors, analyzers, etc…) (e.g. combination of pH, temperature, pressure and dissolved oxygen and NIR data, for a bioreactor unit operation)

• **Process (line) model**
  Model based on data collected from the various unit operations of the complete process line, from raw materials up to the end product.

• **Product model**
  This is a future model based on data collected from the various unit operations of the complete process line, combined with clinical data.

The following picture shows the relationship between the different models.

![Product Model (including clinical data)](image)

### 2.8. SIPAT IT Architecture

SIPAT has a multi-tier architecture. Each SIPAT system is composed from a database layer, an execution layer and a graphical user interface layer.

The **GUI layer** is realized through a Windows GUI which runs on a client PC and requires the .Net framework 2.0. The GUI includes the configuration interface, the visualization and the Model Builder. The supported client operating systems are Windows 2000 and Windows XP. Support for Windows Vista will be released in a future version.

The **database layer** is realized with a SQL Server or Oracle database. This database can provide for different degrees of high availability like database mirroring or clustering. The supported databases are the Standard or Enterprise Edition of SQL Server 2005 and Oracle 10g. To ensure a reliable PAT system, it is recommended to run the database on a system specifically dimensioned to run one or more databases with good monitoring and backup.

The **execution layer** includes the SIPAT methods, interfaces, chemometrics background calculations … The execution layer components are designed with a strong focus on scalability and reliability. Because of this, these components run as separate
Windows Services. They can be combined on one system or spread over different computer systems as required:

- interfaces to the different analytical instruments can run on one or multiple computer systems
- the same remark applies to the OPC interfaces (these can run on the system of the OPC server, avoiding the use of DCOM)
- other SIPAT components that can run separate from each other include the Method Execution, the chemometrics interface and the online chemometrics interface.

The communication between the SIPAT execution components happens through TCP/IP. To minimize the chance of data loss, instrument interfaces can log all gathered data to separate log files as backup. The SIPAT execution components can run on Windows 2000 and Windows XP. The .Net framework 2.0 is required.
The execution components of different PAT methods (Base Station and High Level) can run centrally on one or multiple computer systems or decentrally close to the instruments depending on the IT strategy within your company.

A standard installation of SIPAT requires one database for each SIPAT Base Station or High Level SIPAT, but other architectures are supported (e.g. sharing one DB across all Base Stations in one site). Future versions of SIPAT will also support distributed setups for the database, allowing long-term archiving in a separate data warehouse.

2.9. SIPAT and process control

Process controls are carried out by the Process Control System (PCS) by making use of simple controls (PID's) or more advanced, like APC (Advanced Process Control) or MBPC (Model-Based Predictive Controls). For this a control model is required to perform complex and indirect controls.

The unit operation model or process model serves as a basis for the development of a control model. This model is used to perform process control actions (feed-back and feed-forward controls) and corrections.

The PAT system (with the SIPAT Execution Module and the build-in MVDA module) is taking care of the quality aspects of the process and is making this information available to the control system. The control system can on its turn take care of the control and correction actions. Both systems are real-time interfaced by an OPC interface to perform feed-forward / feed-back control.

The implementation of PAT into the control system and the ability to produce quality by design or right first time, is achieved by moving from using the PAT infrastructure for just monitoring to PAT integrated into the control system. This last one allows real-time product release.

As the statistical / MVDA world and the control world are different fields of expertise, and difficult to merge together, we believe we have strength to offer here. Siemens has established a team of experts who are skilled in these different expertise fields.
In general this is relatively new for the pharma industry, but is applied already for more than a decade in the hydrocarbon process and pulp & paper industry. Here we are making use of the long-lasting experience we have built, in these industries and translated it to the pharma industry.

**SIPAT Base Station**

As PAT will eventually also be used to control (“design, analyze and control manufacturing”), it needs to be integrated into the control layer. This can result in the integration with the package unit (unit operation machine). Before starting the batch, a user needs to know if the PAT environment is ready for use. This can be done by checking the status. Afterwards an operation is started on the unit (e.g. through the batch system), the package unit will start the operation and the corresponding PAT method also needs to be started. Results coming out of the PAT method need to be translated into control actions and results need to be stored in the process historian (either SIPAT has link to the historian or data passes through the package unit towards historian, both scenario’s are possible). The Raw data are stored in SIPAT Archive.

**SIPAT High level**

To be able to apply the overall process model, the High Level PAT needs data from all unit operations, raw materials etc…This means it has to interface with the central process historian.

A typical view with a unit operations trend, looks as follows (with the green curve, the golden batch trajectory, the red curves the control limits and the black curve the actual process trend, being build-up in time).
In case the actual process is going out of the acceptance boundaries (red line), a diagnosis function can be called, to investigate the root cause of a process deviation. This can be for example a contribution plot to find out the main cause for a certain process deviation.

2.10. SIPAT and MES
The integration of the PAT system into the MES (Manufacturing Execution System) allows having full transparency on the status of the product in the manufacturing chain. The integration of SIPAT with the LIMS, the Production Data collection system and the Production Performance Analysis tool (all components of the Siemens Simatic IT MES system) results in having access to real-time quality and manufacturing performance information. The combination of these components forms a true Quality Management System.

SIPAT follows the Siemens component-based philosophy for manufacturing infrastructures, achieving the possibilities to have full transparency from lowest level up to the ERP system, resulting into quality, manufacturing performance, supply chain and maintenance dashboards. In this way PAT is an important component for realizing transparent manufacturing operations, which can produce according to market demand, just in time (JIT).

2.11. PAT for development and manufacturing
PAT has also benefits, when applied in development, especially in process development and later on tech transfer to commercial manufacturing. The role of PAT in development
is mainly to collect process knowledge on equipment / product interaction, equipment behavior and impact on final product quality. This will facilitate and fasten process up-scaling and transfer.

The scheme below shows the infrastructure required to facilitate process development and transfer to commercial manufacturing. SIPAT fully supports this and allows interfacing with knowledge Management Systems.

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**2.12. SIPAT Stepwise PAT implementation**

SIPAT supports a stepwise PAT implementation according to 2 dimensions:

- SIPAT can be implemented for one Unit Operation, multiple Unit Operations and/or the full process. We call this dimension the width of the PAT implementation.
- Because of its modularity, SIPAT can be implemented on different integration levels. We call this dimension the depth of the SIPAT implementation.

It is very important to define a clear scope (width and depth) and implementation strategy for every SIPAT implementation.
Our Roadmap is a step-wise approach for a gradual PAT implementation in which validation requirements are fully integrated.

The approach consists of the following 6-steps:

**Step 1 “Preparation”:** confirm scope and objectives, team assignment, business case development and define the deliverables.

**Step 2 “Assessment”:** assess process and product aspects related to Quality (CTQ process steps and parameters)

**Step 3 “Analysis”:** data mining of existing process and quality data, gather new data (introduction of additional process analyzer tools), perform DoE, develop mathematical models of the production process via MVDA tools.

**Step 4 “Control”:** definition and implementation of control and correction strategies.

**Step 5 “Release”:** definition and implementation of release criteria and supporting infrastructure.

**Step 6 “Optimization”:** continuous improvement and further fine-tuning cycle
3. FURTHER INFORMATION

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