



# How Medical Device Manufacturers Can Improve Quality by Applying the Principles of Process Analytical Technologies (PAT)

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## **Abstract**

This white paper reviews how the Process Analytical Technologies (PAT) originally developed by the FDA for the pharmaceutical industry can also improve quality and efficiency in medical device manufacturing. The underlying principle of the PAT approach is that quality should be designed into the product based on a fundamental understanding of the critical manufacturing processes. This understanding is derived from the wealth of data collected by real-time process analyzers, which is then analyzed, organized and stored using multivariate tools and highly integrated information management systems. These tools provide the basis for a process control methodology that manages product quality in real-time, instead of the traditional batch-based approach. This leads to the implementation of a Real-Time Release strategy, where product quality is evaluated in real-time, on a part-by-part basis, based on the process data. This ensures not only a higher level of product quality, but also improves throughput and efficiency. To demonstrate how the principles of PAT can be applied to medical device manufacturing, a simplified example consisting of a single resistance weld process is explored. From developing the process using a series of DOE trials, to volume manufacturing using the real-time release strategy, and the collection of detailed device history records, we show how the PAT process can be applied to a medical device, and how much the manufacturer stands to gain.

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In September 2004, the FDA published the report, “Guidance for Industry PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance,” in which it made the following statement regarding the current state of pharmaceutical manufacturing:

“Conventional pharmaceutical manufacturing is generally accomplished using batch processing with laboratory testing conducted on collected samples to evaluate quality. This conventional approach has been successful in providing quality pharmaceuticals to the public. However, today significant opportunities exist for improving pharmaceutical development, manufacturing, and quality assurance through innovation in product and process development, process analysis, and process control.”

While this was written specifically about pharmaceutical manufacturing, it could just as easily be applied to the manufacturing of medical devices. After all, a great many parallels can be drawn between the goals, practices and challenges in manufacturing either type of product in this highly-regulated industry. In fact, the underlying principles of PAT can be applied to virtually any type of manufacturing environment, regardless of industry.

The goal of the manufacturer is the same in both the pharmaceutical and device industries: Efficient manufacturing that provides safe, effective and affordable products to the consumer. To achieve this, the PAT document provides a framework based on the principle that quality should be built into the product at the manufacturing process level. This is accomplished through a comprehensive understanding of:

- The intended product objectives;
- The physical properties of the product;
- The product design, including selection of sub-components and packaging; and
- The design of manufacturing processes using principles of engineering, materials science and quality assurance.

All of these attributes are just as critical to developing manufacturing processes that ensure the highest quality medical devices. The desired product functionality and performance requirements, the environment it is intended to work in, and the expected lifetime of the device define the

product objectives, and thereby establish the criteria for product quality. How well the device will meet these requirements is a function of the product design, including the physical properties of the materials, the make-up of the assembly (i.e. componentry, packaging), and the processes used to put them together. The emphasis is on *building quality into products*, based on a detailed understanding of all the items listed above, and the recognition that interactions between factors are often as important as any individual factors on their own. Therefore, a focus on the multivariate relationships between the materials, manufacturing processes, environmental conditions, and their combined effects on final product quality is essential to developing an accurate understanding of the critical relationships that determine product quality.

### The Importance of Data

If a detailed understanding of the manufacturing processes is the foundation upon which the PAT principles are based, then *data* is the key to forming a strong foundation. Data provides the basis for understanding and controlling critical processes, and enables manufacturers to efficiently and consistently deliver high quality products. In the end, data provides protection to manufacturers and consumers against widespread product failures or recalls. As a result, the principles of PAT require tools and technologies that acquire, analyze and store data that captures all of the critical factors that impact product quality.

By implementing the principles put forth in the PAT guidance, the FDA suggests that the pharmaceutical manufacturer can expect to achieve improvements in quality and efficiency due to the following:

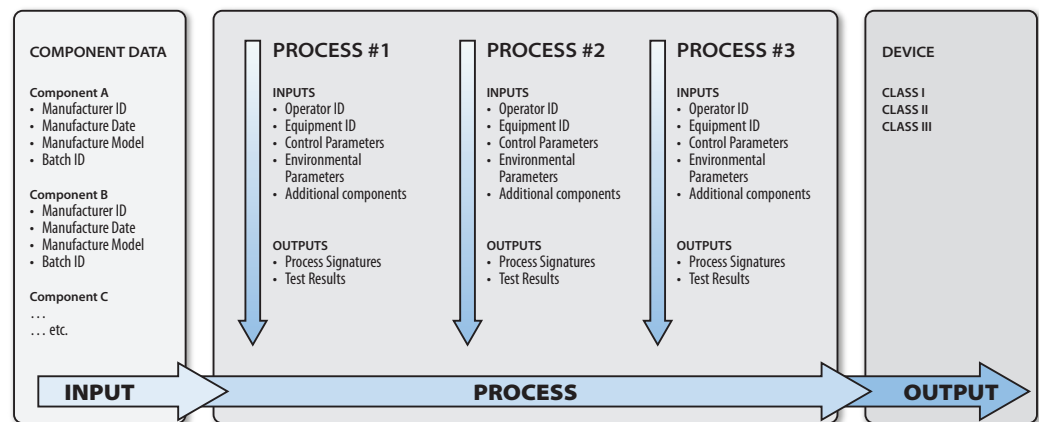
- Decreased process development and validation cycles;
- Reductions in production cycle times using production measurements and controls;
- Prevention of rejects, scrap and re-processing;
- Real-time release of product;
- Increased automation to reduce human error; and
- Continuous improvements that improve efficiency and manage variability.

With a similar focus on data collection and analysis, all of these benefits become equally applicable to the medical device manufacturer. In addition, the emphasis on data collection and storage results in the creation of a detailed quality record for each manufactured device. The accumulation of a comprehensive database of fundamental process data derived from thousands, or even millions

of parts, provides an invaluable tool for continuous process improvement, new process or product development, risk management, and communication with regulatory bodies, such as the FDA.

### Applying the Principles of PAT to Medical Devices

The foundation of PAT is *process understanding*. Ideally, this means that all potential sources of process variability have been identified and explained. For a medical device, potential sources include the properties of incoming materials, process parameters, process signatures, environmental conditions and manufacturing conditions such as operator knowledge and experience, and equipment maintenance. If the interactions between all the critical inputs are understood, then by collecting and analyzing the associated data, it should be possible to accurately and reliably predict the key attributes of the finished product. The relationships between the various process inputs and the final product are illustrated by the chart in Figure 1 below. As suggested by the FDA in the PAT guidelines, this enables the implementation of real-time process control and quality assurance.



**Figure 1:** Schematic illustration of how process variables combine to determine the outputs of complex manufacturing processes

### The Tools of PAT

The FDA guidelines describe a number of tools that are central to implementing the PAT strategy. These include multi-factorial tools for design, data acquisition and analysis, process analyzers, process control tools, and continuous improvement and data management tools. In this section we will explore how each of these tools can be applied to medical device manufacturing.

### ***Multivariate Tools***

It is clear that practically all manufacturing processes can be affected by a wide range of factors, many of which may combine to produce complex interactions that cannot be fully understood based on a simple, single variable analysis. In these cases, a number of inputs must be explored simultaneously, using a *multivariate* approach. Consider, for example, an indenter-crimping process, where a conductor is crimped around a stainless steel pin. Critical sources of process variability might include differences in force applied during the crimp, the displacement of the metal, velocity of the crimp and so on. In addition, certain sub-component and environmental characteristics may also be a factor, such as the operator using the equipment, the inside and outside diameter of the components, their batch IDs or even the ambient temperature at the time the crimp was performed. All these factors may have an impact on the quality of the crimp. If, instead, we considered only the force applied during the crimping process without also including the effects of other potentially critical variables, we would develop an incomplete model of the crimping process. Without a fundamental understanding of how the various inputs interact to determine the process outputs, we would not be able to accurately predict or control product quality.

Developing this level of understanding requires a method of analyzing the interactions between the different process inputs to determine which parameters have a significant impact on product quality. In practice, the number of factors to be considered, and therefore the number of possible multivariate interactions, can be quite large. These types of investigations are typically managed using the Design of Experiments (DOE) approach. In general, this involves systematically varying a small subset of the critical inputs while holding all other parameters constant. The critical inputs being studied are varied across a range of expected or allowable values to fully characterize their combined impact on part characteristics that are critical to quality. Upon completion of the DOE, the data provides a map of the interactions between the various critical inputs and their impact on product quality.

In a very simple case where there are only one or two critical parameters, mapping and analyzing the DOE data is relatively straightforward. This is illustrated in Figure 2(a) below. However, as discussed above, in most cases there are a number of parameters that have an impact on product quality, and the various interactions between

**...many complex interactions cannot be fully understood based on a simple, single variable analysis.**

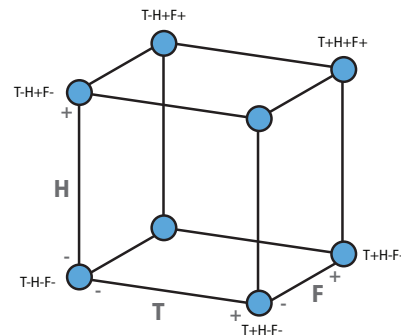
them need to be considered. Figure 2(b) shows how adding a third parameter doubles the number of potential interactions, as the complexity increases exponentially with the number of factors. In these situations, the DOE methodology provides a systematic framework that ensures all key interactions are covered, while also helping streamline the number of trials. Once the trials have been completed, advanced multivariate analytical and data management tools become essential for analyzing and interpreting the data. Ideally, these multivariate tools should combine a database for storing and retrieving large data sets, with advanced statistical analysis functions for uncovering the correlations between the critical inputs and product quality.

a)

Parameter		F-	F+
T	Temperature	T+F-	T+F+
F	Force	T-F-	T-F+

b)

Parameter	
T	Temperature
F	Force
H	Humidity



**Figure 2:** Illustration of full-factorial DOE for (a) two-factor, two-level, and (b) three-factor, two-level parameter space.

This science-based approach of correlating process knowledge to product quality should not be limited to process development. By continuing to acquire process data during manufacturing, the device maker can build a vast database from thousands of parts in a live production environment that takes into account real-world variables. When analyzed with the appropriate multivariate tools, this database of historical records fosters a deeper understanding of the process, which, in turn, provides a framework for continuous improvement. The PAT guidance document states:

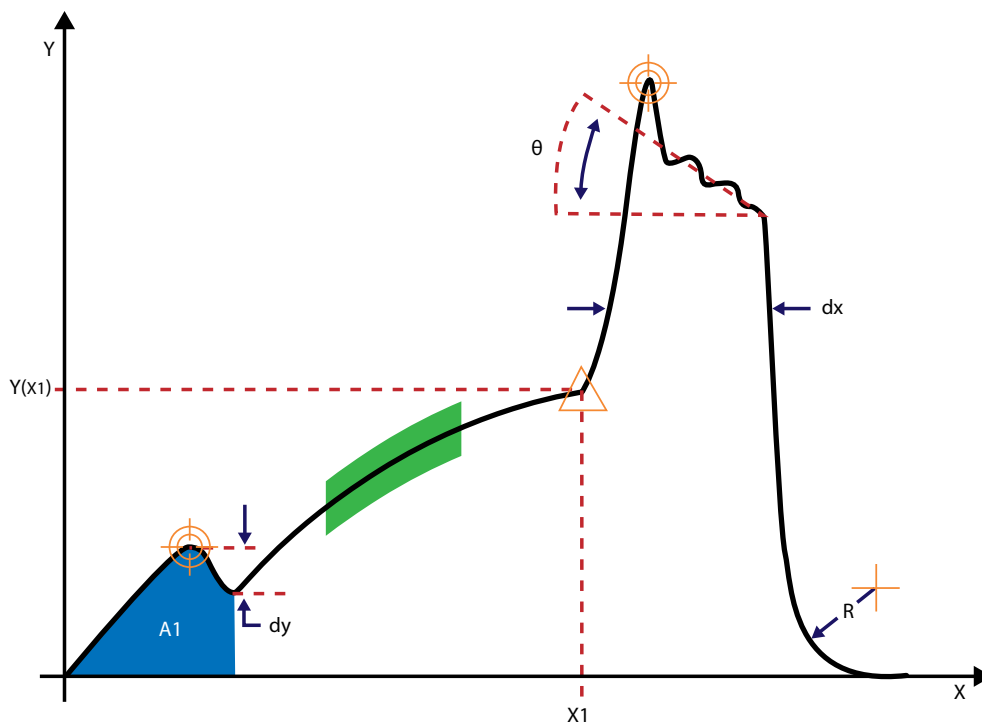
“Experiments conducted during product and process development can serve as building blocks of knowledge that grow to accommodate a higher degree of complexity throughout the life of a product... As this institutional knowledge base grows in coverage (range of variables and scenarios) and data density, it can be mined to determine useful patterns for future development projects... When used appropriately, [multivariate analysis tools] enable the identification and evaluation of product and process variables that may be critical to product quality and performance.”

### *Process Analyzers*

An essential component of the PAT methodology is a class of measurement devices described as *process analyzers*. These devices measure critical parameters during the manufacturing process, providing the data that is collected and analyzed by the multivariate tools described above. These measurements can be made in-line -- that is, without removing the sample from the process -- or off-line, where the sample is removed from the process for analysis and may or may not be returned to the stream following completion of the measurements. While some of the process analyzers described in the PAT guidance are specific to pharmaceutical manufacturing, the principle of in-process monitoring is not. In medical device manufacturing, process analyzers measure variables such as temperature, force, resistance, displacement, visual characteristics and more. These are used to characterize a broad range of electro-mechanical assembly processes, from moulding, welding and sealing, to crimping and gauging.

As highlighted in the PAT guidance, “sensor-based measurements can provide a useful *process signature* that may be related to the underlying process steps or transformations.” A *process signature* is a characteristic curve that is generated by plotting a process variable against a related reference variable, which for a medical device might be something like current vs. time, or force vs. distance. The distinction between good and bad parts is often clearly revealed by differences in the process signatures. This differentiation can usually be boiled down to one or two key features, such as inflection points, slopes, curvatures (i.e. 2nd derivative) or frequency content that can be extracted from the signatures and mapped against product quality in a multivariate analysis. An example of a process signature showing a variety of features is shown in Figure 3. Furthermore, the relationships identified by this analysis reveal which signatures can then be used to monitor and control product quality. As stated in the FDA guidance, “these signatures may also be useful for process monitoring, [and] control ... when these patterns or signatures relate to product and process quality.”

**The distinction between good and bad parts is often clearly revealed by differences in the process signatures.**



**Figure 3:** Example of a process signature, illustrating some typical features that can be extracted from the curve and correlated with product quality.

### Process Control Tools

The *process-control tools* described in the PAT guidance are essentially a collection of strategies for actively manipulating the manufacturing processes to a desired state. This requires that the process-control strategies provide a means for controlling all of the critical parameters that have an impact on product quality. These strategies should incorporate the characteristics of the input materials, environmental conditions and equipment-related factors. This then enables real-time, closed-loop control of the manufacturing process based on the multivariate relationships that have been established between the various inputs and the in-process data collected by the process analyzers.

The role of the process-control strategies is highlighted in the simple four-step method for the design and optimization of manufacturing processes outlined in the PAT Guidelines. This is a generic approach that is applicable to *any* manufacturing process, including medical devices.

1. Identify and measure critical material and process attributes relating to product quality.
2. Design a process measurement system to allow real-time or near real-time monitoring of all critical attributes.
3. Design process controls that provide adjustments to ensure control of all critical attributes.
4. Develop mathematical relationships between product quality attributes and measurements of critical material and process attributes.

Steps 1 and 2 relate to the installation of appropriate process analyzers, ensuring that all critical parameters are monitored, where step 2 emphasizes that real-time, in-process data is essential. Step 3 highlights the need for process controls that allow all the critical parameters to be managed and controlled. Finally, step 4 calls for the development of unambiguous, mathematical relationships between the measured data and the final product quality.

This provides the mechanism for closing the loop between the measured data and the process controls that enables the manufacturer to consistently produce the desired results.

While the PAT guidelines point out how this strategy can be used to address the relevant cGMP (current Good Manufacturing Practices) requirements for process controls in pharmaceutical manufacturing, similar applications apply in device manufacturing. For instance, 21 CFR 820.70(a) (Production and process controls) identifies the need for “monitoring and control of process parameters and component and device characteristics during production,” while 21 CFR 820.75(b) (Process validation) states, “Each manufacturer shall establish and maintain procedures for monitoring and control of process parameters for validated processes to ensure that the specified requirements continue to be met.” These excerpts show that the use of in-process monitoring to control critical processes and ensure product quality is already prescribed in the existing cGMP requirements for medical device manufacturing.

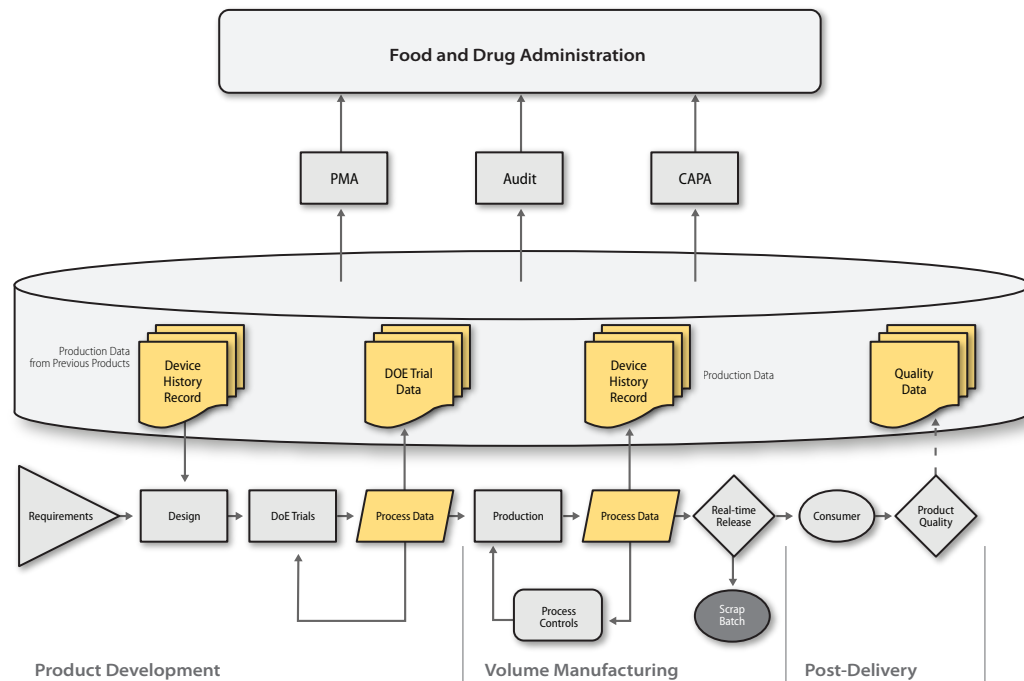
**... in-process monitoring is already prescribed in the existing cGMP requirements for medical device manufacturing.**

#### ***Information Management Tools***

The *Continuous Improvement and Knowledge Management Tools* described in the PAT Guidelines refer to the information-technology systems and tools that manage the collection, storage and retrieval of process-related data over the entire life-cycle of the product. This data can be used not

only to develop but also to justify process or product changes. An illustration of the end-to-end information management structure is shown in Figure 4.

Given the potentially large volumes of parts that are manufactured, and the range of parameters that are tracked and recorded for each part, the amount of data generated throughout the product lifecycle can be massive. Therefore it is important that manufacturers deploy information-technology (IT) systems that are capable of managing and analyzing vast amounts of detailed data, so that they can explore new scenarios by extrapolating from the collected data and accumulated process knowledge. Ideally this would include the ability to store and analyze a variety of data types including text, scalar numbers and full process signatures. In addition, comprehensive data management systems are essential to the efficient collection and presentation of data for communication with regulatory bodies such as the FDA.



**Figure 4:** Diagram illustrating the collection and management of data from all phases of the end-to-end process from development through volume manufacturing to post-delivery management.

### Real-Time Release

*Real-time release* is defined in the PAT Guidelines as “the ability to evaluate and ensure the acceptable quality of in-process and/or final product based on process data.” This represents a fundamental shift away from conventional quality-assurance practices, which have traditionally relied on statistically based, end-of-line batch testing for determining the quality of the manufactured product. In this new approach, the process data alone, which can include subcomponent or raw material characteristics, environmental conditions, in-process data such as process signatures, and equipment-related parameters, is analyzed to determine product quality. This determination is based on the relationships between the process data and the product attributes that were derived using the multivariate tools described previously.

The transition from end-of-line batch testing to real-time release offers significant benefits to both the manufacturer and the consumer, including superior product quality through 100 percent testing, increased throughput and an overall reduction in manufacturing costs through the elimination of end-of-line testing, and enhanced risk management based on detailed, part-by-part test records. For the medical device manufacturer, real-time release is perhaps the most important incentive for implementing the PAT methodology. For a more detailed discussion of the advantages of real-time release, please refer to the whitepaper, “How to Eliminate Destructive Testing”.

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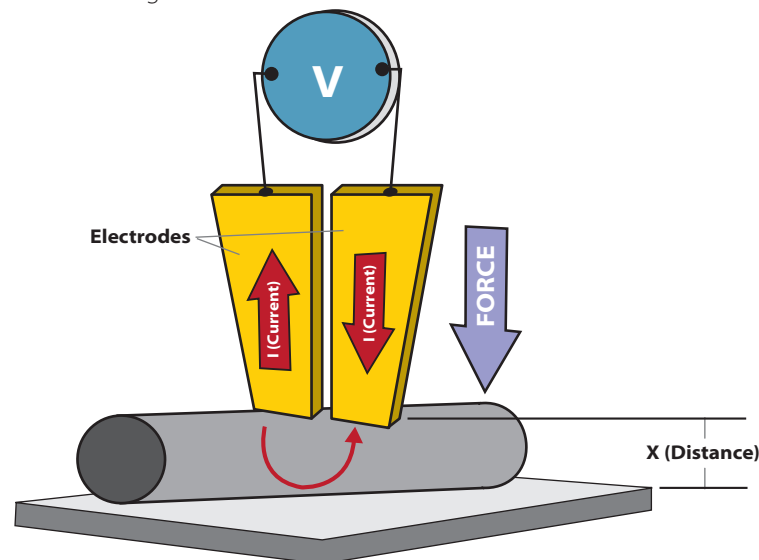
### Integrated Systems

The PAT Guidance document prescribes an *Integrated Systems Approach* where the development, manufacturing, quality-assurance and information-technology teams work together in a coordinated fashion and where information and knowledge are shared and communicated effectively between the various teams. The need for this high level of integration can be traced to the foundation of process understanding and end-to-end data collection and analysis upon which the PAT methodology is based. Maintaining close communication and coordination between the teams enables rapid product development cycles and simplifies the transfer to manufacturing, while maximizing both manufacturing efficiency and product quality. For example, the R&D team can more quickly develop new manufacturing processes and products by taking advantage of the wealth of data collected during production runs of existing products. Furthermore, feedback from the manufacturing engineers and quality assurance

helps ensure that the products and manufacturing processes developed by the R&D teams take into consideration the goals and constraints that are present in volume manufacturing, such as efficiency, repeatability and consistency, and product quality. Similarly, manufacturing and quality-assurance engineers will be able to develop a more effective test strategy when they have access to development data related to the formation of defects in critical processes such as welds, crimps or seals. The corporation as a whole will see an increase in revenue and profits as time to market is reduced, production costs are lowered and product quality is maximized. To achieve this level of communication and coordination, data must be readily accessible to all parties, which requires a strong information technology infrastructure. This includes not only the databases and analysis tools described in the section on information management tools, but also the support and involvement of the IT team.

### Implementation

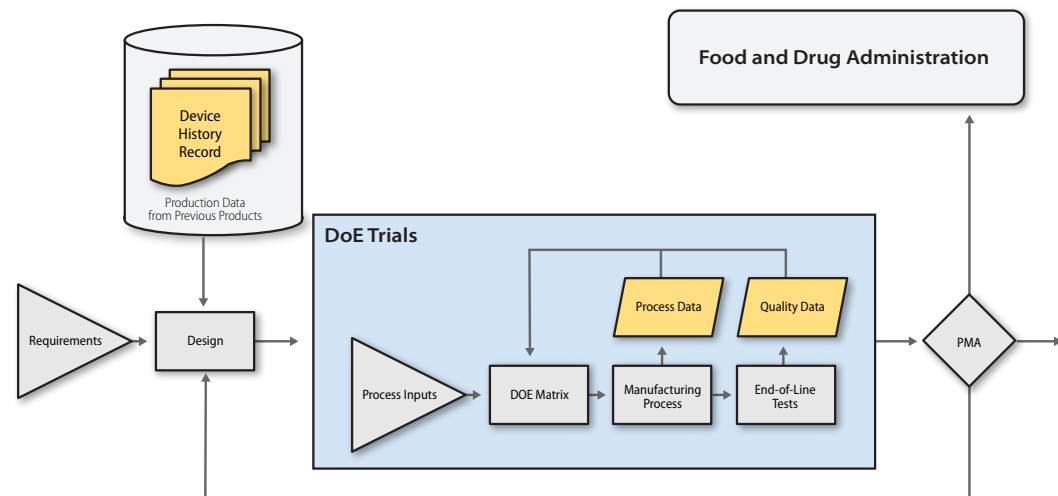
In this section, we will examine a medical device example to illustrate in greater detail how the principles of PAT can be accomplished, and what the benefits are. Let us consider a generic implantable class III medical device. We will assume that this device consists of a number of electrical components, including a small printed circuit board assembly (PCBA), wires and leads that are welded to the components and PCBA, and a molded plastic housing. For the sake of simplicity, we will focus on the resistance welding process that attaches a narrow gauge wire to the PCBA, as illustrated in Figure 5.



**Figure 5:** Schematic illustration of the resistance welding process for attaching a wire to a printed circuit board, indicating the parameters that would be measured by the process analyzers.

## Process Development

During the process-development stage, the manufacturing processes may still be poorly understood, and the relationships between the process parameters and the product attributes largely unknown. To develop the process understanding necessary to implement the PAT methodology, process analyzers must be installed on all potentially critical process parameters to collect process signatures for analysis. In addition, all process inputs must be recorded, including subcomponent or raw material characteristics, environmental conditions, operator or station dependencies and others. The process development cycle described in this section is illustrated by the flow chart in Figure 6 below.



**Figure 6:** Flow chart illustrating the process development cycle

During the development phase of our generic device, looking specifically at the weld process, the device manufacturer might consider a range of choices for the wire and PCB, including manufacturer, wire gauge (thickness), and material composition, such as the metallic composition of the wire and the bonding surface on the PCBA. Other process inputs to consider include environmental conditions such as temperature and humidity; the welding equipment, including calibrations or other settings; and perhaps even which operator is staffing the station. Process analyzers would be used to monitor all the potentially critical variables, including high-resolution measurements of the weld voltage and current, load cells to measure the applied force and encoders or linear transducers to measure the weld distance. Measuring these parameters throughout the weld process yields process signatures that reveal key features such as the dwell

time of the weld, the weld depth and the variability of the current. Collectively, this constitutes the *process data* that is recorded for each sample assembled during the development trials.

#### ***Developing a Test Methodology***

To evaluate the relationships between product quality and the various process variables described above, a test methodology must be developed that will assess how product performance and reliability are affected. For the weld process in our example, the key characteristics are the electrical conductivity of the joint (performance) and the strength and durability of the connection (reliability). Electrical performance can be characterized by resistance measurements, while the strength of the weld can be evaluated by pull tests, where the force required to remove the wire is measured. Long-term reliability can be assessed by subjecting the sample to accelerated aging tests, where it is exposed to high heat and humidity to accelerate any failure mechanisms that may become active when implanted in a human body. The welded joint would then be tested for any degradation in electrical resistance or pull strength.

To fully characterize the effect of the different process inputs on the quality attributes, trials must be performed across the full range of possible inputs. Even with a relatively small number of process inputs, as in this example, the matrix of possible permutations and combinations can quickly become substantial when all possible interactions are taken into account. The DOE approach outlined in the section on Multivariate Tools can be invaluable in reducing this to a manageable matrix of experiments.

#### ***Running the DOE***

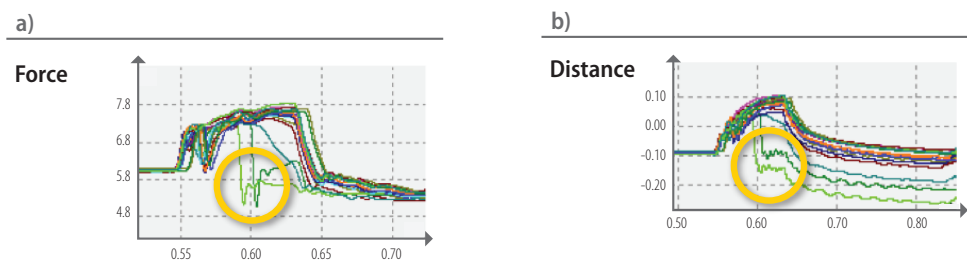
Consider the DOE that might be generated by our weld example. During the development phase, where all potentially critical parameters are considered, the DOE might encompass variations in weld current, weld time, force, distance, temperature, wire manufacturer, wire gauge and wire composition. This would result in a nine-dimensional DOE matrix where the nine parameters are systematically varied across a number of trial runs, with a selection of parameters changed on each run. For each permutation, a number of devices would be manufactured and characterized for performance and reliability, as described above. All the data would be stored in a database for easy access and retrieval for analysis. Multivariate statistical analysis would then be applied to identify causal relationships between the various parameters and the quality of the weld.

**The DOE approach can be invaluable in reducing this to a manageable matrix of experiments.**

Out of this original DOE, the parameters that have the largest impact on the key product attributes would be identified. In this case, let's assume that only five parameters -- weld current, dwell time, force, wire gauge, and wire composition -- have a significant impact on the quality of the weld. Secondary DOEs could then be designed to further refine the empirical models that describe the causal relationships between the different parameters and product attributes. These DOEs should also yield an optimal set of process inputs and control parameters that yield the best combination of product attributes or, put another way, target values and acceptance ranges for each of the critical parameters that will yield the highest quality product.

### Analyzing the Data

Beyond identifying critical parameters and target set points for manufacturing, the multivariate analysis also provides valuable insight into the underlying physical processes that determine product quality. In our weld example, analysis of the DOE results revealed that the quality of the weld was determined by a set of multivariate relationships between just five of the original nine process parameters. For example, we might observe that a high current in combination with a long dwell time results in an inferior weld. Examination of the process signatures then reveals a sudden change in the force and position of the electrode(s) during the weld process, as shown in the charts in Figure 7. This indicates that over-heating due to an excess of electrical energy results in an expulsion of molten metal from the weld pool. The loss of material causes the observed shift in the electrode position and produces a physically weaker welded joint, which may also have a higher electrical resistance. This example illustrates how process signatures can be used to gain insight into the underlying physical processes, and how defects are produced. This fundamental understanding can often enable the process to be optimized with fewer iterations, resulting in a shorter development cycle and accelerating time-to-market.



**Figure 7:** Process signatures for a resistance weld process, showing (a) Force vs. time and (b) Distance vs. time. The circles highlight features associated with an expulsion due to overheating of the weld pool.

Finally, the data collected and analyzed through the DOE can also be used to form the basis for a Premarket Approval (PMA) submission, which is required by the FDA before a manufacturer can market a new medical device. A successful PMA submission must be accompanied by enough data for the FDA to judge the safety and effectiveness of the new device. This is more easily accomplished when there is a comprehensive dataset demonstrating that the critical processes are well understood, and the relationships between the process controls and product attributes have been established. In addition, by implementing a real-time release process based on in-process monitoring, the manufacturer would be able to ensure a higher standard of quality through 100 percent product testing. Altogether, the PAT methodology would allow the manufacturer to present a convincing argument that the manufacturing processes are robust and well-controlled, and would ensure the product safety and effectiveness required for PMA approval.

**Implementing a real-time release process based on in-process monitoring, can ensure a higher standard of quality through 100 percent product testing.**

### Production

The process knowledge derived from the development DOE provides the foundation for developing and refining the production processes. The development and manufacturing teams work closely together, using the DOE results to develop a volume manufacturing process that is optimized for both quality and throughput. This includes implementing a monitoring strategy that ensures the relevant process signatures are recorded, while also controlling and maintaining the critical processes at their optimal settings. The process-monitoring-and-control strategy should be applied with the goal of implementing a real-time release methodology to provide the most efficient manufacturing processes and highest-quality product possible.

In our wire-to-PCBA weld process example, the development team has determined that the quality of the weld is a function of the multivariate relationships between five of the input variables (weld current, dwell time, force, wire gauge, and wire composition). Based on these relationships, the associated parameter settings would have been optimized to ensure the highest quality, consistency and throughput. Working with the development team, manufacturing would then develop a monitoring strategy that includes evaluating the physical characteristics of the wire (wire gauge and composition), the process equipment parameters (dwell time), and the process

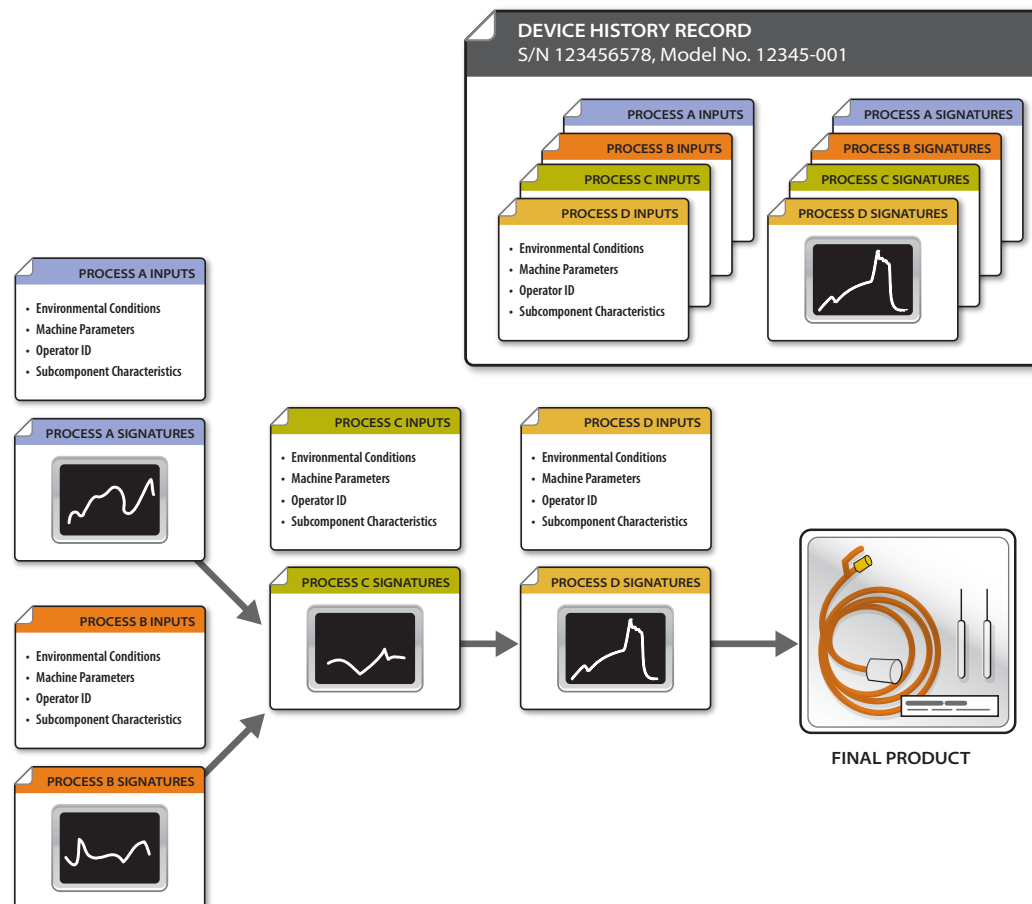
signatures (weld current vs. time and force vs. distance). With this monitoring strategy in place, all the critical inputs would be measured and recorded on a part-by-part basis. Applying the criteria developed from the DOE trials to the measured data in real-time would then allow the quality of the weld to be evaluated in real time on the production floor.

In addition to providing real-time pass-fail determination, the process-monitoring strategy described above also provides a mechanism for process control. For example, variations in wire gauge that are still within an allowable range would be detected and recorded at the incoming inspection stage. This information could then be used to calculate adjustments to the weld current and dwell time according to the multivariate relationships, thus ensuring the optimal weld conditions are maintained. In other words, by continuously monitoring critical variables in production, the engineer, or even the process equipment, can fine tune the appropriate controls to keep the process running effectively.

### Quality Records

As discussed above, the data gathered by the process analyzers is critical to the real-time release methodology, and provides continuous feedback for maintaining and controlling the manufacturing process. However, there is also considerable value in the data records themselves. If we consider the weld example we have been following, a data record would be created for each part that would include the five critical variables. In addition, for completeness and to guard against failure modes that have not yet been identified, other potentially relevant parameters should also be recorded, including environmental conditions such as temperature and humidity, incoming material parameters such as the wire manufacturer, batch ID, date code, and part number, and machine data such as station number and operator.

It is important to realize that this is just one out of the 20 or 30 process steps that might go into assembling the final device. For each of the other steps, similar data records would be created, consisting of raw material or subcomponent parameters, process signatures, environmental conditions and machine-related data. In an integrated environment, each of these datasets would be stored in a database and linked to a unique identifier associated with the finished device, such as a serial number and model number. The overall collection of process records would form a single, comprehensive DHR that captures all of the relevant manufacturing data, covering every step in the end-to-end manufacturing process. This is illustrated by the diagram in Figure 8.



**Figure 8:** Schematic illustration of how a comprehensive DHR is compiled from the data recorded at each of the steps that comprise the overall manufacturing process.

### ***New Defects***

The detailed data contained in the DHR provides a number of benefits to both the manufacturer and the consumer. As mentioned already, it is extremely useful in the event that a new defect mechanism appears and a defective part or parts are released for shipment. Because this is a new type of defect that was not previously identified, it might not be captured by any of the current tests or screens. When this happens, the manufacturer must raise a Corrective and Preventative Action (CAPA) investigation to identify the root cause, develop and implement the necessary fixes, and demonstrate that the defect has been contained. By extracting the DHRs for each of the defective units and comparing their process data with that from known good parts, it is possible

to identify the distinct characteristics that are associated with the defect. Algorithms can then be developed and applied to the rest of the historical data to identify any other parts that also share these concerns. All other similarly affected parts can then be quickly identified and recalled based on their unique identifiers. In this way, the impact of the newly identified defect can be contained and minimized. The recall of defective devices protects the consumer while the manufacturer avoids a mass recall where the majority of parts were actually unaffected and would not have posed any risk to the consumer.

#### ***Quick Availability of Data for FDA Audits***

The comprehensive quality database is also invaluable in supporting the manufacturer during an FDA audit as it provides a detailed record of any process variations that may have occurred at any one of the many steps in the end-to-end manufacturing process. In a similar manner, this same confidence may be applied to the introduction of minor changes based on the extensive historical data and fundamental process knowledge. For example, this might allow the manufacturer to implement cost-reduction measures without the need for a full re-submission to the FDA. This is, in fact, one of the primary drivers of the PAT methodology in pharmaceutical, to lower the barriers to change by taking advantage of the extensive data and process insight provided by process analytical technologies.

**The comprehensive quality database provides a detailed record of any process variations that may have occurred at any one of the steps in the manufacturing process.**

#### **Conclusion**

In examining the principles and benefits of process analytical technology, it is clear that they are just as relevant to a medical device manufacturer as they are to a pharmaceutical producer. In both cases, the objectives are the same, to efficiently manufacture products to the highest standards of quality, as governed by the FDA. The PAT methodology provides a framework for achieving this objective based on a detailed understanding of the process inputs and variables and the interrelationships that determine key product attributes. This framework emphasizes the use of multivariate tools that leverage in-process monitoring techniques for providing real-time visibility into the quality of the product, allowing the manufacturer to maintain tighter controls on the manufacturing processes, maximizing throughput and efficiency. It also enables real-time release from manufacturing, which ensures product quality through 100 percent testing, while eliminating the need for costly end-of-line

destructive testing. Finally, the detailed device history records that are created for every part facilitate communication with regulatory bodies and provide greater protection for both the manufacturer and the consumer. The end result is a breakthrough that would seem almost contradictory: Superior product quality and reduced risk from a methodology that actually lowers manufacturing costs.

To date, the FDA has only applied the PAT guidance to the pharmaceutical industry. However, it seems likely that the same approach will eventually be introduced to medical device manufacturing, if not all FDA-regulated industries. Manufacturers who adopt this data-intensive and analytical approach to all phases of their product lifecycles, from process development and manufacturing to highly detailed quality records, will secure an edge over their competition and, in the long run, will be better prepared to fully benefit from PAT-style guidelines when they are adapted for the medical devices industry. In this era of intense competition and regulatory and public scrutiny, this could be the key differentiator that enables long-term, sustained market leadership.

If you'd like to reduce costs and improve quality through the application of the PAT methodologies, contact Ron Pawulski - Director Sales, Medical at

(Ph) 613-254-7054

Email: [ronaldp@sciometric.com](mailto:ronaldp@sciometric.com)

Company Website: [www.sciometric.com](http://www.sciometric.com)