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The Holistic Approach to Pharmaceutical Manufacturing

Product Lifecycle Management Support for High Yield Processes to Make Safe and Effective Drugs

for

Dassault Systèmes

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Executive summary

There is agreement that the pharmaceutical industry is in transition; yet not everyone seems to recognize that to transform themselves, companies must shift more attention to manufacturing operations. Why is this so critical? Manufacturing is at the center of both the product lifecycle and the supply chain, and according to the FDA, manufacturing accounts for 25% of pharmaceutical companies' cost[1]. The critical need for pharmaceutical product safety and efficacy means companies must fully understand, carefully design, rigorously test, and tightly control the end-to-end production process to have good business results and to gain and maintain regulatory approvals.

Traditional approaches to product and process design rely on results from off-line analysis and are costly and time-consuming. Data from one department is not easily accessible by others. The resulting production processes often have low yields, leading to low availability and high cost pharmaceuticals. As a result, regulators are calling for scientific and risk-based approaches such as quality by design (QbD) and process analytical technology (PAT) that integrate design and manufacturing.

The urgency to transform pharmaceutical operations goes beyond regulators' zeal to shareholders' interests. As companies see patents expire and opportunity opening in developing markets, many are seeking to lower costs and increase yields. Some companies are also moving toward personalized medicine. While medicines targeted to small populations are a good path to maximum efficacy and safety, this strategy leads to a proliferation of products. Additionally, sales, supply and production bases are going global. All of this leads to complexity in not only product development, but also process design, manufacturing, procurement, quality and regulatory compliance.

Fortunately, there is a proven path to undertake the necessary business and technology transformations: product lifecycle management (PLM) with production floor support. PLM is a holistic approach to merging product and process knowledge that spans the stages of a product from conception through commercialization and includes the many disciplines involved. PLM rests on software that creates a multi-way information connection between disciplines including product development, process engineering, production, quality, and regulatory affairs. PLM enables these groups to communicate more reliable, accessible, timely information about the products and processes by which they are made. As a result, each group can begin to cope more effectively with challenges and business changes.

PLM as both a business approach and a software suite is proven in other industries, such as aerospace, automotive and medical devices, where product safety is critical. In addition to storing and managing data about a product, PLM solutions can search for data across a range of systems and documents, analyze relationships across process and product data, and guide not only product and process design, but also planning, simulation, and in a few cases, execution in production.

Adopting a new approach to managing information about validated processes can be challenging. Each company and facility must be pragmatic and take reasonable steps to leverage all of their resources effectively. PLM is a big vision with a broad suite of software to support it. Companies that already have the basics in place can move rapidly, but most companies will begin with specific elements that serve immediate needs and build out to this holistic vision.

The complexity of today's pharmaceutical market requires more efficient drug development and production. PLM has the opportunity to make pharmaceutical production more effective and with lower risk – even in this vastly complex environment. Leaders are actively implementing PLM and are reaping the benefits of fewer problems, lower costs, higher yields, employees armed to make good decisions, and audits that make everyone more confident as they access the information they need.

[1] Implementing Quality by Design, Presented by Helen Winkle of FDA CDER at PDA/FDA Joint Regulatory Conference September 2007

Industry challenges

The pharmaceutical industry is in transition, with an array of external forces amplifying pressures on internal practices. These external forces include expanding global markets with more competition, increasing price pressure, and shifting regulations in each region. This comes at a time of expiring patents for many blockbuster drugs and fewer high-revenue products in the development pipeline.

These forces are driving companies toward changes to improve profitability at the same time as providing safety and efficacy for patients. Across the industry, active pharmaceutical ingredient (API), ethical, generic, vaccine, and bio pharmaceutical producers must shift their business processes to succeed.

Making medicines for smaller and more specific patient populations – or even personalized medicines – is a clear path to both better profits and drugs that are safer yet more effective. Despite the sound business logic, this is not an easy path, given that the resulting product proliferation adds significantly more complexity to business operations. Moving a multitude of product variants through development, into and through trial production, regulatory approval, and full-scale production quickly and efficiently is an enormous challenge.

Even high volume makers are responding to pressure for improved profits. One angle is to improve yields. Other approaches include global expansions, partnerships, and faster reactions to market conditions. These can also lead to more complexity and challenges in managing production processes and product outcomes.

In high or low volume environments, the production process not only determines yield, it is also a major factor in product quality, safety, efficacy and cost. Thus, production is pivotal to the company's ability to get products approved, generate revenues from them, gain good margin, and deliver public health benefits from needed pharmaceuticals.

Historically, pharmaceutical companies have not invested in manufacturing and supporting information systems as much as they have in R&D and marketing. This relative neglect of manufacturing has led to a long list of industry problems and negative results that regulators, shareholders and the public all want to change. Figure 1 shows some of these, along with causes. Some production processes suffer as much as 50% waste. The result is a very high level of effort and cost to achieve high quality product.

These inefficient current production practices are neither sustainable nor profitable with the cost-sensitive environments of national health insurance programs and emerging markets. The move to "go global" and produce medicines for smaller patient populations will only compound these problems.

Problem	Cause
High production cost for products	Low manufacturing yield and efficiency, high waste, long time to test, etc.
Drug shortages	Manufacturing problems
Lack of improvements based on new technologies	Fear of changing validated manufacturing processes
Slowed development and access for investigational drugs	Inability to move new drugs into manufacturing efficiently and predict scale-up effects
Need for intensive regulatory oversight	Inability to analyze reasons for manufacturing failures

Adapted from: 9/2007 Presentation: *Implementing Quality by Design* by Helen Winkle of FDA CDER at PDA/FDA Joint Regulatory Conference

Figure 1: An array of pharmaceutical market problems result from manufacturing issues that information systems can help to solve.

Limitations of current approaches

Pharmaceutical manufacturing executives must recognize where their current approaches fall short and develop a path to enable company success. Representatives from regulators as well as the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) have presented some of these shortcomings in a systematic way. Briefly, they include:

- Quality by test. Off-line analysis can result in low yield, as it allows products that will not pass final tests to go through the process. The result is increased cost, cycle time, and risk, as the company scraps products and requires a second production run to get acceptable quality product out.
- Issue correction without prevention. A primary focus in manufacturing on corrective action, not preventative action raises the risk that problems will recur, wasting cost and time. Part of the challenge is that prevention must typically be built into the design of the production process itself, and many companies have processes that are not designed to stay within the boundaries for high quality production outputs.
- Silos of data and knowledge. Most companies have data owned by different departments or disciplines. For example, production data from one product often is not readily available for designers of follow-on products and their production processes. The data is in different forms and thus not often used as context for forming an overall knowledgebase about the product and production process. This is true from stage to stage (development to clinical trials to full production), but also in some cases among the groups that service production and process development, such as statistics and multivariate analysis, spectroscopy, mathematical modelling, and risk assessment.
- An empirical or variable-by-variable approach to pharmaceutical development. This results in a costly and slow process that is also vulnerable to blind spots because it cannot account for the interaction between variables that frequently cause problems in trials and in scaled-up full production. Even in multi-variate approaches, the focus on an average rather than the distribution of outcomes (i.e., minimizing the likelihood of batches that are out of specification) can limit production success.
- Change-resistant processes. Once validated, the production process becomes fixed and focused on reproducing outcomes. This limits the companies' interest in pursuing new technologies and process improvements that would result in higher yields at lower cost.

Understanding these shortcomings of the current process development approach, regulators and the ICH have started to promote holistic approaches. Across the industry, leading pharmaceutical producers are beginning to shift their business processes to new approaches that better leverage knowledge.

The holistic approach

Holistic, meaning "relating to or concerned with complete systems rather than with the analysis of, treatment of, or dissection into parts"[2] suggests that many elements are involved and interacting. Ideally, processes create continuity in several dimensions:

- Throughout the product lifecycle
- Across disciplines
- Between products and production processes
- Among trading partners
- From one generation of product to the next

Figure 2: Product lifecycle management is an approach supported by software that can gather, store and analyze multiple disciplines' data into a useful knowledge repository

Figure 2 shows an approach other manufacturing industries have adopted that encompasses all of these factors. It is commonly called product lifecycle management (PLM). PLM is a holistic approach to manage products from early concept through all stages of development and production through to end of life.

The goal of PLM in any form is to better leverage all available data to improve product and process design, planning, testing and production. In today's industry, the product lifecycle might end in moving off patent or in splitting into several versions for smaller patient populations (shown in top left of Figure 2).

In either case, this ability to build a knowledge base from every aspect of the process contributes to the success of all other aspects and phases of a product's life, and to the success of other products in the portfolio. In the pharmaceutical environment, this reduces the need for regulatory oversight: safe, efficacious products are the natural outcome of this holistic PLM approach.

One initiative that PLM supports is quality by design (QbD), outlined in ICH Q8 Product Development standards. While some people think that QbD is purely a statistically-focused approach, the concept is much broader. QbD is a product/process lifecycle approach founded on continuous improvement as the FDA illustrates it in Figure 3. Notice how similar the PLM and QbD models are, each representing a closed loop cycle.

Adapted from: FDA's view of QbD from 2006, as presented in *Pharmaceutical Quality for the 21st Century A Risk Based Approach Progress Report*

Figure 3: Quality by Design is a cycle in which product and process design and performance create a closed loop of knowledge and continuous improvement.

[2] Mirriam-Webster on-line dictionary: http://www.merriam-webster.com/dictionary/holistic

Figure 4a. Typical current silo state: Minimal cross-discipline understanding

Figure 4b. PLM system support enables cross-discipline knowledge sharing and better context for all groups' decisions

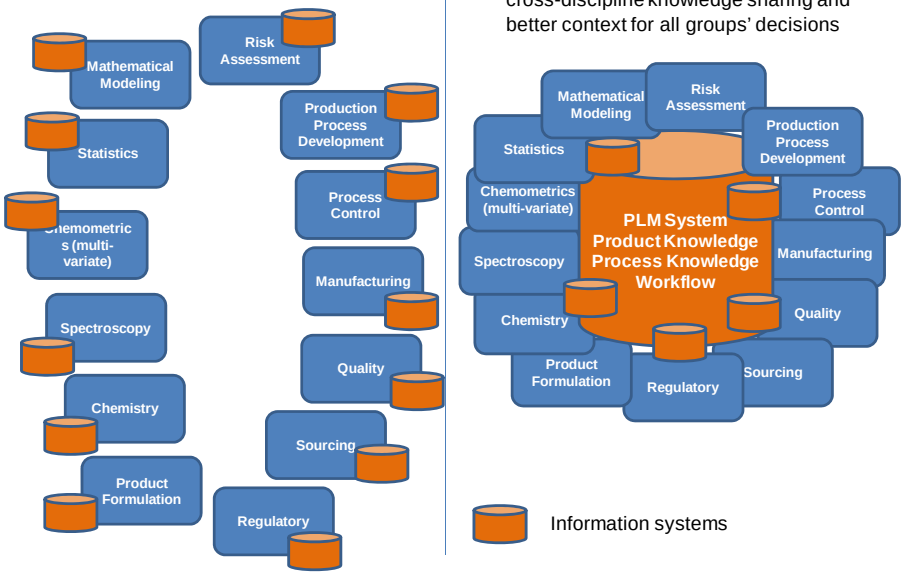

Figure 4: Traditional multi-disciplinary silos (4a) with independent information systems create challenges that a PLM approach (4b) can overcome with common data management, advanced analysis, and support of knowledge from many disciplines.

Because of the need for analysis, QbD efforts have used largely esoteric mathematical, analytical, and statistical methods. While these are the critical scientific foundation, they may actually mask the overall holistic QbD program for staff who are not statisticians, but who have an important role to play.

Figure 4 shows the struggle most companies have to achieve QbD, or any lifecycle approach. As Figure 4a illustrates, the separate information environments means that the various teams often cannot leverage each others' work fully. They typically use different terminology, have different viewpoints, use and create different data, and leverage independent information systems. While everyone involved is theoretically striving toward the same goal, these information disconnects can lead to a lack of understanding and incomplete risk analysis.

Figure 4b illustrates the PLM approach supported by a centralized and industry-specific PLM application suite, which for pharmaceutical includes regulatory business process and submission workflows, portfolio and formulation management, manufacturing analytics, supply chain scorecards and sourcing applications, in addition to engineering and equipment design applications. The PLM platform brings together all relevant information and delivers structured processes by which disciplines can work together to proactively improve product quality. Using structured approaches helps to minimize process and product variation and risk. PLM has helped to lower cost, increase yield, and deliver significant benefits to the companies who use it, and to their customers.

For example, in the early product formulation stages, quality, process engineering, and manufacturing are involved to ensure the team fully considers lessons learned from previous products. This helps to prevent blind spots and disconnects, thus reducing risks and timelines. Both QbD and PLM have product yield and quality in mind from the earliest discovery stages. In this way, PLM and QbD also improve innovation, shorten overall product introduction times, and support regulators' confidence.

PLM system support for manufacturing

PLM is not only a conceptual framework, but also the name for software applications to support it (Figure 4b). PLM software is increasingly viewed as an enterprise application suite that is parallel in scope and importance to enterprise resource planning (ERP) and customer relationship management (CRM). For example, heavily regulated aerospace and defense manufacturers and high volume manufacturers such as automotive and electronics companies all commonly use PLM software. PLM provides an integration of the data from multiple departments as well as a suite of applications.

PLM platform: At the heart of PLM is data management and workflow. In particular, PLM specializes in data storage and management. In addition to structured database data and process plant design models, it can also manage "unstructured" data from drawings, documents and other sources. The PLM platform is specifically designed to manage processes for product and process development, testing, and execution, supporting projects, processes, and change procedures with structured workflow and a complete traceable record.

Product design: A set of applications for structuring the product parameters and attributes as well as the formulations that will achieve those outcomes is the foundation for product development. In addition, PLM often includes the means to relate risk analysis, statistical analysis, and chemical data to each product, recording the basis for design decisions made at each step for each product.

Manufacturing process design and validation: New systems are available to simulate process control systems and conduct tests to establish the process design space for high quality and yield as dictated by current good automated manufacturing practice (GAMP) as shown in Figure 5. They design, validate, and generate software code for PLCs and process control systems. Beyond mathematical approaches, these new systems run design data through various scenarios on the actual process control equipment. This delivers a streamlined approach to installation, operation, and performance qualification (IQ, OQ, PQ), and factory acceptance test (FAT) test phases. By debugging control system software during the design cycle, start-up on new lines and equipment can be faster and the resulting production will typically show high yield. Eli Lilly's project manager reports their results: *"Using this software, our team delivered the project three months early, simulated the whole plant (actuators and sensors), and rapidly implemented the control system while increasing production quality. The integration tests using this tool acted as support for qualification."*

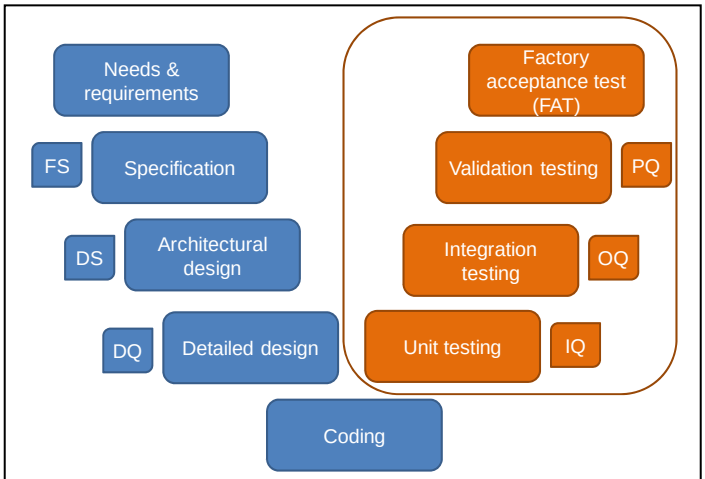

Figure 5: Some PLM suites now include process simulation software to support IQ, OQ, and PQ of process control code that can significantly reduce test and validation times in the GAMP V-cycle of system development and validation.

Quality assurance: Software to manage and control the corrective and preventive actions (CAPA) and product complaints processes can be particularly powerful as part of the PLM environment where they integrate directly to product and process design, validation and change processes.

Regulatory affairs: In some cases, PLM also includes templates for regulatory submission and process support to categorize and track all communication to and from relevant regulators. Again, having the regulatory documents integrated to the product record can improve the consistency and speed of access.

Supply chain management: As ingredients are a critical foundation for product efficacy, companies must also have software to support sourcing, supplier performance monitoring, and allowing the supply network to fully participate in product development and production with track and trace up and down the supply chain.

Manufacturing management: Manufacturing execution systems (MES) and associated electronic batch record (EBR) systems capture product and process data in-line to give a real-time view of the manufacturing process. They can enforce procedures and trigger required sign-offs by operators, supervisors, and inspectors. This can clearly result in higher yields and more consistent compliance to SOPs and regulatory requirements.

Data search & retrieval: Systems with capabilities for data search across a wide array of technical, statistical and other types of data can accelerate effective use of the broad knowledge base around each product, process, partner, and ingredient or material. New search-based applications deliver even more concrete support for good business decisions from web crawling, relating seemingly unrelated data, and deployment in dashboards or reports – all without user training or schema design and application coding.

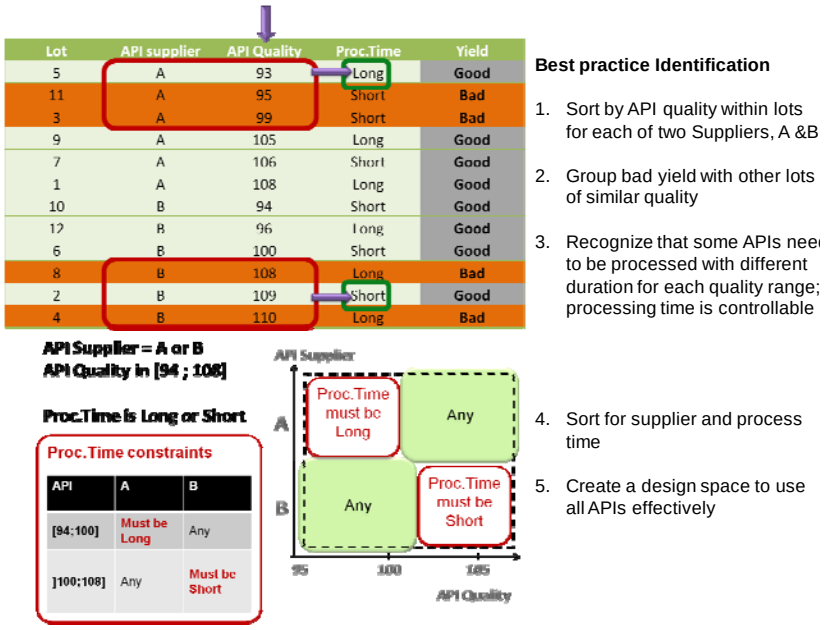

Figure 6: Analyzing existing data to create an effective design space does not need to be a complex black-box process, but can easily relate to daily production activities and sourced ingredients.

Intelligence: Once the relevant data is found, interpreting it requires sophisticated data analysis to relate product outcomes to process data. Today's top applications allow analysis and correlation across multiple domains and formats. Using the design data together with actual production data helps to examine relationships that impact yield and quality.

Analysis for best practices: Fully leveraging knowledge to reduce quality risk is a matter of correlating multiple process parameters to actual product outcomes and yield. While multi-variate analysis (MVA) is widely used, this black box approach can be difficult for manufacturing teams to understand. Figure 6 shows a process to distill best operational practices. In this example, production must select appropriate ingredient lots based on processing time needs. Notice that this approach to control the process and optimize quality and yield focuses not on the average results, but rather minimizing the out-of-target results. Sanofi Pasteur uses such a system. *"This tool is particularly successful where other, more classic analysis tools fail. By producing simple and explicit rules that explain the functioning of our vaccine production processes and by highlighting the parameter correlations that may cause these processes to deteriorate, this tool helps us to improve process quality, security, and profitability,"* according to René Labatut, VP Global Manufacturing Technology.

These applications support many of the information management needs of ICH Q8 Pharmaceutical Development, Q9 Quality Risk Management, and Q10 Quality System. As such, they will also support the specific needs of regulators in various markets even beyond the EU, U.S. and Japan. Figure 7 shows a simplified, linear view of the scope of this full suite style PLM that includes manufacturing and maps the scope of various ICH and FDA guidelines against these major business process areas.

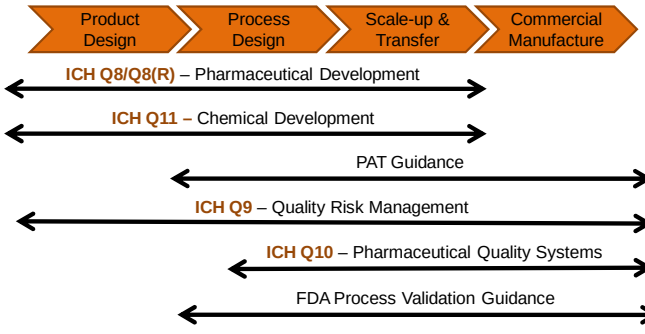

Figure 7: PLM supports business processes from product development through commercial production as at top; the arrows below show the scope of various guidance documents.

Using all of these PLM applications, pharmaceutical manufacturers can deploy an integrated process across the lifecycle of the product and connect the teams that are ultimately responsible for improving the manufacturing process and the quality of products. This starts with improving process specifications to better ensure product critical quality attribute (CQA) outcomes and continues through to developing ongoing operating requirements and best practices that reflect holistic knowledge. Regulators are also suggesting that using a QbD style design space allows post approval process changes within that envelope. An exciting, longer-term aspect is that PLM makes it much easier to build results of analysis back into current and future product and process development cycles.

Q8 Approaches to Pharmaceutical Development		PLM System Support Capabilities
Minimal approach	**Enhanced, QbD approach**	
Fixed manufacturing process	Manufacturing process adjustable within the design space	Structured change management based on specifications and analysis
Focus on reproducibility	Focus on control strategy and robustness of the process	Virtual manufacturing with simulation of the process and product outcomes
Off-line analysis	PAT tools used for feed forward and feedback process control	Process design creates control parameters, and data management handles data from process control
Quality assured by testing	Risk based control strategy (real-time release)	Risk management analysis data stored and in context and accessible
Empirical development	Systematic approach to development	System support for development process using scientific & empirical data
One variable at a time	Multivariate experiment	Multiple variable analysis to minimize out of spec, not average, results
Reactive lifecycle management	Preventive lifecycle management (and continual improvement)	Multi-disciplinary data and collaboration from earliest product/process concept

Adapted from: 10/2008 Presentation: *QbD: A Global Implementation Perspective The EU Perspective* by Ricardo Luigetti of EMEA at the Siena Conference on Product and Process Optimization

Figure 8: While ICH Q8 will accept the traditional "minimal" approach, it pushes for the QbD approach, which PLM enables and fosters.

Figure 8 shows examples of how PLM can support the holistic development and production approach regulators recommend in ICH Q8. The first two columns are derived from how an EMEA representative described the two acceptable approaches to development, the minimal or current approach on the left and the QbD approach in the middle column. The right hand column shows how PLM can support the enhanced approach.

Pragmatic ways to get started

PLM is a big vision for product and process development, validation, and execution. To gain the benefits, most companies will require new approaches, mindsets, and information flows. The magnitude of the change is, we believe, one reason pharmaceutical companies have only recently started to move to PLM practices and QbD submissions. Another is that the software support has been scattered, and is just coming together in PLM software suites recently.

Each company will have its own path to move toward the holistic PLM approach. Specifics will depend on the company's current practices, stages in their products' lifecycles, technologies in place, etc. It's often best to start with a specific product, process or project to gain confidence, but the goal must be to generate a company-wide shift over time.

In short, moving to PLM will usually need a champion with executive level support to effect the required changes in people, processes and technology. To keep support, companies must get quick wins. What follows are some basic concepts to help managers get each of these areas started on the journey.

- Participate in training or education or workshops to get your team up to speed. Public sessions relating to both QbD and PLM are relatively common. If only a few of your team or certain disciplines have attended these sessions, we recommend enrolling entire cross-disciplinary teams in overview sessions. As teams begin to share knowledge, they will gain better understanding and begin to establish common terminology and expectations.
- Involve cross-disciplinary teams in designing new processes to move toward a holistic approach. These new processes may focus on creating a knowledge inventory, defining CQAs, reducing variability in ingredients or in processes, formulation scale-up, or simply opening lines of communication between disciplines at critical points in each group's process.
- Technology that is proactive and holistic across the product lifecycle can enable both process change and education. It's important to have the total PLM roadmap in mind, but some companies will start small and build out. There are quite a few possibilities for starting points, including:
    - Leverage a system that supports effective production process design with simulation and verification of results for each product and variant to be produced on that line.
    - Implement a system that helps find quantitative and qualitative data in multiple electronic sources quickly and efficiently to foster early collaboration between product development and manufacturing experts.
    - Use technology to deliver the data and analysis you need to characterize and optimize the manufacturing process. Technologies might include plant data systems to capture actual data from processes and operations intelligence that analyzes product and process data.
    - Set up electronic batch records to enforce processes, make data more coherent and available, and automate according to 21 CFR part 11. These systems also speed audits, process knowledge gathering, non-conformance analysis, and recalls.
    - Use a tool that can analyze data from manufacturing operations to identify best practices.

Urgency to improve for safety and profit

Companies in every position in the pharmaceutical industry are under unprecedented pressure from regulators and shareholders to improve performance. This typically requires an improvement in manufacturing yield and repeatability. In addition, new opportunities are emerging to serve worldwide markets and, in some cases, with drugs targeted to smaller populations offering improved safety and efficacy as well. Companies with PLM-based development and production capabilities will be in a position to reap the profits by handling a variety of products in ways that regulators in each market will accept.

With the resulting complexity, pharmaceutical companies must develop a cross-discipline lifecycle knowledge base with instant information access. Other industries with human safety issues and varying global regulations such as aerospace, defense, and automotive have proven the value of PLM software. While these industries are not finished improving, they have managed to reduce costs, improve efficiency, and adhere to very high quality and safety standards.

The pharmaceutical industry is on the brink of a new era. People, paper, and domain-specific systems can no longer keep up with the complexity and business pressures. Leaders are turning to PLM as a holistic approach based on product and process knowledge. Moving from inconsistent data in disconnected systems to a PLM environment with supporting software allows companies to manage data in a way that improved yields, enhances confidence, more clearly identifies risk, and is capable of managing the complexity of increasingly personalized medicine. All of this is likely to lead to satisfied regulators and happier shareholders.

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