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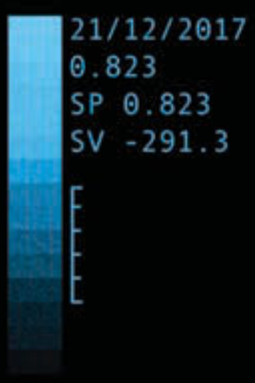

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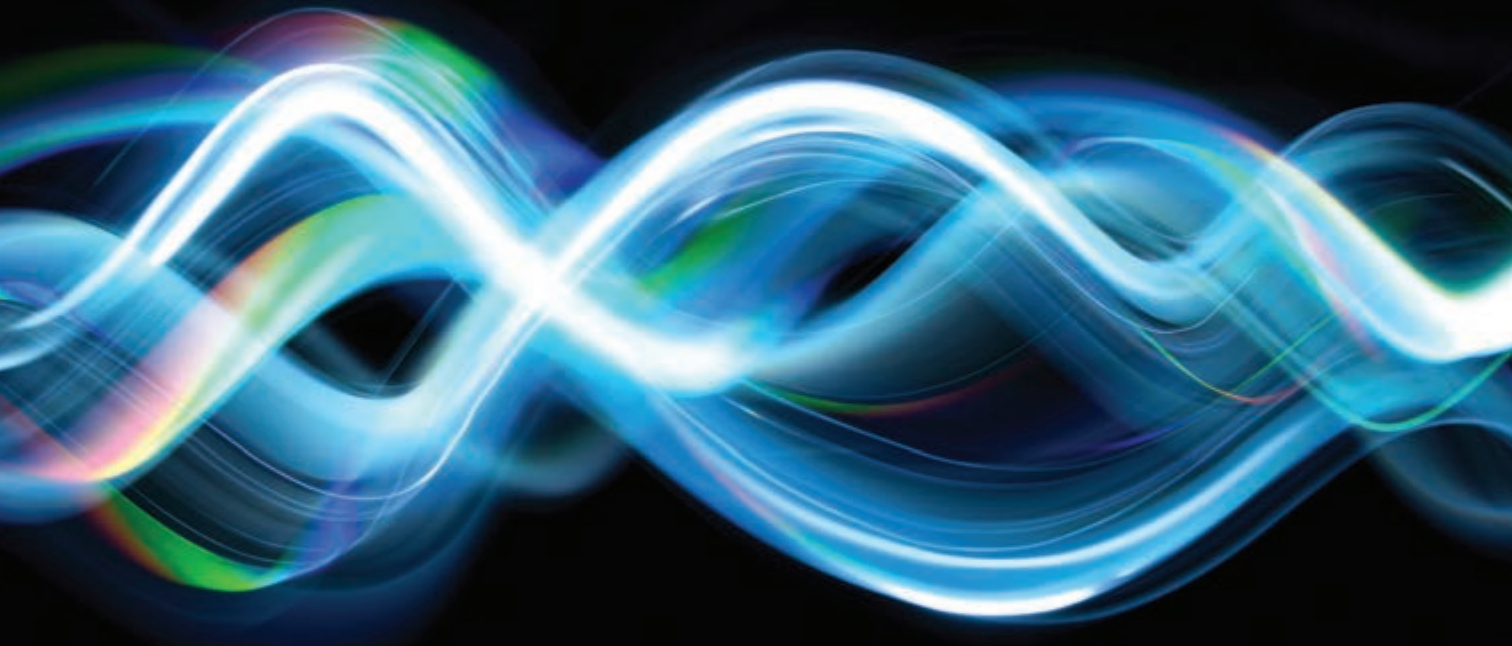

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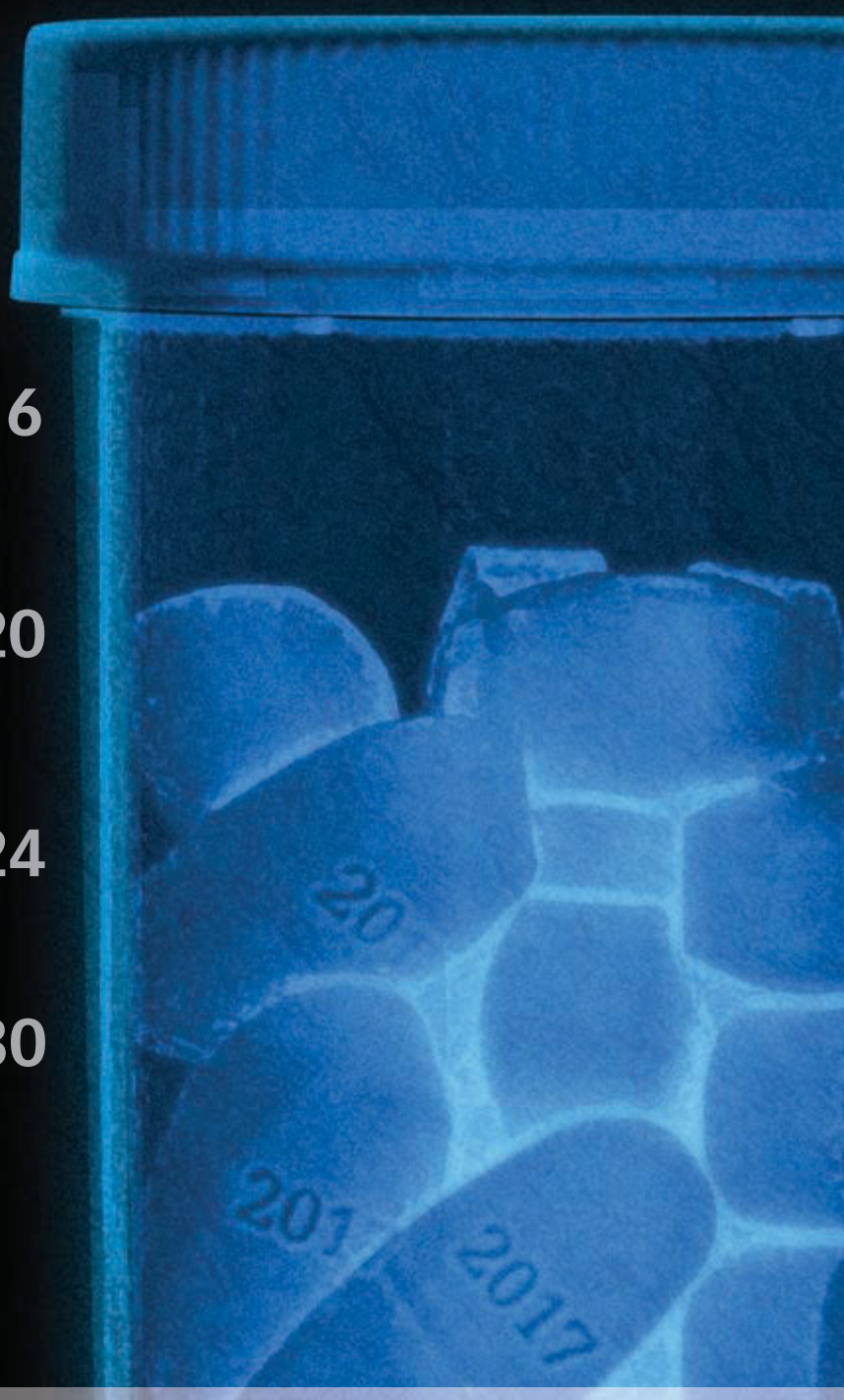

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That's a Wrap

Penetrating the layers of 2017 regulatory actions helps pharma construct a productive narrative

UNFORTUNATELY FOR mummies, their cinematic fame somewhat fell by the wayside when zombies took over as pop culture's new favorite not-quite-dead terror.

Researchers, however, have not yet lost interest in mummies (apparently due to a widespread shortage of zombies in the scientific research community) and have now enlisted the help of X-ray technology to further their work.

Just recently — and for the first time ever — scientists, researchers and art curators utilized Argonne National Laboratory's Advanced Photon Source synchrotron technology to look inside the linen-wrapped remains of an 1,800-year-old Egyptian mummy. The technology — the brightest X-ray source in the Western Hemisphere — speeds up electrons along a 3,600-foot circular track to produce high energy X-rays. The APS technology is used for research across a multitude of scientific areas on a regular basis. In the pharma industry, the X-ray technology can offer researchers a picture of a protein's structure, which has aided in the development of inhibitor drugs such as Abbott Labs' HIV drug, Kaletra, and Roche's melanoma drug, Zelboraf.

As I wrote this month's regulatory review cover story, researchers in Illinois were using this advanced X-ray technology to non-invasively investigate the mummified remains of a five-year-old girl unearthed in Egypt in 1911 (I'll let you decide whose job is more fun). While most would argue that pharma regulations come wrapped in red tape rather than resin-soaked linens, both tasks involve penetrating layers upon layers of details.

In the mummy's case, using X-rays to study the wrappings, skeleton and internal matter enables researchers to gather clues that will shine light on the life, culture and trade networks of the Roman Empire. When speaking about pharma and regulatory intelligence, gathering and analyzing regulatory data against the backdrop of the industry enables manufacturers to derive meaningful outputs that can be used to guide regulatory strategy.

Essentially, it's all about constructing a story, piece by piece. Personalized medicines, global harmonization and quality were the stars of 2017's regulatory tale, while political change in the United States and Europe left mysteries that have yet to unfold.

X-ray technology is valuable to the study of these ancient artifacts because the mummies will be completely unharmed during the process. It is our hope that this month's cover story, as well as the Regulatory Intelligence Brief (complete with charts and links) from Meredith Brown-Tuttle, principal consultant for Regulatorium, posted on our website, will provide our readers with a painless review of 2017 regulatory actions. We can't promise you immortality, but maybe we can settle on helping to preserve your regulatory sanity.

BY KAREN LANGHAUSER, CHIEF CONTENT DIRECTOR
KLANGHAUSER@PUTMAN.NET

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FDA Implements Rapid REMS

FDA aims to make its risk evaluation and mitigation strategy easier, and changes are in the works to help manufacturers meet the required safety measures

WHEN I think of REMS, I immediately think of rapid eye movement sleep — what we all dream of having every night! But as I get older, my mind doesn't seem to shut down as easily, and I find myself staring at the ceiling and cursing my alarm clock when it goes off as the sun rises.

So when I saw an FDA blogger talking about REMS, it piqued my interest that maybe the agency approved a new sleep remedy or non-habit-forming medication to help my predicament. But no such luck. Instead, it was referring to its risk evaluation and mitigation strategy (REMS), which applies to certain FDA-approved drugs that require drug manufacturers to outline specific safety steps to be taken before a patient can be given the medications.

Drug companies develop REMS programs — which involve the patient, healthcare providers and manufacturers — and then the FDA reviews and approves them. The plans are designed to help ensure that the benefits of a prescription drug outweigh its risks. For example, if a drug could potentially cause birth defects, a REMS program might require that a patient be asked her pregnancy status before beginning that drug.

The Agency can request a REMS from the manufacturer both before and after a drug is approved. According to Theresa Toigo, MBA, RPh, associate director for Drug Safety Operations in the FDA's CDER, each REMS program is unique and targets a specific risk or risks associated with a particular drug or drug class.

"Depending on the risk or risks involved, a REMS program could include a range of requirements such as providing a patient or healthcare professional with an information sheet, enrolling a patient in a registry prior to taking the drug, requiring special training for a prescriber, or requiring that a patient's lab values be reviewed before he or she can be given the drug," Toigo said.

As with other FDA regulations, REMS requirements have raised concerns about clinical and administrative burdens placed on healthcare professionals, as well as concerns that those requirements could delay a patient's course of treatment.

So what is the FDA doing to address those concerns and ease the burdens? Toigo shared an update:

- FDA revised the draft recommendations on the format and content of REMS documents. The revised REMS document template includes a section for each participant so they can focus on their own specific program responsibilities.
- The REMS@FDA website has been redesigned to prominently display the reorganized REMS document in a way that is easily searchable.
- REMS has been integrated into a Structured Product Labeling (SPL) format to facilitate making REMS information available for existing healthcare systems and workflows. SPL also can be used to capture and present REMS information in a format that is easily shared.

THE FEDERAL DRUG ADMINISTRATION WILL MAKE EVERY EFFORT TO EASE THE **BURDEN OF REMS REQUIREMENTS.**

- FDA published a report highlighting best practices for healthcare workers when counseling patients about drugs that require a REMS. This will inform the patient about benefits and risks of the drug, how to mitigate the risks and help them make more informed decisions.
- The agency conducted a feasibility assessment about the use of continuing education credit for training under a REMS and reported the findings, including scenarios for incorporation of CE into REMS programs.

These changes came as a result of FDA's recently completed REMS Integration Initiative, which started back in 2011, with the goal of developing guidance on how to determine when a REMS is required, improving standardization and assessment of REMS, and better integrating them into the healthcare system.

FDA says it will continue to evaluate REMS and make sure the program is responsive to industry needs, i.e., in part by implementing the REMS Platform Standards Initiative, which included a recent draft guidance on the REMS format and content (template).

Rest assured, the FDA will make every effort to ease the burden of REMS requirements. So patients don't have to lose sleep about their medication — the FDA's goal is to maintain patient access while ensuring safe use of a drug.

KATIE WEILER, MANAGING EDITOR
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DCAT Week ‘18 Preview

DCAT week examines the key drivers, best practices and trends impacting pharmaceutical manufacturing and supply

DCAT WEEK, geared toward the business of pharmaceutical development and manufacturing, brings together thousands of senior industry executives for high-level meetings, strategy sessions, education programs and networking opportunities. Organized by the Drug, Chemical & Associated Technologies Association (DCAT), the event will take place in New York City from March 19-22, 2018.

DCAT is a not-for-profit, member-supported, global business development association with 400+ corporate members that includes innovator and generic drug companies and suppliers of ingredients, development and manufacturing services, and related technologies.

Innovation drives the pharmaceutical industry, so how is product innovation impacting manufacturing and supply, sourcing and procurement, and the supply lines of emerging pharma companies, which are an important source of new product development? DCAT Week ’18 will feature several education programs that will answer those questions.

New to DCAT Week, the *Executive Insights: Manufacturing and Supply* program will feature on-stage interviews with leading pharmaceutical executives who will share insights on the key drivers influencing pharmaceutical manufacturing and supply. These include how technology and product mix are impacting demand and supply, global manufacturing competitiveness, key issues influencing make-versus-buy decisions and specialized technologies such as continuous manufacturing.

Innovation in Sourcing and Procurement will offer best practices and lessons learned from leading executives in sourcing, procurement and supply management on how to drive value and performance in the pharmaceutical customer-supplier relationship. Topics include: advanced sourcing in new product development; innovative approaches in project management and supplier metrics to successfully move manufacturing of a molecule from in-house to external production; and best practices in collaborative supply-chain planning.

Emerging Pharma: Strategies for Optimizing Manufacturing and Supply will examine how emerging pharma companies can develop and implement the optimal manufacturing strategy for their drug candidates. The program will provide: insights on how drug pricing and the payer/reimbursement environment are impacting manufacturing decisions; best practices for the selection and management of CDMOs or CMOs; and manufacturing considerations in the due-diligence process when partnering with larger pharmaceutical companies in licensing deals, product acquisitions or full company acquisitions.

Further information on these programs and the other DCAT Week ’18 education programs may be found here: https://www.dcatweek.org.

FUNNY PHARM

”That’s one way to scale up production!”

— Jim Meckstroth

Funny Pharm comics, drawn by professional cartoonist Jerry King, appear on PharmaManufacturing.com. Readers submit suggested captions. Above is July’s cartoon and winning caption.

FACING PHARMA'S CAPA CHALLENGES

A RECENT survey conducted by *Pharmaceutical Manufacturing* indicated that the industry needs an integrated, systematic approach to corrective and preventative action.

Often considered the core of a company's quality management system, a corrective and preventive action (CAPA) process investigates and solves problems, identifies causes and takes action to prevent recurrence. Yet, despite an increased emphasis on quality management, many pharma manufacturers continue to struggle with quality problems because of ineffective corrective and preventive action processes.

So why does CAPA continue to challenge the industry? The recent survey found that more than 57 percent of manufacturers are not getting a comprehensive view of how quality management applies across their organization. Much of the industry appears to be lacking an integrated, systematic approach to CAPA.

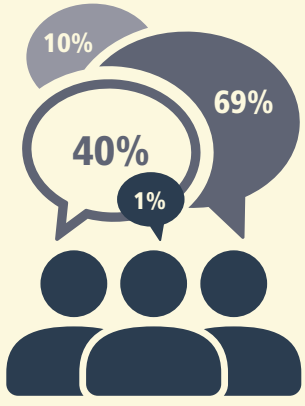
Because CAPA is compulsory for compliance with cGMP regulations, there's a tendency to treat it as another box to check. But beyond compliance, an efficient CAPA process is a powerful tool that can significantly improve quality systems and process understanding across an entire enterprise.

In their quest to achieve a single managed view of the process, pharma companies struggle to break down the silos in which they might have several different CAPA processes being used across departments and plants. Often companies have to chase the same complaint at multiple facilities. Consequently, the struggle to resolve issues is compounded because problems are not visible across the entire organization. Centralized reporting tools are necessary to pull all processes together and provide high-level visibility into what's driving quality performance.

An effective CAPA process is a tool that can enable a quality system to bring continuous improvement to all aspects of the business. But corrective and preventative action struggles persist because many systems in place are disparate and manual-based. CAPA-related data is siloed, preventing enterprise-wide visibility of quality. Current CAPA-related challenges point to the industry's need for a fully integrated, cloud-based quality management system that offers the ability to automate the corrective action process. This systematic approach to CAPA will bring the industry closer to its quality goals.

PHARMA'S CAPA PROGRESS

INDUSTRY SURVEY INDICATES A NEED FOR AN INTEGRATED, SYSTEMATIC APPROACH TO CORRECTIVE & PREVENTATIVE ACTION.



CAPA METHODS USED

Software ● Manual or Spreadsheets
● Hybrid Solutions ● Other

58 PERCENT

say that their quality management system does not enable them to see trends in risk across the entire organization

TOP CHALLENGES IN CURRENT CAPA PROCESS

1. Effectiveness Check — 38%
2. Root Cause Analysis — 37%
3. CAPA process does not have access to other systems, data or processes — 15%

To download the full research report, visit info.pharmamanufacturing.com/exploring-pharma-capa-challenges_qc

Rx-Reg Vision

By Karen Langhauser,
Chief Content Director

A PAINLESS LOOK INSIDE THE MOST IMPACTFUL REGULATORY TRENDS AND ACTIONS FROM 2017

KEEPING UP to speed with the ever-changing global regulatory environment is enough to make anyone's head spin — yet it's vital when it comes to ensuring ongoing compliance, as well as making the right decisions for pharmaceutical organizations.

The benefits of proper regulatory intelligence are vast, especially at a time where speed-to-market is increasingly important. Successfully implemented regulatory intelligence can shorten time from filing to approval, increase the likelihood of marketing approval and help identify new opportunities in drug development. It can also help pharmaceutical organizations plan ahead, aiding in better prediction of regulatory review times and helping to proactively avoid potential compliance pitfalls.

What follows is what we hope will be a helpful contribution to your regulatory intelligence efforts: a brief discussion of some of the most impactful regulatory initiatives from the past year and how they play into current trends in pharmaceutical manufacturing.

PAVING THE WAY FOR PERSONALIZED MEDS

The personalized medicines market — treatments tailored to the individual patient — is growing rapidly, with revenue predictions as high as $5,208.68 billion by 2022.[1] Regulatory agencies play a large role in shaping the infrastructure that enables developments in personalized medicine.

PDUFA VI

On Aug. 18, 2017, the President signed into law the Food and Drug Administration Reauthorization Act (FDARA). This new law includes the reauthorization of the Prescription Drug User Fee Act (PDUFA), intended to provide the FDA with the necessary resources to maintain a predictable and efficient review process for human drug and biologic products.

Aside from the more visible changes to the fee structure and fees, PDUFA VI also aims to do more to integrate patient perspectives into the development and regulatory review of new medicines. Launched as a new initiative in 2012, as part of PDUFA V, patient-focused drug development (PFDD) incorporates the patient's voice into the development and review process. The FDA has committed to hold 24 disease area-specific PFDD meetings with individual patients and patient groups over the course of PDUFA VI.

PDUFA VI has the potential to strengthen the FDA's ability to advance the science of patient input with actions, such as placing dedicated experts into review divisions to engage with patients, patient advocates and sponsors during drug development.

21st Century Cures Act

The 21st Century Cures Act (though technically signed into law in December 2016 — a little early for our 2017 recap) is intended to provide the FDA with tools aimed at modernizing regulatory programs. In July 2017, the FDA announced a detailed work plan for the steps the agency is taking to implement different aspects of Cures, which included elements that further the goals of the personalized medicines initiative, including:

- The Center for Biologics Evaluation and Research (CBER) implementing the Regenerative Medicine Advanced Therapy (RMAT) designation, enabling the FDA to facilitate an efficient development program for, and expedite review of, new regenerative advanced therapies.
- CDER, working with CBER, outlining a plan for the development of patient-focused drug development guidances.

"PDUFA VI and the Cures Act work hand in hand to bring the patient into the drug development process and ensure that drug development is actually working to the benefit of patient outcomes," notes Lawrence Liberti, VP executive director for the Center for Innovation in Regulatory Science (CIRS). CIRS, a non-profit subsidiary of Clarivate Analytics, brings together regulators, pharma manufacturers and health technologies assessment (HTA) agencies for the purpose of advancing regulatory and HTA policies and processes used to facilitate access to medicines.

GLOBAL ALIGNMENT

The past year saw significant progress in the ongoing quest for global alignment of regulatory expectations. Harmonizing regulations across the world would greatly reduce the complexity of the drug development process, ultimately bringing new drugs to market faster.

ICH Guidances

A key organization when it comes to global alignment is the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH's mission is to achieve greater worldwide harmonization in the production of medicines by developing guidelines via a process of scientific consensus between global regulatory agencies and industry experts.

"ICH's aligned guidances allow pharma companies and agencies to have greater clarity surrounding regulatory expectations," says Liberti. "In the last year, we've seen an increase in the number of participants that are formally recognizing ICH as an important way forward. Having alignment across growing markets will bring further clarity and predictability to the regulatory and development processes."

Notable new members approved over the past year include regulatory agencies from Brazil (ANVISA), Korea (MFDS) and China (CFDA), while regulatory agencies from Cuba (CECMED) and South Africa (MCC) were added as observers.

As part of the ICH process, draft guidelines are transmitted to the regulatory authorities of the ICH regions for internal and external consultation. In 2017, the U.S. FDA released several draft guidances of ICH harmonized guidelines in various stages of the

ICH process, including revised ICH S5 Guidelines, an addendum to E9(R1) "Statistical Principles for Clinical Trials" and a Q&A on Q11 "Development and Manufacture of Drug Substances."

"ICH really sets a good level playing field, and I think adherence to ICH will be a key factor in promoting global alignment," says Liberti.

PIC/S

The Pharmaceutical Inspection Co-operation Scheme (PIC/S) aims to harmonize inspection procedures worldwide by developing common GMP standards and providing training opportunities to inspectors. In 2017, the organization published a revised GMP guide, as well as unveiled a new strategic plan with a strong emphasis on training and better communication with heads of regulatory agencies.

In his contribution to the 2017 CPhI Annual Report,[2] Bikash Chatterjee, president and chief science officer, Pharmatech Associates, points to regulatory disparity as the greatest hurdle to broad adoption of standards (such as ICH guidances), but says "that hurdle is rapidly disappearing as a result of the success of the PIC/S."

THE PAST YEAR BROUGHT WITH IT IMPORTANT REGULATORY INROADS IN PERSONALIZED MEDICINES, GLOBAL HARMONIZATION AND QUALITY.

And participation is growing. In September 2017, the PIC/S Committee invited Iran's IFDA, Turkey's TMMDA and Mexico's COFEPRIS to join, effective January 2018 — bringing the total to 52 participating authorities.

Earlier in the year, PIC/S became an ICH Observer, which allows the co-op to attend ICH assembly meetings and to participate in other ICH activities. Collaboration between the two groups serves to strengthen the role both organizations play in the quest for a global pharma marketplace with shared regulatory compliance.

ADVANCING QUALITY

Global regulatory agencies continue to stress the need for ongoing improvements in product quality and are taking action by developing regulatory approaches that support continuous improvement in quality processes.

Submission of quality metrics data

In an effort to encourage the industry to implement state-of-the-art quality management systems, the U.S. FDA is in the process of initiating a quality metrics reporting program. Through this program, the Agency intends to use quality data submitted by the industry to help develop compliance and inspection policies and improve the Agency's ability to predict drug shortages.

While the revised draft guidance for "Submission of Quality Metrics Data" was published by the FDA in late November 2016, plans are in the works for a voluntary rollout of the program starting in January 2018, with the intention of making the program mandatory in the future. The past year, however, has brought much resistance surrounding this new quality metrics program — even after the agency's revisions, the industry still has viable concerns about the program.

In March 2017 several trade/technical organizations, led by the Association for Accessible Medicines, submitted commentary on the revised guidance, requesting further dialogue between the agency and industry before the FDA proceeds with its proposed metrics collection efforts. The letter stated that "such a program would require substantial resources, present significant operational challenges and complexities, and draw resources and management attention away from other programs that drive continual quality improvement."

Additionally, points out Siegfried Schmitt, principal consultant, PAREXEL, the metrics collection program is still a proposal that remains isolated to the U.S. FDA. "So far no other regulatory agency has stated that they would be interested in establishing a similar concept in their jurisdiction. With an isolated concept, there is little likelihood of widespread enthusiasm within the industry to participate in the trial," says Schmitt.

Emerging technologies

In September 2017, the FDA issued final guidance on "Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization," providing recommendations to companies interested in the Agency's Emerging Technology program.

While the guidance seeks to advance the use of emerging manufacturing technologies, such as continuous manufacturing or 3D printing, improved product quality is the true endgame. According to the guidance, not only should emerging technology be novel

to the pharma industry, but it should "have the potential to modernize the pharmaceutical manufacturing body of knowledge related to product quality."

Modern-day drug innovation requires adopting modern-day manufacturing approaches, and this guidance is an attempt by the FDA to break down some of the traditional barriers to enable a safer, more efficient drug manufacturing environment.

WORLD EVENTS

2017 brought significant political change — the effects of which still remain somewhat of a wild card when it comes to regulatory impact.

Brexit

On March 29, 2017, the United Kingdom notified the European Council of its intention to withdraw from the European Union by March 2019. For pharma manufacturers, this move raises concerns about the European Medicines Agency, especially for companies that want to continue marketing drugs in the European Economic Area after the UK withdraws from the EU. Brexit presents challenges in several areas, notably regulatory procedures, quality testing, supply chain management and intellectual property.

In November 2017, associations representing the European and British life science industry published a letter urging Brexit negotiators on both sides to agree to a transition period that will enable continued EU-UK partnership on the regulation and supply of medicines.

Also in November, the EMA announced that it will relocate to Amsterdam, the Netherlands. EMA has developed and made public a business continuity plan to ensure operational continuity while the Agency prepares for its relocation and the UK's withdrawal from the EU. The EMA published additional practical guidance to help pharmaceutical companies make all necessary changes to their marketing authorizations by the end of March 2019.

Trump presidency

Early in his presidency, Trump lashed out against the FDA, calling its approval process "slow and burdensome," while vowing to deregulate the drug industry. The crux of Trump's message was that reducing regulatory standards would lead to more treatments reaching the market and lower drug prices — a message that was met with concerns over drug safety.

Trump's first major FDA-related action came in the form of nominating Dr. Scott Gottlieb as the Agency's 23rd Commissioner. Sworn in in May 2017, Gottlieb echoed Trump's desire to overhaul the FDA, striving to reduce the red tape that he has often said hampers pharmaceutical innovation. Pharma critics initially voiced concern over Gottlieb, who had served on the boards of several major pharma companies and had strong ties to Wall Street. While it's almost too early to form an opinion, so far, Gottlieb has seemingly found a way to work within the FDA's system while still aggressively pushing new agency actions and policies — in particular those aimed at lowering drug prices. Under Gottlieb, that Agency has prioritized access to cheaper, generic medicines, including posting a list of brand-name drugs that lack generic competition, and fast-tracking approvals of associated generics.

In November, Trump nominated Alex Azar II, a former top Eli Lilly executive, to be the next Secretary of the Department of Health and Human Services (HHS), promising that Azar will be "a star for better health care and lower drug prices." If confirmed, Azar will succeed Tom Price, who resigned after news broke that he spent close to $1 million on air travel in his first seven months. As HHS secretary, Azar would oversee numerous agencies including the FDA and the Centers for Medicare and Medicaid Services.

The nomination is controversial, however, considering Azar spent five years serving as president of the U.S. arm of Eli Lilly at a time when the drugmaker was highly criticized for dramatic price increases. Azar had his first confirmation hearing before the Senate Health, Education, Labor and Pensions committee on November 29th. In the hearing, Azar attributed high drug prices in part to patent abuses that stall market access to more affordable generic drugs. "This is the most important job I will ever have in my lifetime, and my commitment is to the American people, not to an industry," Azar assured.

A LOT HAPPENS IN A YEAR

While the aforementioned regulatory actions stand out among the hundreds of guidances published in 2017 by regulatory agencies around the world, by no means is this a comprehensive list.

The past year brought with it important regulatory inroads in personalized medicines, global harmonization and quality. While political change in 2017 has left open questions for the year ahead, regulatory progress on the whole was encouraging.

REFERENCES

[1] *Personalized Medicine Market Trends in Personal Care Products by 2022. Crystal Market Research (Nov 2017).*

[2] *Chatterjee, Bikash. An Argument for Change – The Promise of the Next Decade. CPhI Annual Industry Report 2017. UBM (Oct 2017).*

DESIGNING THE NEXT GENERATION OF QUALITY MANAGEMENT SYSTEMS

Pharma companies are recognizing the imperatives to enhance agility and improve responsiveness to market needs

By Álvaro Carpintero, Miguel Ángel Morán, Elena Pretto, Kartik Reddy and Vanya Telpis, McKinsey & Company

AS PART of a maturing industry, pharmaceutical companies are under significant pressure to both innovate and successfully manage increasingly complex operations, more stringent regulatory requirements and frequent consolidations. Many are rethinking their quality management systems (QMS), recognizing the imperatives to enhance agility and improve responsiveness to market needs without increasing quality-related costs.

Creating a lean and agile QMS will be a key source of competitive advantage for these companies. Lean and agile systems have three characteristics:

- The ability to capture customer feedback and regulatory changes, build them into operations and launch new products rapidly.
- A streamlined structure that enables both compliance and operational efficiency, even when faced with increased business complexity.
- The flexibility to incorporate different modalities easily.

While the benefits are clear, a misalignment between the QMS and a company's operational requirements can have downsides and drive costs. For example, a major U.S. automotive company with a strong quality reputation saw its JD Power IQS ranking fall by more than 15 places after introducing a new entertainment system in its vehicles. The system was complex to operate and frequently malfunctioned. The company responded with a multiyear effort that fundamentally changed how it thought about quality. In pharma, a similar misalignment can result in major quality or compliance issues that lead to hundreds of millions of dollars in remediation costs.

INDUSTRY TRENDS DEMAND A NEW APPROACH

Recent pharma industry trends have significant implications for QMS.

- Technology advances have increased the diversity of products and processes. Products may have more

elements (for example, the drug itself, software and a device), while traditional product lines (small and large molecules) have matured and new processes are increasingly more complex.
- Mergers and acquisitions are bringing more and new modalities under the same corporate roof. It is fairly commonplace for companies to face the challenges of integrating QMS from multiple businesses.
- Regulators are using technology to gain access to data and tools that enable more frequent and more in-depth audits with an end-to-end scope. This increased scrutiny demands more extensive sharing of information and a greater emphasis on its integrity. At the same time, advanced analytics are greatly enhancing the ability of regulators and industry players to process this information and derive new insights.

Creating a lean and agile QMS to respond to those trends is not easy:

- Understanding end-to-end processes is challenging in a larger and geographically dispersed organization.
- Legacy QMS have become unnecessarily bulky over time and misaligned with business processes, due to incremental changes in response to quality incidents or audit observations. A pharma site has, on average, 100 to 500 change controls per year.
- Digital technologies and sophisticated data mining have changed the nature of products and innovation in the industry. Companies are increasingly moving toward providing end-to-end solutions comprising products and services.
- The widespread adoption of cloud-based solutions creates new challenges in redefining the paradigm applied to control changes and new-version releases without impeding innovation.

HOW TO DESIGN/IMPLEMENT A LEAN, AGILE QMS

Companies must take a set of steps to implement each element of a lean and agile QMS.

1. Capturing feedback and applying new insights in operations and development. Recent research shows that pharma companies lag behind other industries in capturing customer feedback and incorporating it into future designs. Many companies struggle with the implementation of regulators' guidelines, resulting in multiple citations over the past few years.

Capturing voice of the customer. Customer feedback is no longer restricted to formal channels, such as product quality complaints and service reports. Capturing information from other avenues is increasingly a formal part of the QMS across industries, though pharma is lagging in this. For instance, consumer companies routinely track and respond to product issues on social media even before a formal complaint is raised. Digital tools can process large amounts of social media data to identify emerging quality issues early. These other avenues are also increasingly monitored by regulators and could trigger increased scrutiny.

Applying lessons across network operations. To avoid a repetition of issues, CAPA and governance systems are critical for enabling an organization to rapidly share lessons learned across the network. One company adopted a systematic process to evaluate the relevance of each audit observation to all sites, regardless of whether the observation involved central or site SOPs. The resulting "CAPA implementation matrix" not only reduced risk but also helped in harmonizing processes across sites.

Integrating and harmonizing QMS with development and operations. A company can facilitate speed to market by harmonizing the reviews (for example, through the use of similar metrics and formal forums in which R&D and operations participate) and using similar procedures during later stages of product development. For example, automotive manufacturers have developed shared modules and platforms across different car models to significantly accelerate the development process.

Leveraging the power of advanced analytics. Advanced analytics is enhancing companies' ability to understand critical process parameters and material attributes during the commercial phase, resulting in demonstrated reductions in batch failures and deviations. It is equally important for companies to feed these insights back to the early development phase.

Establishing a high-performance quality culture. While the feedback loops are important to lay the foundation for agility, culture is critical for truly transformative change. Do employees handling customer complaints and feedback see their work as merely a compliance activity or as a critical input in the quality system? Are people rewarded for going the extra mile to collaborate across functions, including development and operations? Does the organization encourage a bias toward proactively addressing quality issues?

2. Streamlining the QMS

There are three types of complexity/inefficiency in QMS:

- Lack of coherence between the core business system and QMS processes
- Complex SOPs that are difficult to read and understand
- Extensive documentation requirements that limit productivity

INTEGRATING QMS FROM MULTIPLE COMPANIES OR BUSINESS UNITS

IN AN INDUSTRY where M&A has become commonplace, many pharma companies have faced the challenge of integrating QMS from multiple companies (which is similar to integrating separate QMS used by each business unit).

There are a wide range of integration approaches, including "full harmonization," which requires significant time and resources and results in a complex system; "pick one," which works well for similar product types; and "clean sheet," which is used when none of the legacy systems is effective. However, based on our experiences supporting many companies in this process, we have identified five key lessons to take into account when integrating multiple QMS.

Lesson 1: A QMS is the way a company manages its business. Several sub-lessons flow from this:

- Quality objectives should be clearly linked to business objectives and strategy
- The QMS should be easily understandable, and should clearly establish the link between quality policy and ground-level execution
- Sufficient flexibility within the system is needed to incorporate business-unit or site-specific nuances and enable continuous improvement
- The system should enable the sharing of lessons learned and best practices across the business so that it can respond agilely to changes
- To readily adapt to regulatory changes, the system should be dynamic and have sufficient controls

Lesson 2: A QMS needs to find the equilibrium between compliance and business goals (see Exhibit). Because there is a lot at stake, an imbalance can result in significant costs. To ensure equilibrium, a QMS should clearly articulate not only the quality compliance and business benefits, but also the cost of implementation and buy-in. Moreover, the QMS should be lean, both to enable adherence and avoid unnecessary costs and longer lead times.

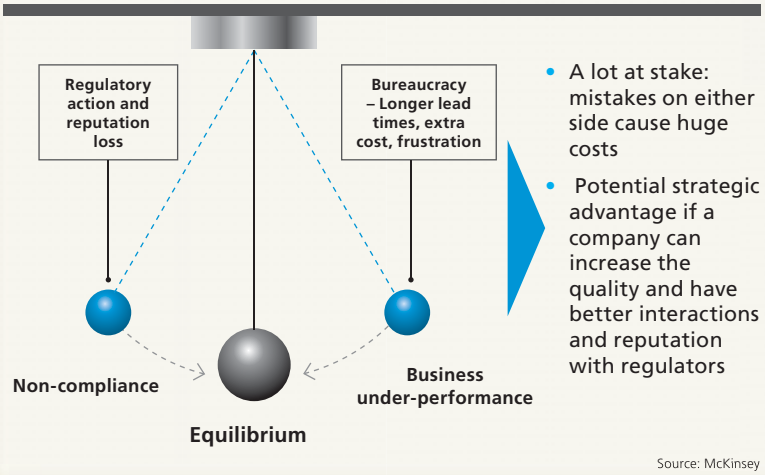
Lesson 3: External best practice is the base case, and should be adapted to business and culture. Although the company should consider external examples, it must start by understanding its current performance and the adaptations needed.

Lesson 4: A QMS effort should have a risk-based prioritization of key factors that influence regulatory compliance. To avoid "boiling the ocean," the company should design a very targeted and lean QMS, applying an external perspective on risk. It should also select the key processes to review first based on this risk assessment.

Lesson 5: A QMS should use a systems-based approach in which all the elements work well together. The company should take into account regulatory audit knowledge and expertise so that the QMS can be easily adapted without performing an audit of all the company processes. The company should also ensure that all elements of the QMS are well connected and work together effectively.

Exhibit 1

The QMS needs to be pragmatic, balancing compliance risk with simple-to-use and simple-to-understand processes



Source: McKinsey

The latter two issues are highly visible and apparent in day-to-day operations. Companies often respond by streamlining how SOPs are written and designing better documentation templates based on lean principles. But this approach does not radically change the QMS structure or thoroughly review its key elements. As a result, it is unlikely to be truly game changing.

In contrast, a lack of coherence between the core business system and QMS processes is more difficult to diagnose. The mismatch can be manifest in planning delays, slow decision making or low operational effectiveness. At one site, a culture assessment revealed that the mismatch between the QMS and business processes had reduced productivity, which in turn created pressure on the production system and increased quality risks.

Regardless of the product type or modality, many business processes are substantially the same. This makes it possible to design QMS with a relatively small number of procedures. For example, an Indian company's sites had developed a large number of different quality control procedures that served the same purpose and could be reduced by 80 percent. McKinsey's POBOS benchmarking suggests that a typical site has 40 to 60 percent more SOPs than its product complexity requires, and 30 to 40 percent more change controls per SOP than needed.

3) Making the QMS more flexible

We have observed four common QMS archetypes.

- **One size fits all.** Some companies use a single QMS that incorporates the highest level of regulatory standards to be followed by each modality. This archetype has the advantages of ensuring compliance by the entire organization, requiring only one quality organization, and driving the highest standards for each modality. However, it increases the regulatory burden and cost of quality and reduces flexibility and speed to market for some modalities.
- **Modular.** Other companies use a single QMS with different modules. Each product modality selects which modules are applicable. This archetype provides a fit-for-purpose QMS for each offering and can be managed by one quality organization. The ability to select only the applicable module enables agility and flexibility and increases speed to market. However, to avoid spending extensive time and resources to assess each product, the company needs a rigorous process to define the regulatory requirements for each offering up front.
- **Hybrid.** Some companies use a universally applicable QMS aligned to business processes at high level, but delegate responsibilities to teams and business units. This archetype ensures harmonization and enables the use of universally applicable SOPs, while also promoting flexibility by delegating responsibility to units that best understand product needs. This approach results in diminished oversight, because lower levels of the organization control compliance.
- **Fully separate.** In the fourth archetype, each modality has a fully separate QMS. This helps ensure compliance by each modality and promotes a leaner system within each unit is covered by a separate QMS. However, the use of this archetype results in a duplication of functions, increases administrative activity when transferring products across units, and reduces speed to market.

As this rundown of the archetypes' pros and cons suggests, there is no "magic bullet" for addressing the challenge of designing a more agile, streamlined and flexible QMS. In any given situation, the right answer depends on the context in which the company operates and the maturity of the current system.

GETTING STARTED

A periodic reexamination of a QMS can identify significant opportunities for simplification. But it is important to avoid the trap of making incremental changes. Although a fundamental redesign of the QMS is challenging, it is essential in many cases.

To get started, a company should consider several questions:

- How are our operations changing? Which digital industrial technologies (known as "Industry 4.0") is the company adopting and what are the implications for quality?
- What will our product portfolio of the future look like? Does the quality organization have the skills (such as relating to software or device quality) required to build quality into the products of the future?
- How is the QMS perceived? Do employees regard it as an enabler or as an unnecessary roadblock?

Finally, a company should recognize that expertise is not sufficient by itself to enable a successful QMS transformation. The company's leadership needs to support and participate in the effort. The most successful and long-lasting changes are those driven from the top down, with every part of the organization truly called to action.

PAT for High Shear Wet Granulation Monitoring and Control

The use of analytical techniques, including new technologies, has been shown to measure properties that correlate directly with finished tablet quality

By Tim Freeman, President, Freeman Technology Inc.

GRANULATION PROCESSES are used routinely across a number of industries to transform the properties of powder blends, often with the aim of producing an optimized feed for subsequent processing. High shear wet granulation (HSWG) is a flexible, efficient and reproducible technology and the preferred choice for many pharmaceutical applications. Combining short processing times with the capacity to deliver dense, uniform granules, HSWG is particularly suitable for producing an optimized feed for tableting and is an integral step in many oral solid dosage manufacturing processes.

An important aspect of current efforts to transform the efficiency of pharmaceutical manufacturing is the identification of Process Analytical Technology (PAT) that supports the better understanding, monitoring and control of key steps such as HSWG. This is especially true as the industry embraces continuous manufacturing, which tends to be associated with higher levels of process control than batch. HSWG monitoring and control is complicated by the fact that granules are typically an intermediate within a process, rather than the end product. Learning how to control the critical process parameters (CPPs) of a HSWG process so as to produce a tablet with defined critical quality attributes (CQAs), after several subsequent stages of processing, is a significant challenge.

In this article, we consider the process of high shear wet granulation, the benefits associated with it — particularly within the context of tablet manufacture — and strategies for characterizing the resulting granules. A particular focus is the use of analytical techniques, including new technology for continuous, in-line measurement, that characterize bulk properties of the powder rather than properties of the constituent particles. Such technologies have been shown to measure properties that correlate directly with finished tablet quality highlighting their value for HSWG monitoring and control.

BENEFITS OF GRANULATION

One of the primary reasons to granulate a fine powder blend is to improve flowability. Fine powders are usually relatively cohesive, exhibiting poor flow properties that can compromise performance in downstream processing steps or during product use. Larger granules, in contrast, tend to flow more freely delivering greater manufacturing efficiency. Beyond this, granulation delivers a range of other valuable benefits that include:

- **Enhanced homogeneity and**

a reduced risk of component segregation. This can be particularly helpful in ensuring the content uniformity of a finished product, for example, in tableting blends containing low levels of an active pharmaceutical ingredient and/or very fine APIs dispersed in much coarser excipients.

- **Denser particles with a lower packed volume.** Larger, denser particles can pack efficiently relative to finer, more cohesive ones which trap air. Granulation can therefore reduce storage volume needed for an equivalent mass of product.
- **A reduced dust hazard.** Reducing dusting can be an important health and safety gain, particularly when dealing with high potency APIs.
- **Improved compressibility.** Engineering an optimal level of compressibility into a granular feed can directly enhance its performance in subsequent processing steps.

Beyond these generic benefits, HSWG offers further advantages for a number of pharma applications. Like other wet granulation technologies, it is suitable for a wide range of materials and for almost any drug dosage. It offers short processing times, minimal binder use, and enables the granulation of certain types of highly cohesive material that cannot be successfully processed with low shear techniques.[1] Relative to low shear processes, HSWG also produces denser, less friable granules. These advantages help explain the popularity of HSWG within the industry, however, its practical implementation can be challenging.

Though HSWG is an inherently simple process, it presents two major challenges that impact practical implementation, the first of which is the difficulty of scale-up. Differences in equipment geometry and/or process dynamics from scale-to-scale complicate the transfer of optimized processing conditions. For example, a large scale unit may need a water addition of 22 percent to reach the same endpoint that a smaller scale unit reaches with a water addition of 26 percent. This is a big issue in the development of batch processes, which may go through several scales of operation prior to commercialization, and could complicate the early definition of design space.

The other challenge is accurate endpoint detection, identification of the point at which the granules have reached a state that is optimally compatible with their intended application. Here problems arise because granules are an intermediate, rather than the product of interest, in the majority of applications. In tableting, for example, developing correlations between CPPs for the HSWG process and tablet quality relies on the implementation of a statistical design of experiment (DoE) study that involves processing granules through the tablet press and assessment of the CQAs of the finished product (e.g. assay, weight, hardness, dissolution and disintegration). This lengthy, iterative approach is sub-optimal from the perspective of efficient process development and scale-up, and ultimately from the perspective of ongoing optimization and/or control of the HSWG.

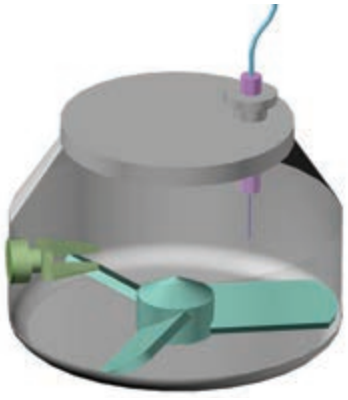


Figure 1: A schematic of a high shear wet granulator showing impeller, chopper and inline sensor for process monitoring.

The identification of PAT that is able to measure a parameter, during granulation, which securely and relevantly quantifies the quality of the exiting granules offers the opportunity to streamline the development process. To support the use of HSWG as a precursor to tableting, this requires PAT that is able to measure variables that correlate directly with the CQAs of the finished tablet, thereby eliminating the need for full product work up to assess granule quality.

SELECTING PAT FOR HSWG

When considering how best to characterize the product from an HSWG process, one approach is clearly to measure discrete properties of the granules themselves such as a particle size. Typical aims of the HSWG step within a tableting process are to improve blend flowability, reduce/eliminate segregation, and enhance compressibility so as to ensure high throughput in the press and target product quality. Particle size may impact all of these behaviors, but so do many other parameters. The flowability of powders, for instance, is a function of many different properties of the constituent particles, including shape, density, surface texture, porosity and hardness/friability, all of which may be impacted by granulation conditions. Looking at just one influential variable may therefore be less than optimal when it comes to establishing robust correlations with performance in the press and with tablet quality.

An alternative strategy is to directly measure bulk powder properties such as flowability of the granulating mass or the exiting granules. Dynamic powder testing is an at-line technique

that quantifies powder flowability by measuring the axial and rotational forces acting on a blade as it is rotated through a powder sample.[2] With dynamic testing, dry or moist powders can be measured in a consolidated, moderate stress, aerated or even fluidized state to simulate the process environment and generate highly relevant data. Furthermore, in addition to flowability, dynamic powder testers are able to measure other bulk powder properties that are directly relevant in quantifying granule quality. These include compressibility and permeability.

Experimental studies using HSWG to prepare optimized blends for tableting have shown that the properties of finished tablets can be predicted from dynamic measurements of the wet granules.[3] A direct relationship was observed between the basic flowability energy (a measure of confined flow properties in a low stress state) of the wet mass and of the dried granules, and tablet hardness. This work clearly highlights the potential for bulk powder measurements to fulfill the defining requirement for PAT for HSWG processes. The introduction of new, equally successful techniques for in-line, real-time measurement that operate on closely similar principles is therefore an exciting development.

A NEW PAT FOR HSWG

The key features of a drag force flow sensor for in-line granulation monitoring are shown in figure 2. An optical sensor interrogator processes and analyzes the signal from the sensor, and complementary temperature measurements are made to enable the automatic correction of any temperature-related drift in the measurement baseline. The sensor typically has a diameter of just 1-4 mm and can be mounted directly inside a granulator.

Material flowing past the sensor causes a deflection, the magnitude of which is precisely measured using the sensitive fiber-optic strain gauges on its inner surface to generate Force Pulse Magnitude (FPM) data. In a granulator, FPM peaks with each passing of the impeller blade giving a sinusoidal signal. Filtering and averaging of this signal yields a smoothed FPM data stream that provides robust and highly sensitive measurement of the flow forces within the in-process material. These dynamic real-time measurements of the granulating mass correlate directly with properties such as granule size and density, which change during the course of a HSWG.

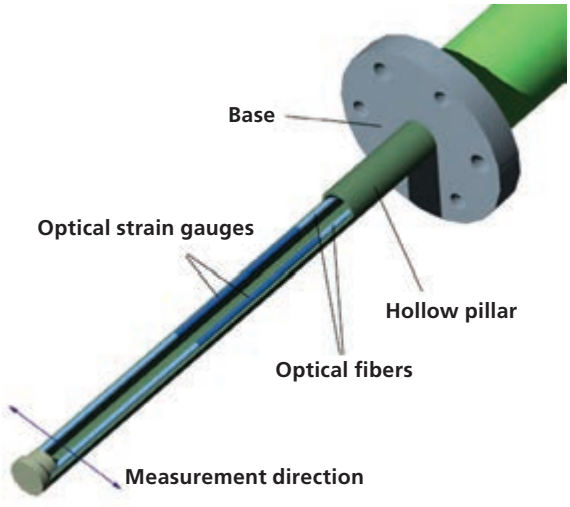


Figure 2: Schematic of a drag force flow sensor for the real-time measurement of flow forces within in-process material.

UNDERSTANDING THE PROCESS OF HSWG

In a high shear wet granulator (see figure 1) dry ingredients are energetically combined with a liquid binder to form relatively large granules that are typically dried and milled prior to use.

The first step is blending of all the dry ingredients potentially including a binder in powder form. The addition of a solution, typically water, dissolves the binder (where present) and wets the particles, promoting adherence. The running speeds of the impeller and of the chopper are then increased to begin the process of wet massing and the formation of granules. Agitation within the granulator is dominated by the action and speed of the impeller with the chopper serving to break up larger agglomerates, to deliver faster processing.

The properties of the exiting granules are influenced by the:

- running speed of the impeller/chopper
- rate of water/solution addition
- total amount of water/solution added
- granulation time

Control of these variables steers the granulation to a desirable endpoint.

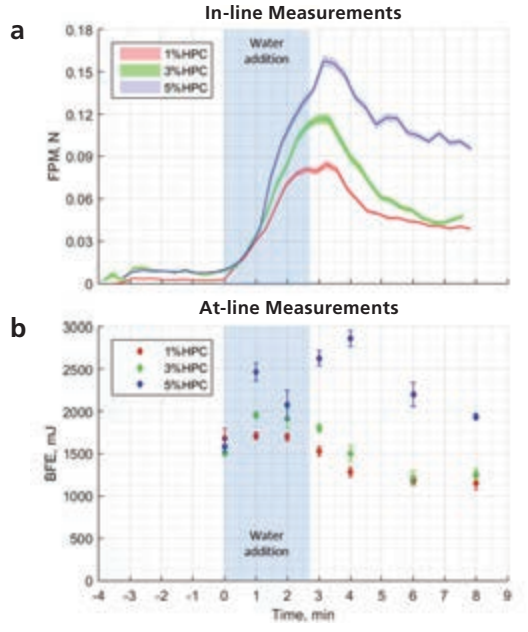


Figure 3: An in-line drag force flow sensor (a) tracks the progression of HSWG processes in an analogous way to at-line dynamic powder flow measurements (b).

In principle, this approach is akin to using the power drawn by the impeller motor for granulation monitoring — a traditional practice at the commercial scale — but it is orders of magnitude more sensitive. The practical benefits of the technology include:

- Minimal intrusion into and disruption of process flow
- Differential measurement that is not subject to baseline drift
- Relative insensitivity to the adherence of process material on the sensor surface
- High reliability/minimal maintenance (no moving parts)
- High frequency measurement rates (up to 500 samples per second) for real-time monitoring

Figure 3 shows data measured using an in-line drag force flow sensor (Lenterra Flow System, Lenterra Inc.) to monitor the progression of HSWG trials carried out to produce three batches of a placebo pharmaceutical formulation containing different levels of hydroxypropyl cellulose (HPC).[4] The addition of water to the dry blend is associated with a pronounced increase in FPM, which peaks shortly after the end of the water addition period highlighting the endpoint of the granulation which is conventionally recognized as occurring shortly after water addition is complete. The data clearly differentiates the granules produced at 1, 3 and 5 percent HPC and shows that higher binder contents lead to the formation of stronger granules.

For comparative purposes, BFE data measured during the same trial using a dynamic powder flow tester (FT4 Powder Rheometer, Freeman Technology) are included (see figure 3). These results show similar trends to those observed in the FPM data indicating that, like dynamic powder testing, the in-line drag force flow sensor offers the ability to measure the granulating mass in a way that directly correlates with the quality of tablets produced from them. This highlights the technology's significant potential as a real-time, in-line PAT that can be used in an analogous and complementary way to at-line dynamic powder testing to optimize HSWG processes.

PROMISE OF NEW TECHNOLOGIES

A primary aim of the PAT initiative was to encourage the pharma industry to embrace innovative technology in order to reach new levels of manufacturing efficiency. Identifying the most effective analytical techniques for the monitoring and control of critical processes such as HSWG is vital for efficient process development, scale-up, monitoring and control, and remains an ongoing task. Though widely used within the industry, HSWG processes do not scale-up easily and can be difficult to control effectively.

New in-line technology that enables the real-time measurement of flow forces within a granulating mass can be highly effective for monitoring granulation and shows significant potential for sensitive, accurate, real-time endpoint detection. Rather than relying on a classical approach of measuring a single granule property, this technology quantifies the flow behavior of the powder bulk as a function of process variables such as water content, formulation or granulation conditions. In this respect it is highly complementary to at-line dynamic powder testing, which has already been shown to have significant value for the optimization of HSWG processes, particularly within the context of tablet manufacture. By delivering data that can be directly correlated with the CQAs of finished tablets, these technologies offer opportunities to streamline and accelerate the development of both batch and continuous tablet manufacturing and, going forward, to directly support their advanced control.

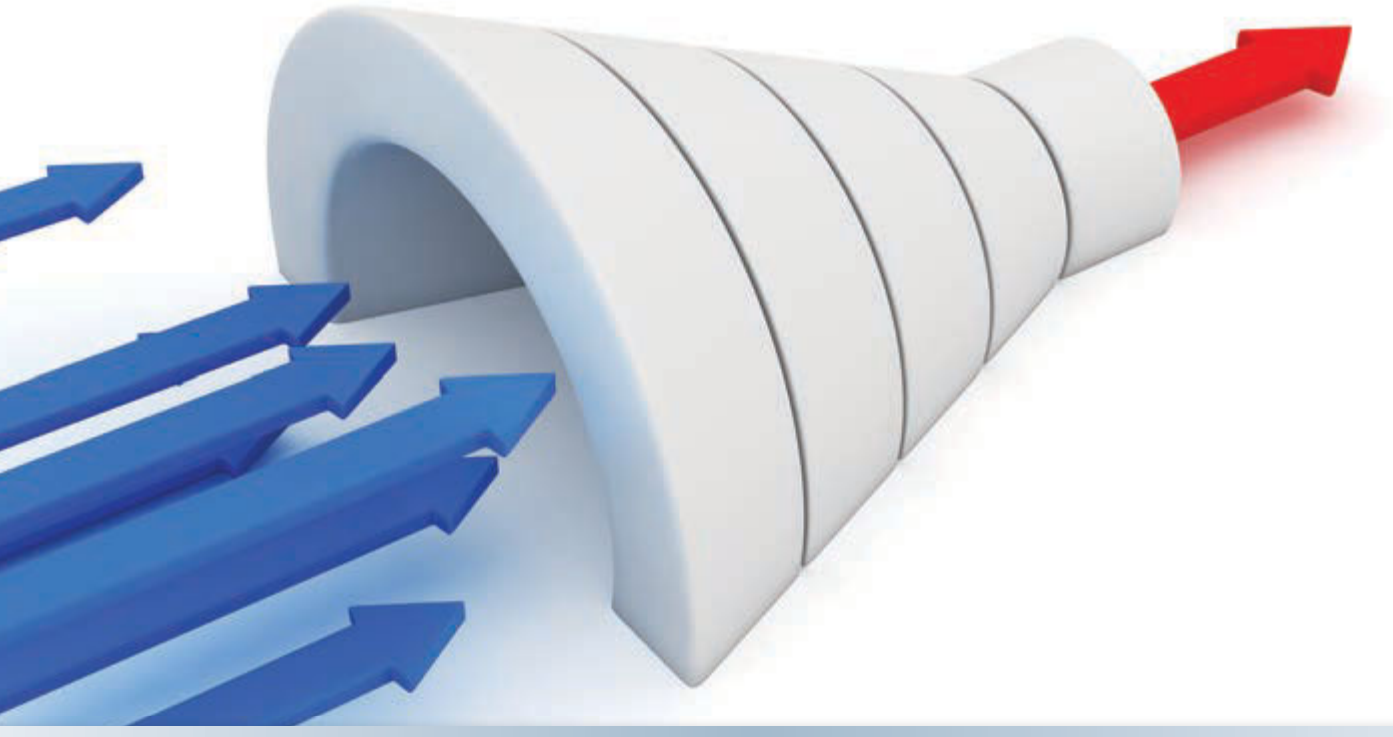
REFERENCES

[1] *Handbook of Pharmaceutical Granulation Technology, 3rd Edition, ed D. M. Parikh, Informa Healthcare, 2010*

[2] *Freeman, T. (2014) Choosing a Powder Tester. Freeman Technology e-book.*

[3] *Freeman, T. (2014) In Pursuit of Wet Granulation Optimization. Pharmaceutical Manufacturing.*

[4] *Narang, AS. (2016) PAT for High Shear Wet Granulation: Wet Mass Consistency Reported by In-Line Drag Flow Force Sensor Is Consistent With Powder Rheology Measured by At-Line FT4 Powder Rheometer. Journal of Pharmaceutical Sciences. 105:185-187.*



LEAN LAGGARDS: Exploring the State of Lean in Pharma

The pharmaceutical industry continues to face challenges when it comes to lean implementation and sustainable lean progress

By Robert Spector, Director, Clarkston Consulting

PHARMA COMPANIES continue to face challenges of globalization, complex supply chains and hyper-competition — all while demand for treatments continues to increase. As a result, the need for greater throughput, higher quality and reduced costs has become a top priority.

Over the last two decades, lean programs have become a popular approach to addressing these challenges in the pharmaceutical industry, as evidenced by the number of published case studies, conferences devoted to the topic and published articles. Unfortunately, the industry has seen little overall progress in becoming more "lean," as indicated by the lack of improvement in inventory turns performance. In recent years, performance across the industry has lagged that of the previous decade with gains not appearing to be sustainable due to a widespread lack of understanding of lean's strategic value at the senior leadership level, and how it should be optimally applied.

INVENTORY TURNS AS A LEAN METRIC

Lean is a business improvement approach that focuses on process improvement in new product development, manufacturing and distribution in order to cut lead times, improve quality and customer responsiveness, resulting in enhanced revenues, reduced investment and costs. Pioneered by Toyota in the 1950s and widely adopted across industries, lean's objectives include using less human effort, less inventory, less space and less time to produce high-quality products as efficiently and economically as possible while being highly responsive to customer demand.[1]

Although there is no universally accepted measure of a company's "leanness," inventory turns are a reliable indicator.[2] The trend of inventory turns over time indicates how well a company is progressing in terms of becoming more lean and improving its processes. Lower levels of inventory directly correlate to improvement

in the competitive edge factors of speed, quality and cost. That's why the companies that have successfully implemented lean have focused intently on reducing inventory, sometimes characterizing inventory as "evil." Similarly, noted lean experts such as Richard Schonberger view inventory as a catch basin for a multitude of business ills.[3]

Inventory turns also straightforwardly correlate with the bottom-line measure of business success — cash flows. Reduced inventories mean more cash in the bank, freeing up cash that can be used for other purposes. However, reduced inventories are beneficial only if the reduction derives from process improvement — the core of lean. If a company cuts inventories without improving processes, then stock-outs and lost customers will far outweigh any benefits of increased cash flows.

In addition, inventory is a standard financial metric and is readily comparable company-to-company, as well as over time within a business. It is also highly visible — walk around a facility characterized by high levels of inventory and you can conclude that the facility is not lean.

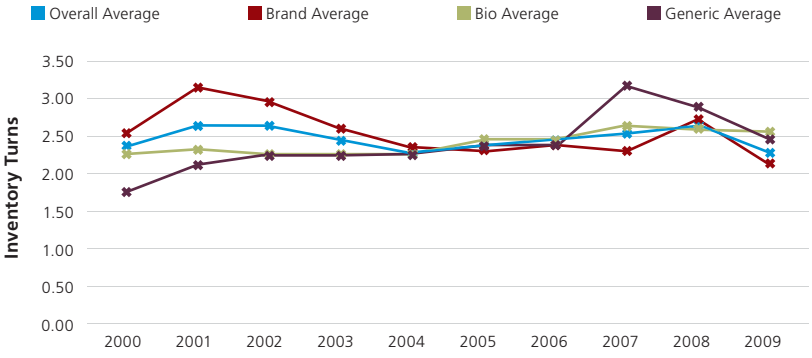
HISTORICAL CONTEXT

Historically, the pharmaceutical industry has ranked at the very bottom in terms of the trend of inventory turns improvement.[3] The pharma industry has been a late adopter of lean, due to the lack of a "burning platform" for change. In the 1990s when profit margins were at historic highs, little attention was paid to the competitive edge elements of speed and cost with the focus of money and resources on R&D rather than operations.

The little attention that operations did get was focused on compliance rather than process improvement.[4]

Exhibit 1

Average Pharma Inventory Turns (2000-2009)



The standard practice of ensuring that more than enough of each product was available to meet customer needs coupled with a lack of attention to operational efficiencies led to excessive inventories. Further, the sales and market-share strategy of pushing more and more inventory into the pipelines also drove up inventories.

At the end of the 1990s, new pressures began forcing a change in mindset. The government and society exerted tremendous pressure on pharmaceutical companies to reduce costs and improve quality. As more brand drugs lost their patents in the 2000s and early 2010s, price increasingly became a key competitive factor. With globalization and modernization, demand for mission-critical treatments dramatically increased with capacity constraints becoming more commonplace. In addition, the global counterfeiting of drugs increased the regulation of safety and quality.

As the 1990s ended and the new century began, pharma companies such as Pfizer, AstraZeneca and GSK increasingly looked at lean as an approach to address these challenges by driving improvements in cost, quality and supply.

REVISITING LEAN'S PROGRESS: SEVEN YEARS LATER

An analysis performed in 2010[5] utilizing data from the top pharmaceutical companies by revenue on the trend of inventory turns indicated that the average inventory turns remained essentially flat over both the previous five- and 10-year periods. While there were some companies that had shown improvement, there wasn't a strong enough trend to draw definitive conclusions.

A follow-up analysis was recently completed to determine whether there has been any improvement over the last seven years since the previous analysis. The top 20 pharma companies by revenue are listed in chart 1, along with their inventory turns for the corresponding annual period. The average inventory turns for these companies is also shown.

The overall trend in inventory turns has not changed since the previous analysis period seven years ago. Only Amgen has shown a consistent upward trend over this time frame. Gilead Sciences has shown progress since 2012, but given this short time frame it is likely premature to draw meaningful conclusions. Aside from these two companies, there aren't any companies in this data set that show

	INVENTORY TURNS							
COMPANY NAME	2009	2010	2011	2012	2013	2014	2015	2016
Johnson & Johnson	3.48	3.52	3.23	3.03	2.86	2.81	2.66	2.60
Pfizer Inc.	0.98	1.53	1.77	1.43	1.40	1.54	1.42	1.58
Merck & Co., Inc.	1.46	2.52	2.61	2.53	2.46	2.54	2.82	2.58
Amgen Inc.	0.97	1.05	1.06	1.18	1.16	1.50	1.63	1.58
AbbVie Inc.	N/A	NA	5.27	4.49	4.19	3.94	3.09	3.30
Celgene Corporation	2.15	1.70	1.89	1.33	1.11	1.04	1.01	0.90
Bristol-Myers Squibb	3.19	4.15	3.99	2.92	2.94	2.35	2.88	3.50
Gilead Sciences Inc.	1.60	1.54	1.53	1.56	1.64	2.15	2.07	2.25
Eli Lilly and Company	1.57	1.75	2.20	1.89	1.78	1.73	1.52	1.48
Abbott Laboratories	4.11	4.40	3.04	2.41	3.39	3.39	3.34	3.30
Biogen Inc.	1.36	1.38	1.43	1.39	1.47	1.59	1.44	1.44
Roche Holding AG	2.49	2.48	2.39	2.16	2.10	1.83	1.90	1.87
GlaxoSmithKline plc	1.74	1.93	1.94	2.02	2.13	1.70	1.75	1.69
Novartis AG	2.11	2.40	2.96	2.36	2.32	2.49	2.74	2.59
Sanofi	1.96	1.84	1.97	1.79	1.73	1.71	1.67	1.60
AstraZeneca PLC	3.24	3.53	3.26	2.56	2.60	2.78	2.18	1.68
Bayer	2.38	2.71	2.88	2.86	2.74	2.60	2.49	2.39
Bristol-Myers Squibb Company	3.19	4.15	4.08	2.92	2.94	2.35	2.88	3.50
Teva	1.90	1.95	1.83	1.77	1.84	1.97	2.04	0.00
Overall Average	2.22	2.47	2.60	2.24	2.25	2.21	2.19	2.10

a strong upward trend, indicating that the status quo for the pharma industry has not changed from the last time this analysis was completed.

While some progress has been made in the industry in this century, it has clearly been incremental rather than industry changing. In the last 10 years, pharma has improved its inventory turns performance relative to other industries,[6] however, it still ranks near the bottom relative to other industries. And while there is a plethora of published success stories, it appears that these successes have not been enough to "move the dial" for pharma companies for their overall company inventory turns.

Finally, it appears that where lean has been successfully applied in the pharmaceutical industry, progress has not been sustainable. While in the 2000s there were a small number of pharma companies such as Johnson & Johnson and AstraZeneca that did exhibit an upward trend in inventory turns, since that time these leaders have not shown continued progress, and in some cases have regressed. Utilizing the inventory turns metric, it is difficult to find many pharma companies that have made sustainable progress with lean initiatives, with only a few companies on the short list, including Amgen and several smaller revenue companies such as Juniper Pharmaceuticals and Atul Pharmaceuticals.

WHY HAS THIS HAPPENED?

What can explain the dichotomy between the published lean success stories and lack of sustainable progress? There are several potential causes that can be linked together by a common theme: a lack of full understanding of lean's strategic value, and how it should be applied to recognize its full potential and ensure sustainability.

Lack of Senior Management Commitment.

Lack of senior management focus and commitment is a widely accepted reason given for lack of successful implementation and success of virtually every type of business improvement initiative, including Six Sigma, Agile Manufacturing, Employee Engagement, ERP, Reengineering, etc.[4] The most successful improvement initiatives are driven by top management, e.g., Jack Welch at GE or Larry Bossidy at Allied Signal, and are driven top-down on a company-wide basis, across departments, functions and geographic borders. However, in the pharma industry

lean initiatives are typically applied in an isolated manner, i.e., in one manufacturing facility or solely in manufacturing operations, rather than as a concerted effort across an entire company as Six Sigma was done at GE.

Pharma industry executives do not appear to see lean as being strategic enough to warrant their attention and thus are not actively involved in the change — a prerequisite for success.

A word search of the annual reports for the top pharma companies by revenue from 2014-2016 was conducted. The terms included "lean," "Just-In-Time," "Operational Excellence" and "Continuous Improvement." For 12 of these companies, none of the searched terms were found and of the remainder, only two companies, — Amgen and AstraZeneca — drew any meaningful connection between these initiatives and strategic benefits.

The minimal mention of those terms suggests that most pharma executives have little concern for lean-related initiatives and feel that the investment community would not either. When pharmaceutical executives perceive lean as worthy of initial support, but not strategic enough to warrant continued attention, they may turn to other items deemed more strategic. As a result, lean implementations can fail, or in the case of successful implementations, performance can regress.

One example of a company that in recent years has successfully bucked the trend is Amgen. On the first page of the 2016 Letter to Shareholders, the CEO, Robert A. Bradway, directly links the company's focus on OpEx to earnings and margin improvement over the last few years. In their communications, Amgen touts their transformation program and the use of Continuous Improvement (CI) tools as a "core capability and a competitive advantage."

Since 2009, Amgen has demonstrated an upward trend in inventory turns of 6.54 percent, which translates directly into free cash flow improvement of the same rate. These funds can be spent on product development, equipment, pay increases, share buybacks, dividends, etc. When measuring the success of a lean program, if the company's progress isn't accompanied by a significant upward trend in inventory turns, lean isn't being applied correctly.

"Operations only" focus.

The vast majority of lean implementations in the pharma industry appear to be isolated to manufacturing operations drastically limiting lean's potential value. A recent manufacturers-only study[6] divided total inventory for each company into its components: purchased/raw material (RM), work-in-process (WIP) and finished goods (FG). In this study, improvement showed up only in the WIP percentage, i.e., internal manufacturing related processes, which is evidence of lean initiatives solely focused in manufacturing operations. Successful application of lean across the supply chain would be evidenced by reduced inventory in all areas.

Over the last two decades or so, there has been an increased amount of activity in the pharmaceutical industry to outsource production to Asia in pursuit of lower costs. An increasing number of Asian contract manufacturing organizations have been securing more outsourcing orders from large pharmaceutical companies. While labor costs are significantly lower in Asia (although they have been steadily rising over the last few years), outsourcing has brought on a new set of challenges, specifically lengthening and adding more complexity to the supply chain and quality issues — elements completely at odds with the goals of lean. In addition, lean adoption has been much lower in Asia,[7] which means there is much less likelihood of outsourcing to a facility that will have the same level of leanness as in the United States., resulting in a loss of the lean gains that have been achieved in the past.

Along with work-in-process inventories, pharma industry supply chain inventories (raw materials and finished goods) have been growing, which is evidence of lack of overall supply chain leanness. The longer overseas transportation times issue is frequently addressed by building more inventory in the supply chain, which only results in more quality issues and excessive costs in the areas of inventory, warehousing and transportation. While outsourcing to Asia has resulted in lower labor costs, the net benefits appear dubious. Focusing on applying lean solely in one node of the supply chain greatly limits the potential value.

Another key segment of the pharmaceutical value chain that has received little attention is applying lean to product development. The potential value here is enormous: every day saved in bringing a major new drug to market is worth nearly $250K in cost savings and more than $1 million in revenue; a month is worth $7.6 million in cost savings and tens of millions in revenue.[8] Other industries have successfully applied lean to product development and achieved tremendous success with Best in Class performers able to bring products to market 25 percent faster on average.[9] While there are case studies of application of lean to pharma product development, these are few and far between, likely due to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a lack of recognition of the potential to apply lean in this area and how to do so within the pharma environment.

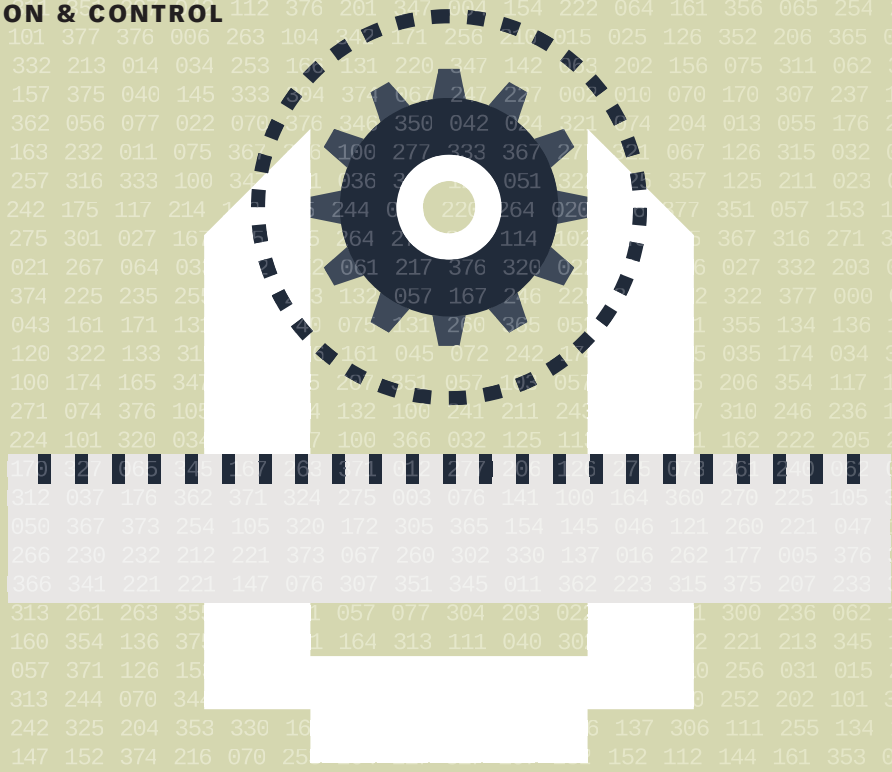
Cost reduction focus.

When properly implemented, lean results in strategic, financial and operational benefits in the areas of speed, quality and customer responsiveness. However, when reviewing lean case studies in the pharma industry in goals of the program and benefits achieved, cost reduction is typically the primary value driver, with other benefits such as quality and supply receiving secondary mention. Why is the cost focus mindset so prevalent? Labor costs are easy to measure, while the strategic benefits of improved speed, quality, flexibility and customer satisfaction are more challenging to quantify. Executives justify their support of initiatives based on financial results, and labor costs are the easiest to quantify. Even the traditional language of business cases shows this bias — benefits are typically listed as "savings," which imply cost reduction.

While the primary focus on cost reduction is evident across industries, it is more prevalent in the pharma industry in part due to legacy culture issues. Moving beyond cost reduction to benefits in revenue enhancement requires cross-functional collaboration, for example, marketing, sales and operations and sales working collaboratively to increase market share by capitalizing on enhanced speed and increase capacity, or operations and product development collaborating on building quality into new treatments. Yet pharma functions, divisions and geographic units remain strongly independent with the silo mentality deeply entrenched at most drug companies. This lack of collaboration also drives the isolation of application mentioned earlier to one part versus the entire supply chain. Lean cannot be delegated by pharma company leadership — culture change needs to be driven top-down by senior leaders.

There is a lot to be gained by companies in the pharma industry by implementing lean. As few pharma companies have been able to implement sustainable lean, a pharma company that focuses on lean as a strategic tool will clearly have advantages over its competitors and can capture additional market share. While the challenges to successful lean implementation may seem daunting, they are not insurmountable.

Editor's note: *In part II of this series, the author will discuss what pharma companies can do to address these challenges to ensure their lean efforts are successful and sustainable over the long term. For the complete listing of references associated with this article visit: www.pharmamanufacturing.com*



IMPROVING PERFORMANCE AND REGULATORY COMPLIANCE WITH INSTRUMENT CALIBRATION

Growing sophistication of smart field instruments makes calibration quicker, more reliable, less expensive and less prone to error

By Michalle Adkins, Director, Life Sciences Consulting, Emerson Automation Solutions

JUST AS manufacturers have moved from clipboards and hand-written data collection to automated electronic systems for batch records, many are doing similar things for field instrumentation calibration. In addition to being less labor-intensive, these newer approaches make the documentation less prone to error and more suitable for presentation to regulatory groups.

This dovetails with changes on the verification side. FDA/ICH Guidances for Industry describe verification as a continuous process with three key elements:

- Detect unplanned departures from normal operation
- Collect and analyze product and process data related to quality
- Maintain facility including qualification of equipment.

The third element includes instrumentation calibration. It is nonsensical to imagine operating a critical manufacturing process or plant without verifying the information coming from instruments as true and accurate. If a process has been validated based on a specific reaction happening at 85°C (±1 °C), verification ensures the temperature instrument monitoring the reaction is accurate and capable of delivering a reading with an appropriate degree of precision every time.

UNDERSTANDING CALIBRATION REGULATORY REQUIREMENTS

The Code of Federal Regulations Title 21, Part 211.68 says automatic, mechanical or electronic equipment can be used in drug manufacturing, and if it is used, "It shall be routinely calibrated, inspected or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained."

This regulation places the burden for creating a compliant calibration program on the facility. It does not specify how or how often any specific instrument must be calibrated or checked. At the same time, when the facility is being inspected by a government agency for regulatory compliance, those details will certainly be examined. A

facility will have to defend its calibration practices within its larger validation and verification programs.

So ask yourself if your calibration program is appropriate for the instruments you're using today, or if it still reflects the needs of less sophisticated process instruments of years past.

STREAMLINE CALIBRATION RECORD KEEPING

Electronic records for product movement and manufacturing have largely replaced expensive and troublesome manual techniques. Unfortunately, in a surprising number of facilities, manual recordkeeping for process instrument calibration and maintenance persists. Since calibration tasks tend to be manual by nature, recordkeeping by hand often follows, but better methods are available.

Just as electronic batch records improved manufacturing processes, they can also do the same for calibration. Consider the typical steps for a temperature sensor:

- Find the appropriate instrument, identify it positively, and remove it from its mount
- Find the relevant test and calibration protocol for the specific instrument
- Heat up the dry-block calibrator to the first test point and take the first reading
- Reset the dry-block temperature, wait for it to change to the new value and repeat the reading
- Do this as many times as specified, typically five test points for a critical instrument
- Write the relevant information on a test sheet, or type it into the computer terminal
- Write out the calibration sticker and return the instrument to service or the stockroom.

A technician working under pressure and in a hurry might inadvertently write down incorrect information. Other typical mistakes include testing the wrong instrument, testing to the wrong set of calibration points, testing against an incorrect standard and so on. In any situation where a human being has to read and write numbers, mistakes will be made. While automating calibration to the extent of removing the human element entirely isn't possible for all instruments, there are ways to automate calibration and recordkeeping.

SMART INSTRUMENTS SIMPLIFY PROCEDURES

Smart field instruments have the ability to communicate well beyond simply sending an analog process variable. Protocols such as HART and WirelessHART provide the means for a smart transmitter to store a great deal of configuration and calibration information, including:

- Its own tag number
- Measuring units and range
- Calibration history
- Calibration test points
- Self-diagnostic functions
- Alarm points, and more.

These capabilities have greatly improved the calibration picture. A smart transmitter can be linked to control and monitoring systems via a digital data network, which can communicate its internal diagnostic information along with the basic process variable. Since verification is a process rather than an event, it is possible to monitor the condition of all process instruments on a unit continuously while the process is running. Internal diagnostic routines can warn of a problem developing with any instrument.

Calibrations still need to be performed, but they become opportunities to verify known performance, rather than to correct drift and errors. Calibrating a given modern smart instrument should thus not reveal any surprises.

For an increasing number of process instruments, the diagnostic routines built into the transmitter are able to examine the sensor element itself and find changes capable of affecting performance. The nature of these capabilities varies from one technology to another.

For example, the way a Coriolis flow meter measures liquid movement is much different than the method by which a capacitive sensor measures pressure. Nonetheless, each instrument knows what it should see in normal operation, and any deviation indicates something may be wrong, and it can warn operators and maintenance personnel accordingly.

MODERN CALIBRATION PROCEDURES

Many calibration programs are built around old and often obsolete assumptions. In years past, when a new

Table 1

Manual Calibration Techniques by Instrument Type

- Temperature: dry block test
- Pressure: manual or automatic pump used to create simulated air pressure
- Level: varies by instrument type, with degree of difficulty ranging from low (dP instruments) to very high (time-of-flight instruments)
- Flow: varies by instrument type, with degree of difficulty ranging from low (dP instruments) to very high (mag meters and other non-contact instruments)
- Analytical: requires simulation of the media property which the instrument is measuring, such as a calibrated bath solution for a pH sensor

production-grade mechanical pressure gauge was going to be installed in a production unit, it went first to the calibration bench. The technician would compare it to a 4A certified test gauge, and if there was any deviation, it was a simple matter to open the case and make adjustments via setscrews. This approach is built on three key underlying assumptions:

- The gauge needs to be checked and possibly adjusted because it can't be trusted out of the box
- A qualified technician can improve the instrument's performance by tweaking it
- Regular ongoing calibration at short intervals on the bench is necessary to verify it is not drifting out of its measurement tolerance range.

The reality today is much different because none of those assumptions are correct. Here's what should happen now with a new smart pressure transmitter:

- The technician takes it out of the box. It has been calibrated at the factory to a standard far more precise than a 4A gauge, and there is a certificate documenting the actual calibration process. An electronic version of the certificate can be uploaded to the calibration database
- The technician can check it on the bench if required, but there are no setscrews to tweak
- Anything the technician tries to do to improve calibration will only degrade performance. Unless the transmitter has been damaged, it should be installed as-is
- The technician may need to do some more configuration steps, not calibration, but these are done electronically through a computer or hand-held communicator
- In day-to-day operation, a quality pressure transmitter will exhibit great stability over long periods of time, and should a problem develop, self-diagnostic functions will detect it.

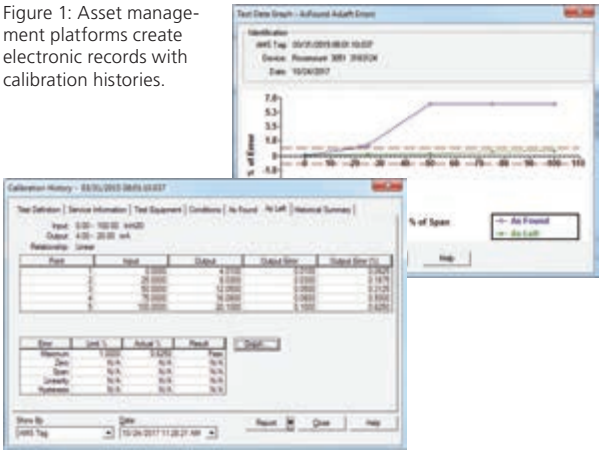


Figure 1: Asset management platforms create electronic records with calibration histories.

With today's smart instrumentation, calibration is typically not something a technician does to fix a problem, but instead it is used for verification of correct function. The difference may be subtle, but the implications are huge. Some users embrace these capabilities and realize smart instruments provide the means to reduce the amount of required calibration, while still maintaining reliable operation within a validated process per regulatory requirements.

SOME CALIBRATION IS ALWAYS NECESSARY

The capabilities discussed may reduce the frequency of calibration, but some calibration will always be required. Any component or system can fail, and pharmaceutical manufacturers need to be especially vigilant to make sure everything is operating as designed. Moreover, few facilities have the most technologically advanced instruments installed in every application. Most process units have a mix of mechanical, basic analog electronic and smart instruments — and a calibration program needs to address all these instrument types.

Different types of smart instruments require different calibration techniques. Obviously a temperature sensor has to be tested differently than pressure instrument, but other elements, such as process criticality, also play a part in determining how to handle the checks.

Table 1 lists a variety of common smart instrument types, and gives a short description of how each is calibrated. Most are tested by simulating a process condition. Pressure and temperature instruments are relatively easy to check because it is easy to create an appropriate simulation. Flowmeters are more complex, particularly large ones, since creating a controlled and calibrated flow is not as easy.

Farming out calibration might involve bringing technicians to the site to perform tests. Some instruments may have to be sent off-site to the manufacturer's base facility or lab, although many third-party instrument calibration facilities have mobile calibration rigs.

For instruments needing to remain in place or difficult to remove, calibration is often performed in-situ. This can limit the types of actions possible as it is not always practical to bring certain types of calibration equipment into the field. But for most instruments used in pharma manufacturing, a portable or hand-held interface, such as a HART communicator or a specialized calibrator, can do the job. A HART communicator allows technicians to interface with an individual HART-enabled process instrument. Using the 4-20 mA wiring, it can access diagnostic information, change the configuration and read historical information stored in the transmitter.

Hand-held calibrators have a wider range of capabilities related to calibration functions. Some are more elaborate than others, so individual models do not necessarily have all possible options. Calibrators perform the same basic tasks as a communicator, but add other process simulation abilities, such as a small air pump to test pressure sensors, or sophisticated electronic controls to simulate signals from thermocouples or RTDs.

Calibrators can be loaded with appropriate procedures for the instruments to be serviced during the specific round or shift. They can record all actions in the field, and then sync with an asset management or calibration maintenance management system to transfer field activity. Manual actions are minimized.

Table 2

Electronic Calibration Advantages

- Requires less equipment
- Faster
- Less labor intensive
- More reliable
- More repeatable
- Self-documenting

Whether bench or field-based, calibration is no longer solely a mechanical process with modern smart instrumentation. Sophisticated electronics have extended the amount of information on an instrument's condition, which now often extends to specific calibration issues. The future where process instrumentation can be verified electronically, remotely, continuously and automatically is already here for many smart instruments.

ELECTRONIC DIAGNOSTICS/ASSET MANAGEMENT

As mentioned earlier, smart instruments are capable of sending diagnostic information about various aspects of their condition and performance. Using this information in a calibration program or for condition-based maintenance requires monitoring the most important attributes for a given instrument and acting appropriately. Trying to do this manually can quickly become overwhelming with an instrument population of any size.

Effective companies automate the process of sorting through the information by using an asset management system (AMS). Each smart instrument has its own record in the system (Figure 1), and the AMS can communicate with each instrument through plant networks. Using a communication protocol such as HART, WirelessHART, or a mix of both, the AMS can poll each instrument following a pre-determined interval based on criticality. Each attribute has its appropriate operating range, and any critical deviation can be set up to trigger an alarm.

Some diagnostic attributes are purely the concern of the maintenance group, while others can affect the instrument's ability to deliver its measurement accurately or reliably. For example, consider a typical smart pressure instrument. It is designed to read a range of 0-50 psi, and it sends this signal via a 4-20 mA current loop, with a reading of 46 psi translating to 19 mA. If there is a malfunction in the power supply to the instrument such that it cannot provide more than 15 mA, the instrument will continue to work, but it cannot indicate its full range. The upper third, roughly, cannot be communicated. A smart instrument can recognize this deviation and send an appropriate message or alarm through the AMS.

Such a situation is not part of the calibration program per se, but it is critical information related to the instrument's ability to function properly, which is part of the larger verification program. Under normal circumstances, diagnostic information from smart instruments generally says the instrument is functioning correctly, and therefore there is no reason to doubt the information it is transmitting. If a problem develops, the AMS can warn of it immediately.

Hand-held communicators and portable calibrators can interface with the AMS directly, transferring information, instructions and data in both directions. Communicators and calibrators thus become critical extensions of the AMS. The AMS becomes the main record-keeping mechanism for the larger instrument calibration and verification system. "Dumb" electronic instruments and mechanical instruments can be included in the AMS, but some information for those will have to be handled manually.

CONCLUSION

Consider what it was like owning a car 30 or 40 years ago. A 1975 model or older was far more maintenance intensive, needing tune-ups, spark plugs and oil changes more frequently than today's vehicles. No sensible driver continues to perform all that service on a current model car because it doesn't need it. The same is true of today's process instruments.

Calibration is still necessary, but the sophistication and stability of instrumentation today makes it far easier to work with and less costly to maintain. Manufacturers can work with instrumentation suppliers, like Emerson, to modernize practices and capture significant cost reductions and labor savings, while still meeting all process validation, verification and regulatory requirements.

Process Analytical Technologies

Interviews with product experts about select hardware/software products applicable to PAT/QbD, highlighting key features of each instrument/program

BY EMIL W. CIURCZAK, CONTRIBUTING EDITOR

RATHER THAN simply list a bunch of equipment introductions, I am presenting a smaller number of technologies (hardware and software) applicable to PAT/QbD. The format will be mini-interviews and will touch on the highlights of each instrument/program. Since I have some (professional) personal favorites, I am going "Oprah" in this feature.

1. ENDRESS+HAUSER
TRUSTSENS TEMPERATURE SENSOR

Why is temperature important for process control?
Temperature is often a critical control point (CCP) in pharma, related to product quality, batch yield and cell viability. Without adequate temperature measurement, processes may not run at optimum, putting batches at risk and resulting in lost/recalled product.

What considerations face pharma production in calibration of temperature sensors?
The primary consideration is frequency of calibration. Batch-wise calibration gives unacceptable downtime and lost production. Long periods between calibrations risk producing OOS product. This sensor manages the balance between extremes (See Figure 1).

Figure 1. TrustSens probe, being inserted.

The benefit of a "self-calibrating" temperature sensor?
It provides a solution to frequency as a traceable, self-calibrating temperature sensor. In SIP batch processes, it performs a calibration without removing the sensor or measuring offline. Calibrating each cycle validates the performance of sensors without off-line manual calibrations. It compares the calibrated measurement to pre-defined tolerances, notifying the owner if the measurement is within tolerance. This allows identification of errors between calibrations — before they result in product losses.

Explain temperature sensor self-calibration.
It uses a material that undergoes a ferromagnetic state change at a specific temperature. Via a thin-film RTD sensor, this change is detected and compared with the RTD temperature measurement, providing data via LED or a signal if it is out of tolerance. It calibrates each SIP cycle, adjusts the output, storing 350 date/time-stamped calibrations and generating calibration reports.

2. INDATECH
UV, NIR, RAMAN PROCESS ANALYSIS EQUIPMENT

Where is the primary focus in the process stream?
Their primary focus is monitoring processed materials: tablets, capsules, lyophilized cakes, as well as selected processes. The equipment uses Visible, NIR or Raman with multiple fiber probes, utilizing a modified "Push-Broom" technology.

What is measured and how quickly?
Not only the API and moisture are measured, but numerous physical parameters. For example, illuminating a tablet at one point and measuring the emitted light at various distances (Figure 2), the hardness/density may be measured which, in turn, may be correlated with dissolution profile. In addition, capsules (on an inverted belt, allowing even measurements) can be measured for API and percent fill. Vials, liquid-filled or lyophilized cake, can be measured for API, additives and moisture. Multiple fibers (at the side of the vial) allows the full "cake" to be measured, even when removed from the base.

Any other points along a process?
The multiple fiber optics heads allow the system to follow

materials in hoppers, FBDs and so forth. It is able to use Vis/NIR/Raman, whichever is best suited for the multi-variate analysis, rapidly and in real-time, using proprietary (Part 11 compliant) software.

3. METROHM
INSTANT RAMAN ANALYZER M3

What is the MIRA M3 and why is it special?

The Metrohm Instant Raman Analyzer M3 (Figure 3) is the newest handheld Raman analyzer on the market, fully compliant with 21 CFR Part 11, designed for raw material identification (RMID) in Pharma.

Besides its small size, what are some other distinguishing features?

It has a barcode scanner that activates data collection and uses "Smart Tip" technology to ensure traceability. It runs on two standard Lithium ion or rechargeable AA batteries, ensuring portability. At 1.6 pounds, it is made of billet aluminum, is IP67 rated, and is designed for continuous warehouse operation.

Figure 3. Typical RM scan om M3.

How was it designed with the industry in mind?

The unit was designed for CFR compliance and simplicity. Many handheld Raman analyzers have these features in opposition. Using a "method-based" Raman approach, QA creates a precise, fixed, traceable workflow for the instrument, documenting what it is doing and how measurements are made for review by a regulatory agency. Scanning the barcode, it initiates a workflow from which the analyst cannot deviate.

Can you give more detail on Method-Based Raman?

A "method" encompasses all the parameters of an analysis: controlling the sample name and data collected, display location, scan length, energy used and sampling accessory. It controls these by either an onboard PCA or hit-quality index (HQI) from a library.

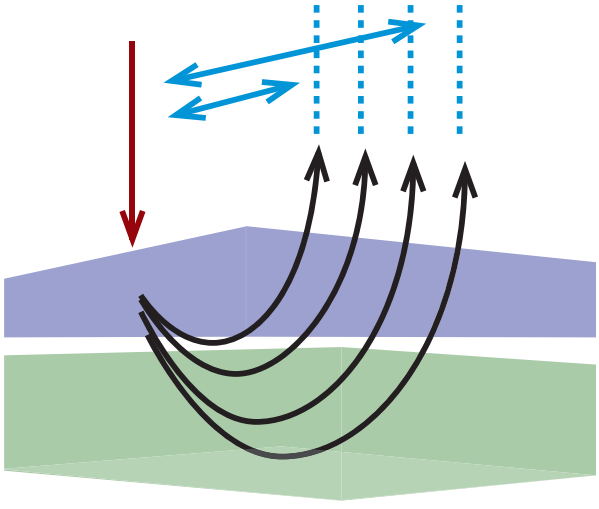


Figure 2. Path (s) light scattered by tablet/capsule, depending on density.

What sampling accessories are available?

There is a vial holder, tablet holder, and short and long focal-length lenses. Each is software identified, aiding traceability. With "Orbital Raster Scan" and method control, dyes and samples in colored bags are easily obtained.

4. TUNE ENGINEERING
IRISK QRM SOFTWARE

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How does one apply the software?

It bridges geographical boundaries, connecting various QRM teams, worldwide, e.g., a QRM professional in Germany wants to know more about U.S. risk perception. He logs onto iRisk, gleaning information about RM prevalent there. This enables him/her to gather information, giving a platform for knowledge-sharing. Ideas and information are exchanged through this platform, building a solid RM framework. Basically, knowledge management is the key to iRisk.

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Collaboration Is Key for the Future

The complexity of today's life sciences industry means the need for collaboration is greater than ever

BY JEAN COLOMBEL, VICE PRESIDENT OF LIFE SCIENCES, DASSAULT SYSTÈMES

THE LIFE sciences industry continues to face new challenges with shifting regulatory and economic pressures, and transitions to new models of care. Because of this complexity, the need for collaboration has become greater than ever. The following three areas are having a profound effect on the industry:

RESEARCH & DEVELOPMENT

We're witnessing a rise in scientific and medical discoveries that has created new domains that didn't exist a decade ago. For example, system biology — an engineering approach to biological scientific research — is now a central piece to understanding complex diseases like oncology.

The industry must constantly search for ways to deliver better results that can decrease operational costs, while reducing time to market. Emerging technologies like automation and virtualization are showing promise as ways to remain competitive and advance innovation. According to FDAReview.org, currently only 8 percent of drugs make it through the development and approval process and into the market. While many insights are derived from the drug candidates that didn't make it, there is still a significant amount of time and money spent on R&D. This is why accuracy in R&D is more important than ever. Through virtual design technology, it has become possible to test drug candidates in a virtual environment. This method of virtual testing enables researchers to identify higher quality candidates that have a better chance of getting to market. By combining in silico and physical experiments, the industry will be better armed to address these new scientific discoveries.

NEXT-GENERATION MANUFACTURING

To accommodate the ever increasing engagement of patients and practitioners in the healthcare ecosystem, the industry as a whole is looking to enable a shift to next-generation manufacturing that will be predictive and adaptive. To be successful, companies must embrace a platform approach that will enable scalability and flexibility, while meeting the evolving regulatory, quality and operational guidelines set forth by regulatory agencies around the world.

Further, the full adoption of Internet of Things and services into production environments, along with modular, flexible, disposable and single-use components will become the norm. "Smart" factories will manage production processes in real-time from the moment an order is placed right through to outbound logistics and will be the center of the manufacturing revolution.

QUALITY AND COLLABORATION

As part of the mandate for perfection there will be a need to better manage global changes, global market registration and total quality processes to help ensure safety and achieve regulatory compliance. To accomplish this, the industry must unite.

BY ELIMINATING ORGANIZATIONAL AND INFORMATION SILOS, WE WILL BE ABLE TO COLLABORATE MORE EFFECTIVELY.

By doing so, we can build more complex and sophisticated portfolios that are necessary to reach more patients worldwide. By eliminating organizational and information silos, we will be able to collaborate more effectively, aligning stakeholders to expand the ecosystem and leverage department expertise to get to the right information faster.

The goal is to create an integrated framework for compliant innovation, embed quality and regulatory best practices early in the development process, and to provide end-to-end product traceability throughout the lifecycle of the product. This process allows for higher quality, compliant products and faster regulatory approvals that will ultimately result in better patient outcomes.

The life sciences industry is beginning to operate in a much more collaborative environment — both internally and externally, and with different players throughout the healthcare ecosystem. Organizations that digitalize their businesses by embracing the principles and technologies that deliver digital continuity across the entire healthcare continuum will win.

By opening the door to strategies that encourage information and idea exchange, life sciences companies will be able to work to capacity and further improve the lives of patients.

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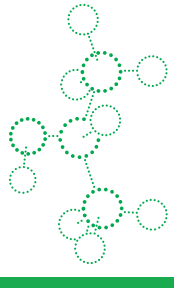

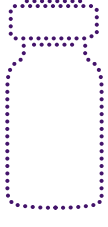

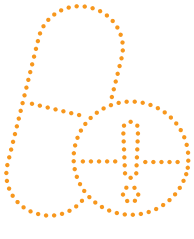

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