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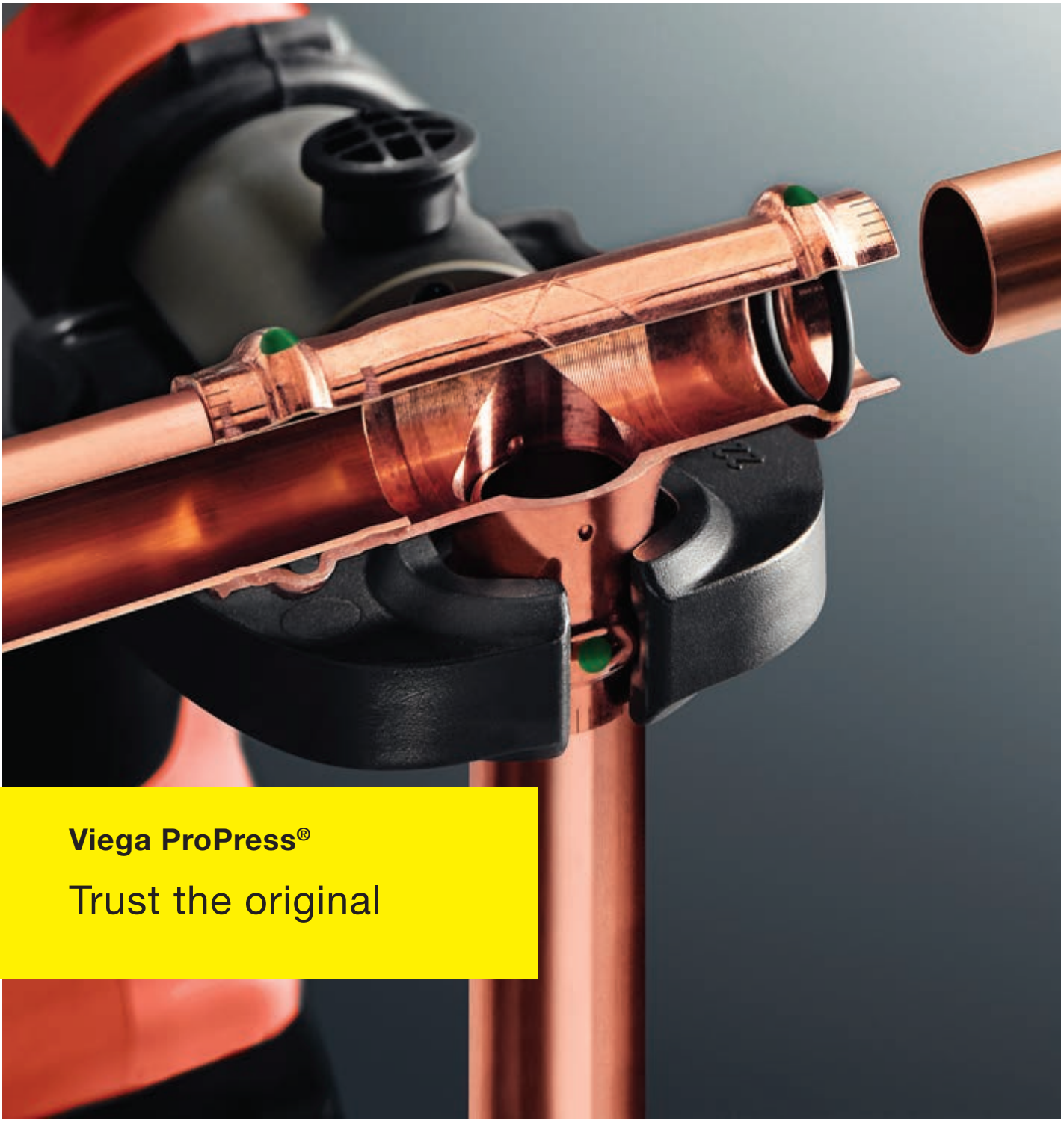

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Pharmaceutical Manufacturing (USPS number 023-188) is published monthly by Putman Media Inc. (also publishers of Food Processing, Smart Industry, Chemical Processing, Control, Control Design, Plant Services and The Journal), 1501 E. Woodfield Road, Suite 400N, Schaumburg, IL 60173 (Phone: 630-467-1300 Fax: 630-467-1179). Periodicals Postage Paid at Schaumburg, IL and additional mailing Offices. POSTMASTER: Please send change of address to Putman Media, PO Box 1888, Cedar Rapids IA 52406-1888. Phone: 1-800-553-8878 ext 5020. SUBSCRIPTIONS: To receive a complimentary subscription go to www.pharmamanufacturing.com. Subscription rate for non-qualified U.S. subscribers is $68/yr. Single copy rate is $15.00. Other international is $200/yr (airmail only). Canada Post International Publications Mail Product Sales Agreement No. 40028661. Canada Mail Distributor Information: Frontier/BWI, PO Box 1051, Fort Erie, Ontario, Canada L2A 5N8..

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Cocktails and Murder

The same public that's outraged over drug prices spends almost three times as much on booze

FOR CLOSE to a decade, I reported on the food manufacturing industry. Between animal rights activists, preachy vegans, health food crusaders and anti-GMO advocates, my job didn't always make me the most popular person at cocktail parties. When given the opportunity to write about the pharma industry instead, I thought, "Here's my big chance to write about an industry beloved by the public and immune from criticism!" *(Note: If there was a sarcasm font, I'd use it here.)*

For this month's cover story, we attempted to tackle everyone's favorite talking point: drug pricing. With our government prohibited from directly regulating drug prices, drug companies can (say critics) set whatever price the market will bear. And sometimes this doesn't sit well with the American public. In 2015, the country was outraged when Daraprim prices skyrocketed overnight from $13.50 to $750 a pill and Turing's CEO quickly became the most hated man in America. A year later, Mylan raised the base price of an EpiPen two-pack from $100 to more than $600, and consumers blasted the drugmaker. Other examples that have flooded the news – from companies conspiring to fix prices on widely-used generic meds to neverending patent lawsuits – don't bode well for the industry's image.

But those in pharma tend to have a different viewpoint. They will quickly point out that despite the high-profile nature of drug pricing concerns, prescription drug spending represents only about 12% of the trillions we spend on healthcare. Despite critics saying that pharma attempts to justify price increases with the need for drug development research funding, drug pricing is not simply about recouping R&D costs on a single med — it's mostly about the cost of failure. Failure, as it turns out, is quite expensive — to the tune of billions — in the drug industry. Only 12% of drug candidates that enter clinical testing are approved for use by patients. Hence, America's drug prices, in part, are what compensates pharma for the extreme risk of developing new drugs.

Our cover story stresses what is just one portion of the very complicated drug cost equation — manufacturing — because besides being the focus of this publication, manufacturing offers some very tangible ways for the industry to reduce costs. (See Jerry Martin's column on page 50). It is not surprising that despite facing pricing scrutiny and a wave of political uncertainty, pharma manufacturers are staying level-headed — continuing to increase manufacturing efficiencies in order to bring better quality products to market quickly and cost-effectively.

I find Trump's infamous "getting away with murder" comment to be an accusation poured with irony. I came across a study that estimated that 73% of the increase in life expectancy over a period of 10 years could be directly attributed to new medicines. Hence, to *deny* a life-saving industry the means to bring new innovation to market is somehwhat murderous. The most recent numbers I could find estimated that the average American spends $185 out of pocket on prescription drugs per year. Interestingly enough, it's also estimated that the average American spends, without complaint, $500 annually on alcohol — something which I think will make a great talking point at my next cocktail party.

BY KAREN LANGHAUSER, CHIEF CONTENT DIRECTOR
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Purple Rain and Opioid Awareness

The FDA has taken several actions to help reduce the number of people who become addicted, or who ultimately overdose from prescription opioids

PRINCE'S MUSIC and his cause of death will never be forgotten. But what about the two million other people in the United States who suffer from substance use disorders related to prescription opioid pain relievers? According to FDA commissioner Robert M. Califf, M.D., the public health crisis of opioid misuse, addiction and overdose is one of the most challenging issues facing the FDA.

The addiction to opioids such as heroin, morphine and prescription pain relievers has been a serious global problem for years, and there could be anywhere from 26 to 36 million people worldwide who abuse opioids, according to the National Institute on Drug Abuse (NIDA). The number of unintentional overdose deaths from prescription pain relievers has soared in the U.S., more than quadrupling since 1999, NIDA says. In 2015, 91 Americans died from an opioid overdose each day.

Several factors have contributed to the severity of the current prescription drug abuse problem, NIDA says. They include drastic increases in the number of prescriptions written and dispensed, greater social acceptability for using medications for different purposes and aggressive marketing by pharmaceutical companies. According to NIDA, opioid prescriptions grew from about 76 million in 1991 to nearly 207 million in 2013, with the U.S. being their biggest consumer globally.

The FDA has taken a number of actions to help reduce prescription opioid addictions and overdoses. They have improved product labeling, pushed for prescriber education and encouraged the development of abuse-deterrent formulations. In addition, the FDA has approved new intranasal and auto-injector forms of naloxone — products to reverse opioid overdoses — which can be administered not only by first responders, but also the general public, and are more readily available.

For naloxone to reverse an opioid overdose, however, it must be administered quickly. That's why the FDA launched the Naloxone App Competition late last year, in an effort to develop a solution to the problem of how to quickly connect naloxone carriers to a person experiencing an opioid overdose. The winner of that competition was OD Help by Team Pwrdby, a startup based in Venice, California, that took home the $40,000 prize. OD Help's concept is a simple, easy-to-use mobile app designed to connect potential opioid overdose victims with a crowd-sourced network of naloxone carriers.

The FDA has also partnered with other federal agencies to address the problem, but more work needs to be done.

"Public and private sector efforts in this area must be continued and strengthened," Califf says. "In particular, I want to call on the pharmaceutical companies that manufacture and sell these drugs to dig deeper into their expertise and resources to prioritize finding solutions to this public health problem…This is the time for both branded and generic drug companies to go beyond marketing and distribution plans and instead commit their expertise and resources to confronting the devastating negative consequences of a class of drugs that brings much needed pain relief, when used appropriately."

THE FDA HAS PARTNERED WITH OTHER AGENCIES TO ADDRESS THE PROBLEM, BUT **MUCH MORE WORK NEEDS TO BE DONE.**

To Califf's point, the pharma industry already is addressing the opioid epidemic a few ways:

1. Researching and developing new abuse-deterrent formulations. For example, Catalent has done significant research toward abuse-deterrent softgel technology, so that the API cannot be extracted and injected. Drugmakers have also made uncrushable versions of opioids.
2. Some pharma companies have changed their marketing tactics. Pfizer, for example, has agreed to disclose in its promotional material that narcotic painkillers carry serious risk of addiction — even when used properly.
3. Manufacturers are researching alternative pain treatments. For example, biotech companies, including Genentech and Biogen, are developing drugs that relieve pain without the risk of addiction.

That said, a comprehensive solution will likely require all the major players to help solve the problem — drug companies, prescribers, insurers and the FDA.

KATIE WEILER, MANAGING EDITOR
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ISPE Names 2017 Pharma Facility Winners

The Facility of the Year Awards recognize state-of-the-art projects using new technologies to improve product quality, reduce the cost of producing high-quality medicines and demonstrate advances in project delivery

THE INTERNATIONAL Society for Pharmaceutical Engineering (ISPE) says its Facility of the Year Award (FOYA) program recognizes innovation and creativity in manufacturing facilities serving the regulated healthcare industry. Projects selected for the FOYA program set the standard for pharmaceutical facilities of the future by demonstrating excellence in facility design, construction and operations.

"We are proud to honor the eight organizations that share ISPE's commitment to innovate and advance pharmaceutical manufacturing technology for the benefit of all global patients," said John Bournas, ISPE CEO and president.

FUNNY PHARM

"Tonight I'm going to party like I'm 19.99 years old."

— Paul Hayase

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

Facility of the Year category award winners include:

Abbott: Winner of the Operational Excellence category for success of its "Operational Excellence – A New Quality Approach" project initiated at the Abbott Diagnostics facility in Longford, Ireland. The site has increased productivity, improved changeover efficiencies, eliminated backorders, and enhanced product quality--while also reducing cost per unit, cycle times, equipment downtime, and inventory holdings.

Bristol-Myers Squibb: Winner of Facility Integration category for its Biologics Development Building and the Clinical Manufacturing Building project located in Devens, Massachusetts. These facilities were recognized as outstanding examples of how to integrate new capabilities within an existing plant through careful design, good collaboration, as well as creative engineering.

Cook Pharmica: Winner of Equipment Innovation category for its Flexible Filling Line project in Bloomington, Indiana. This collaborative development between owner, suppliers and engineering experts delivered a novel application of commercially available and custom developed equipment innovation manufacturing solutions that drove superior commercial market changing technology and supply chain flexibility in a unique "ready-to-use" vial platform.

Eli Lilly and Co.: Winner of the Process Innovation category for its Continuous Direct Compression Manufacturing Kits 2 & 3 project located in Indianapolis, Indiana, and Carolina, Puerto Rico. Their forward thinking approach brought on the implementation of Continuous Direct Compression (CDC) Process and other process innovations in their oral solid

Abbott wins a FOYA in operational excellence category for success of its Abbott Diagnostics facility in Longford, Ireland.

WEBWATCHER

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- Sanofi, Regeneron Allowed to Sell Cholesterol Drug
- FDA OK's Duchenne Muscular Dystrophy Drug for U.S.
- Merck India Workers Strike
- Lundbeck Abandons Alzheimer's Med
- Global Med Use to Reach 4.5 Trillion Doses by 2020

Eli Lilly and Company wins two FOYA awards for its replicate operational continuous oral solid dosage production facilities in Indianapolis, Indiana, and Carolina, Puerto Rico.

dose (OSD) facilities across their manufacturing network.

Eli Lilly and Co.: Winner of the Facility of the Future category for its process development, production platform commitment, and deployment of three replicate operational continuous oral solid dosage production facilities. Fundamental to the success of the project was the development of the progressive mass balance control scheme anchored by advanced automation and PAT technology—key to insuring consistent control, low process variability, and high quality assurance.

Jazz Pharmaceuticals Ireland: Winner of the Project Execution category for its creation of a greenfield manufacturing facility in Athlone, Ireland. Having no prior experience internally on building or operating a manufacturing facility, the Jazz "Project Rock" approach was highly pragmatic, and a model for lean project execution and integration of the investment from "project" phase to licensed GMP operations.

Nephron Pharmaceuticals Corp.: Honorable Mention for its facility in West Columbia, South Carolina. The Nephron S.C., project was recognized for its use and integration of a suite of industry leading technologies such as laser guided vehicles, automated warehousing, robotics to eliminate human intervention and track and trace technology.

Novartis-Penn Center for Advanced Cellular Therapies: Honorable Mention for its Center for Advanced Cellular Therapies (CACT) project in Philadelphia, Pennsylvania, USA. The facility leverages pharmaceutical engineering principles to successfully merge academic, corporate, and medical considerations thereby creating an innovative center to advance personalized medicine.

PT. Kalbio Global Medika: Honorable Mention for its greenfield Biotech Facility project in Jakarta, Indonesia. Kalbio's young and highly motivated project team is an outstanding example of the "can do spirit". It is a fine demonstration of the talent and potential for biomanufacturing in the region.

The 2017 FOYA category winners will be recognized at the ISPE Facility of the Year Awards Banquet on June 6, 2017, in Arlington, Virginia. The 2017 FOYA Overall Winner will be announced at the 2017 ISPE Annual Meeting & Expo from Oct. 29–Nov. 1 in San Diego, California.

For more information, visit www.FacilityOfTheYear.org.

Tech Transfer: Let's Take It from the Top

Why starting with a top-down approach to process definition and automation means better results at the bottom of the supply chain

BY BOB LENICH, LIFE SCIENCE BUSINESS DIRECTOR, AND BRUCE GREENWALD, PLATFORM BUSINESS MANAGER, EMERSON AUTOMATION SOLUTIONS

INVESTMENTS IN life sciences research are driving a significant uptick in the pipeline of new drug substance compounds. Rapid development of these new compounds into products drives a company's bottom line. But increasing global regulatory requirements coupled with competition from generics and biosimilars means that successful developments have less and less time as the exclusive offering — where pharmaceutical companies regain the bulk of the return on their development investment. Overcoming technology transfer challenges faced when moving product from lab to commercial manufacturing to the patient can help increase exclusivity time.

IMPROVING TECHNOLOGY TRANSFER

At the heart of making the research-to-production process more efficient and getting therapies to patients faster is a focus on improving technology transfer.

Because each stage of technology transfer is commonly handled independently with differing employees, processes, equipment, needs and locations, moving the product from one phase to the next can be cumbersome and inefficient.

To accelerate this pipeline and improve technology transfer effectiveness, four core conditions must be established:

- A corporate culture and associated operating environment that supports utilizing common drug manufacturing steps within and across pipeline phases
- Alignment of the standardized manufacturing and reporting steps to be used across each phase
- A clear pipeline management change control mechanism to pass the common manufacturing aspects to the next phase and to ensure that the current standards are used
- Clearly defined strategies for data collection, organization, comparison and analysis

Ideally, these four conditions will be addressed across all phases of a drug's development process before the earliest stages of research and development take place.

THE NEED FOR A STRUCTURED ENVIRONMENT

Though all stages of the development process are essential to the creation of a new product, different departments tend to be siloed from one another and focused on their own unique needs. Research operates independently of development/clinical, which is entirely separate from commercial manufacturing. With no organizational incentive to connect the production operations of these groups, moving the drug's manufacturing and packaging needs from one stage to the next becomes extremely inefficient.

Groups face significant complications with compatibility between recipe steps, utilized equipment, materials consumed and data collected during different phases. Key individuals involved in technology transfer must successfully hand over critical process parameters and quality attributes, equipment types and characteristics, all the recipe information (steps, sequence, materials, tests, etc.) and all the documented process understanding so that product development will progress successfully in later stages. Further complicating this process is that typically all the manufacturing technology to run production and capture data in each stage are different systems, designed by different manufacturers for different purposes, running the sequences differently and collecting data in different structures.

ORGANIZATIONS MUST FOCUS ON TOP-DOWN MANAGEMENT OF TECHNOLOGY **TRANSFER TO MITIGATE TIME LOST.**

If there is a problem with the product during clinical trials or manufacturing, the problem must be traced through multiple systems with multiple interfaces, without impacting the varied development or production work in progress.

IMPLEMENTING STRUCTURE

Organizations must provide meaningful cross-group incentives and identify clear owners of their product lifecycle management business process. Executive management must lead the development and implementation of this change to both confirm the priority and to resolve conflicts and roadblocks. People driving technology transfer must clearly understand both their own

department's needs as well as the needs of the next stage of development.

Some life sciences organizations have begun to approach technology solutions to this problem. Implementing individual systems geared toward department needs yet designed to work in other stages enables independent phases of the development structure to maintain and customize systems while still allowing for easy transfer, location and auditing across development. Integrated and scalable process control systems and manufacturing execution systems — such as Emerson's DeltaV distributed control system (DCS) and Syncade manufacturing execution system (MES) — facilitate efficient sharing of manufacturing procedures and data across the development chain. By working with an automation vendor early to define control systems and strategies, organizations can significantly simplify cross-departmental transfer.

STANDARDIZING TO IMPROVE EFFECTIVENESS

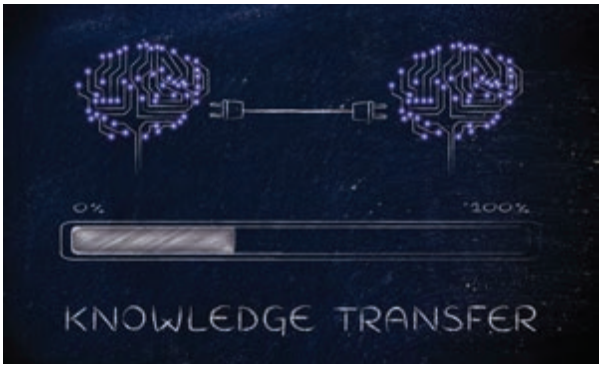
There are many benefits associated with utilizing standards for business processes and the associated technology supporting the execution of those business processes. Top examples include:

- Reduction of variation in work performance
- Reduction or elimination of errors and mistakes
- Improved, consistent quality
- Established scales and increased capacity for efficient task completion
- Visual management
- Seeing when processes are not operating normally
- Improved reporting, analytics and analysis practices

Establishing manufacturing standards across development stages presents challenges. How do you support the process flexibility and variability needed during development while also managing the enforced compliance required for commercial manufacturing? For example, maintaining common standards on recipes in each stage is critical to success. If critical process parameters require different names, sizing characteristics and testing methods between stages, the organization will waste valuable time and resources trying to reconcile this information to troubleshoot process problems and find a remedy. This problem gets compounded as all elements required to define a product manufacturing process (e.g. equipment, materials, recipe steps, etc.) are included.

STANDARDIZING SOLUTIONS

To ensure standardization, a key best practice is early collaboration between life sciences organizations and



automation/IT suppliers to identify a structure for naming the pieces of the manufacturing process and building block objects to execute it. Production elements must always be defined consistently, with top-down direction, so that they can be transferred between stages reliably.

Each stage performs many similar tasks, but on a different scale. Research may be performing a task on a bench-scale bioreactor that manufacturing will complete in a 2,000-liter reactor, but the key elements between the processes are similar. Early engagement with automation and IT application experts can help decouple names, recipes and sequences from the equipment on which they are being performed. This allows scalability across the stages and provides the structure for transferring the process to the next stage.

Because organizations rarely purchase equipment all at once, it is often impossible to standardize all equipment. To account for operational differences, pharmaceutical organizations need to develop equipment class/instance standards that allow them to operate with a variety of equipment. Identifying critical quality attributes (CQA) and critical process parameters (CPP) from the earliest stages of research and development so that these key thresholds are clear is critical to decouple the specifics of the equipment from the production process. When CPPs and CQAs are clearly defined and updated throughout the development process, small differences between equipment can be understood and managed within the recipes quickly and easily.

Standardization can also have a significant impact on validation. The more bespoke solutions that are deployed, the more validation that's required. While there are usually no validation implications in the development lab, once the molecule moves to clinical and production, the level of validation required is directly related to how closely GAMP Category 4 versus Category 5 methods are followed. By using aligned, COTS packages, validation efforts can be reduced, and validation documentation can be leveraged across the manufacturing areas.

THE CASE FOR CHANGE MANAGEMENT

Changes can occur at any stage of the development process. Whether during clinical trials or commercial manufacturing, it is essential to understand the impact of a change as well as enforce the change to maintain consistency across all systems and stages. Even small changes can have big impacts. If commercial manufacturing decides to make a cost saving change to save money on product vials, it is essential to know if there were any critical issues surrounding vial selection as well as the potential impact of having to re-validate all the product labeling. Without a high-quality change management mechanism in place, it can be difficult to identify the full impact as well as track down and consolidate any problems caused by making this vial change, much less avoid issues by predicting them.

TRACKING CHANGE THROUGH THE PIPELINE

Changes made to product development and production need to be made based on informed decisions and managed to meet regulatory requirements. Making informed decisions means having tools with fast access to data at every level and the ability to populate change data across all systems. Building blocks include a DCS and MES with change control and export/import features. Easy import/export of data between systems enables an embedded audit trail that can track and confirm changes as the basis for aggregating change records across multiple stages of the development process.

An additional layer of product lifecycle management (PLM) applications can manage what needs to be changed in each stage and facilitate using the import/export tools of the systems within a stage to ensure compliance. The PLM becomes a key tool for analyzing and communicating necessary changes.

MORE DATA, MORE PROBLEMS

As an organization expands its needs, the storage and organization of data become more fractured and the environment becomes more complex. As a product manufacturing process moves from stage to stage, different personnel will need to make comparisons. A researcher might be keeping copious lab notes, but if those notes are handed off as a large stack of handwritten log books covered in sticky notes, essential context won't transfer. Operators in later stages will be unable to make efficient use of the information.

Each level of the development process will have its own tools for storing data and being efficient, but what happens when that data needs to be recovered? Within each individual system there are good analytical tools, but those tools are often proprietary to the needs of the group controlling the data. This makes data analysis by another group a cumbersome and frustrating process.

Life sciences companies are drowning in data that is lacking context. Finding a way to efficiently analyze this data presents several obstacles. First, an individual must have access to the data. The analyst will also need to determine or develop context for the data once it has been accessed. Further complicating analysis is the need for proper analytical tools to make use of the data once it has been found and contextualized. Even in highly disorganized workspaces, these problems can be overcome, but the time and expense of creating a workaround is far too high for the modern pharmaceutical marketplace.

CORRALLING DATA

There isn't an easy and fast solution to the cumbersome task of data management. Organizations can invest in tools like artificial intelligence that will scrub and sort masses of data for easier use, but these tools are both costly and in their infancy. On the other hand, companies can develop systems to structure data properly from the very beginning, making it easier to collect and use, but this will only help with future data, not the trove of stored data that established companies will already have on hand.

The reality is that many organizations must embrace a combination of the two processes: cataloging old data where possible, and developing clear policies for structured, organized creation of future data. As regulations increase and margins tighten, life sciences companies will need to be nimbler in their handling of data to drive efficiency. The sooner companies start managing data the better, and the less data they will need to contextualize for future projects or when AI becomes a practical reality.

FINDING A WAY FORWARD

Bringing a product through the pipeline from research to market will always be a costly process. However, life sciences organizations are pushing themselves to resist the urge to throw their hands in the air and accept excessive costs and frustrating inefficiencies. To survive in the modern global pharmaceutical marketplace, organizations must focus on top-down management of technology transfer to mitigate time lost in production, quality, regulatory and supply-chain issues. When these organizations make the pipeline process more affordable, easier and faster, they have the potential to save millions, if not billions of dollars while providing more global access to life-enhancing products.

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Lifecycle Management Strategies Can Uncover Hidden Value

Pharma companies are recognizing that LCM planning can breathe life into brands, whether pre- or post-launch

BY GUY TIENE, STRATEGIC CONTENT MANAGER, NICE INSIGHT / THAT'S NICE LLC

THE IMPORTANCE of a solid lifecycle management strategy has been long acknowledged in the pharmaceutical industry. However, more emphasis should be put on the entire pharmaceutical product lifecycle — from discovery through the end of life, not only from launch to patent expiry. The entire network of stakeholders including governments, payers, physicians and patients increasingly requires more value for their investments in new therapies. As Marko Salo, vice president, marketing and sales, for API manufacturer Fermion Oy, puts it, "Value through lifecycle management can be demonstrated by improving efficacy, reducing side effects, simplifying dosing and increasing patient compliance."

Other opportunities afforded by LCM strategies include finding new delivery devices and packaging solutions; more efficient logistics; improved formulations; and improved manufacturing processes aimed at optimizing batch sizes, shortening process lead times and making the process more robust (Exhibit 1).

CONSIDER LCM EARLY IN PRODUCT DEVELOPMENT

Strategic planning ranks among the top five reasons for partnering with a CDMO, according to the 2017 Nice Insight Contract Development and Manufacturing Survey.[1] Thus, CDMO involvement with life science lifecycle management projects continues to rise. In this vein, Fermion, a contract manufacturing supplier of APIs, HPAPIs, and advanced intermediates, offers lifecycle management solutions.

"As an API CDMO, lifecycle management for Fermion often means post-launch R&D activities aimed at quality and cost improvements that lengthen the client's product lifetime, the client business relationship lifetime, and grow the business," says Salo. "When planning the product development strategy with our clients, we consider LCM aspects early on in product development. Pharma companies can utilize the LCM expertise of CDMOs best if they start collaborating with CDMOs from the early discovery stage through to the end of the product's life. This approach allows pharma companies to benefit from the lowest production costs and fewer process issues right from the start. Gaining maximal benefits requires close collaboration between the sponsor and the CDMO LCM teams."

Salo explains that lifecycle management is part of the business strategy and that efforts and resources should be dedicated to an LCM strategy for the long term. The main element in strategy building is identifying external opportunities and threats. "Internal capabilities, projects and partnerships need to be planned so that opportunities can be converted into business, and risks related to threats can be mitigated," he says.

OPPORTUNITIES REMAIN TO FURTHER OPTIMIZE THE VALUE OF A DRUG **AFTER ITS COMMERCIAL LAUNCH.**

One way the experts advise mitigating risk is to assemble a dedicated committee to the LCM strategy. According to Cutting Edge Information, 86 percent of life sciences companies surveyed in 2014 have dedicated teams to manage the lifecycles of their pharmaceutical brands.[2] These cross-functional teams should include representatives from marketing, R&D, manufacturing, process engineering and regulatory affairs. According to Natalie DeMasi, research analyst, Cutting Edge Information, it is important to dedicate teams to brand lifecycle management. LCM strategies are time sensitive, she explains, and delays can derail projects and cost hundreds of millions — if not billions — in lost revenues.[2]

Assembling such a team early in the development process can yield accelerated initial drug development and help engineer an optimal manufacturing process from the start, explains Salo. "Continuous process improvements can then be made to reduce the cost of goods, novel delivery systems and packaging solutions can be identified, and more value is created for patients and payers with improved efficacy, reduced side effects and ease of dosing."

In one case, Fermion developed an API process for a mid-sized pharma company that had an innovative small molecule pipeline. Fermion manufactured clinical trial API batches, and manufactured commercial API after the

Exhibit 1

Prevalence of LCM Strategies: Line Extension
(Percentage of Companies)

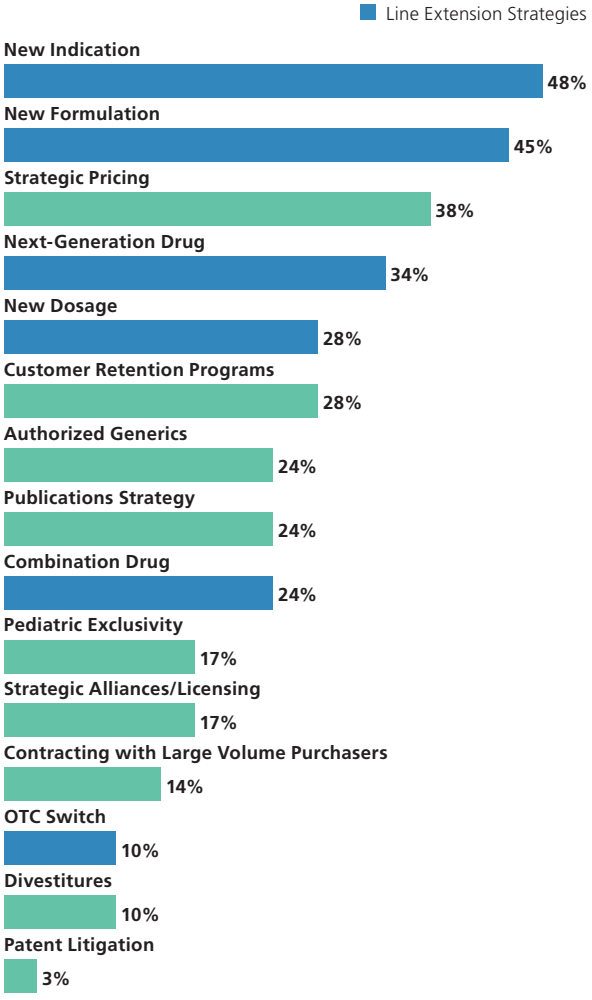

Image Source: Cutting Edge Information

product was launched. Two years later, the client wanted to initiate a program to decrease the manufacturing costs of the product.

"They wanted to maximize profits during the market exclusivity period, but also ensure they optimized everything to do with API manufacturing before the product went off patent," explains Salo.

The API manufacturing process optimization activities included increased batch sizes and yields, removal and shortening of certain unit operations, outsourcing of an intermediate, and optimization of campaigns to reduce bottlenecks. "The project was completed in several steps with careful consideration, not rushing," says Salo. "In fact, the project took almost eight years, but the cost of goods was decreased by 60 percent. Note, that if one decides to aim for a large, but expedient, decrease in cost of goods, then implementing a large number of resources at once can help reaching that goal."

Salo adds that Fermion arranges with clients in writing that certain optimization activities will be done only after launch to save time before launch. "Many of our clients have great ideas in improving the process, but their priority is to get the product to the market quickly. We combine their ideas with our knowledge based on experience with similar products and what works well with our facilities, and the result is a diverse lifecycle management program that can be implemented both pre- and post-launch."

LCM OPPORTUNITIES AFTER PRODUCT LAUNCH

In order to quickly get a medication to patients in need, speed is of paramount importance in development. But opportunities remain to further optimize the value of a drug after its commercial launch, says David Xu, executive director, head of new product planning, Purdue Pharma L.P. "Pharmaceutical product lifecycle management is about maximizing the value of our products to our customers. This includes new indications, improved formulation, new delivery system or packaging, IT solutions, etc., to expand the utility, and improve upon efficacy, safety and the patient experience."

Xu explains that Purdue's approach to LCM stems from understanding customers' unmet needs — including unmet needs from patients, providers, payers, healthcare delivery systems and society. "This understanding improves over time, and the opportunities are ranked for each brand and across the portfolio, in terms of importance and potential impact by cross-functional teams. The selected LCM projects are executed following the same process as a new product in development. Throughout the process, we continue to validate the customer needs and assess the potential solutions against changing market conditions."

One of those is the opioid market. The Centers for Disease Control and Prevention (CDC) states that opioids are responsible for more than six out of 10 drug overdose deaths, and 91 Americans die daily from an opioid overdose.[3] Xu says Purdue Pharma recognized the significant societal unmet need in addressing opioid diversion, misuse and abuse. An LCM strategy was put in place to reformulate OxyContin, an opioid pain medication for which Purdue held the original formula patent until 2013. "After more than 10 years of exploration and trials, we received FDA approval for

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the formulation of OxyContin with abuse-deterrent properties."

ADVICE FROM THE EXPERTS

Salo and Xu recommend the following advice for developing and executing an LCM strategy:

- Begin planning and implementing a lifecycle management strategy in the discovery phase of your product.
- Make sure the LCM strategy is based on creating the most value for the entire network of the pharma industry stakeholders. Different functions may bring different perspectives of the unmet needs and potential solutions. This approach will, in the end, create most financial value to the product owner.
- If using an experienced CDMO, utilize the full expertise of your cross-functional in-house team and enable their collaboration with the CDMO.
- The LCM plan has to be based on true unmet needs. This requires the organization to continuously deepen its understanding of the market and key customers.
- Starting an LCM strategy before product launch enables new indications to be evaluated and prioritized during the product development phase.

"Lifecycle management serves as a vehicle to grow the business, not just to extend the product life," says Salo.

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MISPLACED AIM

TARGETED FOR ITS PRICING PRACTICES, THE PHARMACEUTICAL INDUSTRY CONTINUES ITS LEVEL-HEADED DRIVE TOWARD EFFICIENCY

By Karen Langhauser, Chief Content Director

YOU'VE PROBABLY heard mention of drug prices once or twice over the past year. From Hillary Clinton's tweet heard 'round the biotech world that shot biotech stocks down 4.7 percent with just 111 characters, to President Trump's press conference comment that cost the biotech market $24.6 billion in 20 minutes-time, like it or not, drug prices have become a high-profile item for the public and policymakers.

Industry trade groups are well aware of drug pricing concerns and have responded with attempts to rebrand and reposition pharma amid public scrutiny. The Generic Pharmaceutical Association (GPhA), the country's largest trade group representing generic pharmaceutical and biosimilar companies, recently rebranded itself as the Association for Accessible Medicines in order to stress the cost savings associated with generics. The rebrand coincides with the association's national campaign dedicated to containing the cost of prescription medicines. Pharmaceutical Research and Manufacturers of America (PhRMA), the pharmaceutical industry's largest trade and lobbying group, has also launched a multi-year campaign titled "Go Boldly," focusing on the industry's role in developing new, innovative treatments.

Despite the high-profile nature of drug pricing concerns, according to the "Health, United States" report published by the Department of Health and Human Services in 2016[1], prescription drug spending represented only 11.6 percent of the $2.6 trillion spent on personal healthcare in 2014 (the bulk of expenditures came from hospital care and physician services). And climbing drug costs are only one factor contributing to our country's rise in prescription drug spending. Population growth, increases in per-person prescriptions and economy-wide inflation also increase annual spend.

"While drug prices aren't a huge piece of the overall healthcare cost, they are something that is very visible. Drug pricing pressures are real because that's what people see and complain about. Because of this visibility, drug companies are under pressure to get pricing down," says Bill Brydges, industry veteran and founder of Brydges Group, a consultancy focused on enhancing biopharmaceutical industry efficiency in order to produce higher quality, lower cost products.

At the time this article was written, the details of President Trump's plan for the pharmaceutical industry remained ambiguous. PwC Health Research Institute's annual report[2] calls 2017 "a year of uncertainty and opportunity," and perhaps no industry understands that as well as the pharmaceutical sector. Regardless of potential policy changes coming from Washington, pharma continues its steady drive toward increased efficiency and lower costs — neither of which are new

concepts to the industry — while pursuing innovation that can contain costs and ultimately, help save lives.

TRUMP CARD

"I think every president has his own personality and his own way of working," Pfizer CEO Ian Read diplomatically told NPR "Here & Now" host Jeremy Hobson in a recent interview.[3] Quickly developing a reputation for his shifting tone and somewhat unconventional decision-making process, President Trump has been quite vocal about the drug pricing issue. He opened his January meeting with high-ranking pharma execs by saying, "The U.S. drug companies have produced extraordinary results for our country, but the pricing has been astronomical for our country. We have to do better."

But with the granularity of Trump's plans not yet clear, the industry is merely speculating on the possible effects — if any — that Trump's proposals will have on pharmaceutical manufacturing. While the general consensus within the industry is that it's unlikely that Trump's proposals will turn into policy, the state of uncertainty warrants a discussion of possible "what ifs."

Corporate Tax Reform

With the U.S corporate tax rate being the highest in the industrial world, tax inversion deals are not new to the pharma industry. Put simply, these deals involve a U.S. pharmaceutical company buying a smaller foreign competitor in a lower-tax nation and shifting the company's headquarters overseas to reduce taxes. While many policymakers view this practice as tax-dodging, most pharma execs simply see it as a way to level the playing field.

No matter how you view it, the fact remains that U.S. pharma companies have money overseas that cannot economically be brought back into the U.S. According to data from U.S. non-profit research and advocacy group Citizens for Tax Justice, Pfizer, Merck, J&J, Amgen and Eli Lilly collectively have $250 billion in overseas funds. A Trump tax reform, could, in theory, enable pharma companies to invest that money in the United States.

But in what form? During his January meeting with pharma execs, Trump said, "I want you to move your companies back to the United States. I want you to manufacture in the United States." Yet the global nature of the pharmaceutical industry leads to uncertainty in terms of the feasibility of moving drug manufacturing back to the United States, and even if it does happen, it remains to be seen if this would have any bearing on drug pricing.

Jim Miller, president of business development service PharmSource, said in a recent blog post, "Realistically, moving biopharma manufacturing back to the U.S. in a meaningful way will be a seven- to 10-year process." Miller went on to explain that manufacturing capacity is already tight in the U.S. We don't have enough modern facilities to manufacture drugs in-country, especially as drugs become more and more sophisticated. The alternative — designing and building new facilities (which also involves sourcing key equipment) — takes years and billions of dollars.

FDA Reform

Similar to drug prices, the FDA (and its drug approval backlog) is very visible and thus bears the brunt of criticism from public and political leaders regarding the often-misunderstood drug approval process. Additionally, Trump's executive order calling for a government-wide federal hiring freeze comes at a bad time for the FDA, which is reportedly already short staffed by close to 1,000 employees — although the freeze includes exemptions for public safety, which could potentially include public health.

Unhappy with what he sees as a drug approval process that is too lengthy due to excessive "red tape," Trump is looking to streamline the FDA through reduced regulation. The connection between this and drug costs is the thinking that an overly strict and risk-averse FDA contributes to the amount of clinical data needed to get drugs approved, thus contributing to the overall cost of drug development.

But what are the chances of Trump's less robust FDA coming into fruition? According to Jim Shehan, head of Lowenstein Sandler's FDA Regulatory Practice, it's relatively unlikely. "Radical change is not something the majority of industry is behind. The industry needs a stable, predictable FDA. Larger pharmaceutical companies benefit from having a rigorous FDA approval process in several ways," says Shehan.

While the main concern associated with a less robust FDA review process is patient safety, drugmakers also have concerns that a more relaxed process will make it harder to secure insurance coverage for new medications. Less government oversight is generally welcomed in most industries, but the drug industry relies on that oversight to prove the value of its products to those prescribing and paying for them. Payers need that third-party proof that a new drug is better than what is already available.

"There's not a big groundswell of support for significantly loosening FDA approval standards. Of course, everyone would like things to go faster under

the current system, but what a lot of people outside the industry don't understand is that some of the ideas being proposed — accelerated drug approvals for example — are not radical ideas; they are already in place, and are used regularly," says Shehan.

STEPS AHEAD

The post-blockbuster era pharmaceutical industry is no stranger to the need to increase efficiencies and reduce costs. From R&D to production facilities to its entire supply chain, the industry has been forced to re-evaluate efficiency levels in order to better control the cost of manufacturing drug products. A recent CapEx survey of *Pharmaceutical Manufacturing* readers revealed that the number-one, day-to-day operational goal in regards to manufacturing operations was in fact the drive to boost overall efficiency.

When it comes to designing and building manufacturing facilities, pharma has increased its emphasis on up-front cost savings. Different approaches to virtual plant construction now allow design teams to work out design problems and inefficiencies prior to actual construction. It is not uncommon for design to utilize building information modeling (BIM), a process that involves creating digital representations of the physical and functional characteristics of the facility, or 3-D design software that allows teams to visualize concepts and simulate how designs will perform.

Emerging design review services, such as IDEA2.0, review proposed designs of new or retrofit capital projects before construction begins, looking for ways to optimize efficiency. The service is offered at no cost, with IDEA2.0 instead taking a percentage of savings identified.

"This is an example of things done upfront — before the design is even solidified — that were never thought of in the past. Previously, the emphasis was on quality and speed to market. The cost aspect now has more weight. Quality and speed to market are a now considered a given, with an added concentration on getting the costs down," says Brydges, who partners with IDEA2.0.

Another ongoing efficiency effort by the pharma industry surrounds the idea of continuous processing. Continuous Processing, though not without its challenges (specifically in terms of process monitoring and quality assurance), is now not only accepted but encouraged by regulatory agencies. If properly implemented, CP promises shorter processing times and increased efficiency. Smaller equipment and facilities would make for more flexible operations with lower capital costs. This could translate to safer, lower-cost drugs for patients. (For an in-depth discussion of true continuous manufacturing, see "Next Generation True Continuous Manufacturing" on page 32 of this issue.)

For plants that are up and running, data management — more specifically, data utilization — continues to expand potential cost savings. Pharma plants generate a huge amount of data, and savvy manufacturers are increasing their efforts to put this data in a format that makes sense and can be used to their advantage. Properly contextualizing data gives plants actionable insight into cost-saving areas such as machine downtime, quality issues and supply chain inefficiencies.

"The ability to make data useful is a critical capability as the industry continues to face strong pressure for lower prices and consistent quality. Pharmaceutical companies already have lots of raw data, but must first solve the data variety challenge to extract actionable intelligence. The leaders are driving operational efficiency and productivity through real-time visibility across their plants and CMOs. Additionally, as interest increases in distributed manufacturing for emerging markets and a stronger focus on continuous manufacturing, a standardized analytics layer is the key to ensuring continued high quality," says Ryan Smith, vice president, product and engineering, Sight Machine.

With a focus on manufacturing analytics, Sight Machine can offer clients a contextualized dashboard along with advanced analytics that takes insight from every plant and every supplier and gives them immediate and actionable insight into cost-saving things such as machine downtime, quality issues and supply chain inefficiencies. Their platform is powered by the industry's only Plant Digital Twin — essentially a software model that uses sensor data to mirror a series of manufacturing processes — generating insights for every machine, line batch and plant throughout an enterprise.

Facing scrutiny on its pricing practices and a wave of political uncertainty, overall pharmaceutical manufacturers are staying level-headed. Their focus remains largely inward, as they continue to increase manufacturing efficiencies in order to bring better quality products to market quickly and cost-effectively.

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Pharma Stays on Track

Respondents to our 13th annual Career and Salary Survey find stability and satisfaction despite increased workloads and changing market conditions

By Karen Langhauser, chief content director

EACH YEAR since the magazine launched in 2002, *Pharmaceutical Manufacturing* readers have graciously taken the time to lend their voices to the career and salary conversation through our annual survey. We query readership to gain a sense of how their pharma careers are treating them — both financially and emotionally — as well as to get an idea of how their attitude reflects current and future trends. This year's study yielded 269 total responses.

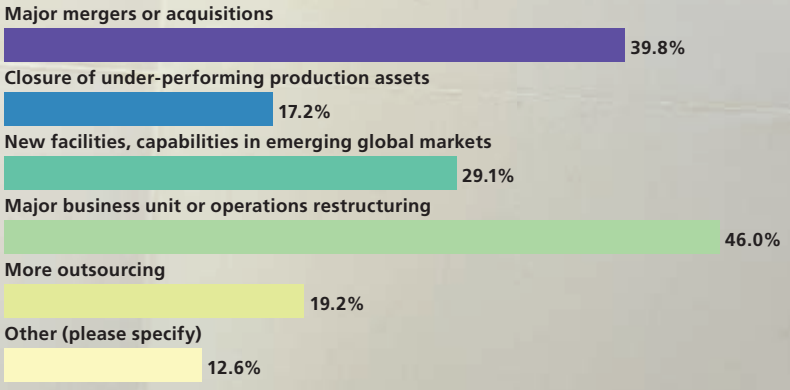
FINDING SATISFACTION

Job satisfaction in pharma is good — more than 89 percent reported their satisfaction levels within the range of "very high" to "okay," which is only ever so slightly down from last year's 92 percent. While job satisfaction has remained stable throughout our past five years of surveys, it is interesting to note that this year's 12.8 percent of respondents who rated their job satisfaction as very high was the highest percentage we've seen in five years of surveys. Considering job satisfaction in United States hasn't gone above 50 percent in the last decade[1], the pharmaceutical industry is beating the odds.

So what is contributing to pharma's high satisfaction rate? A variety of factors, among them challenging work, salary and benefits, opportunity for advancement, job security and work/life balance. When asked about the most important factors contributing to job satisfaction, it appears that those employed in pharma appreciate a challenge, but also appreciate being rewarded for a job well done. Just over 30 percent of respondents ranked challenging work as number one, followed by almost 20 percent citing salary and benefits. This ranking has stayed consistent throughout our past five years of reader surveys.

Speaking of salary and benefits, compensation appears to be healthy and reflects the seniority and experience of *Pharmaceutical Manufacturing*'s readers. For example, 29.5 percent have salaries between $100 and $150K, with the next largest group (16.5 percent) making $80 to $100K annually. In third place were those making between $150 and $200K (14.8 percent). Some 10 percent of respondents indicated their salary was above $200K. Adding to the good news, close to 70 percent of respondents reported getting raises last year, with most (70.5 percent) seeing an increase of 3-5 percent. With the average wage growth in the U.S. at 2.7 percent[2], the 12.6 percent of those who reported earning raises more than 10 percent reveal the pharmaceutical industry's healthy compensation and retention environment.

How have market and competitive forces affected your company recently? Check all that apply.



CONFIDENT & COMPETENT

The most dramatic drop seen in the survey responses came with the question of job security. When asked if they were more or less concerned about job security than last year, only 29 percent noted increased concern. These percentages are way down from previous years (52.5 percent in 2016 and 48 percent in 2015).

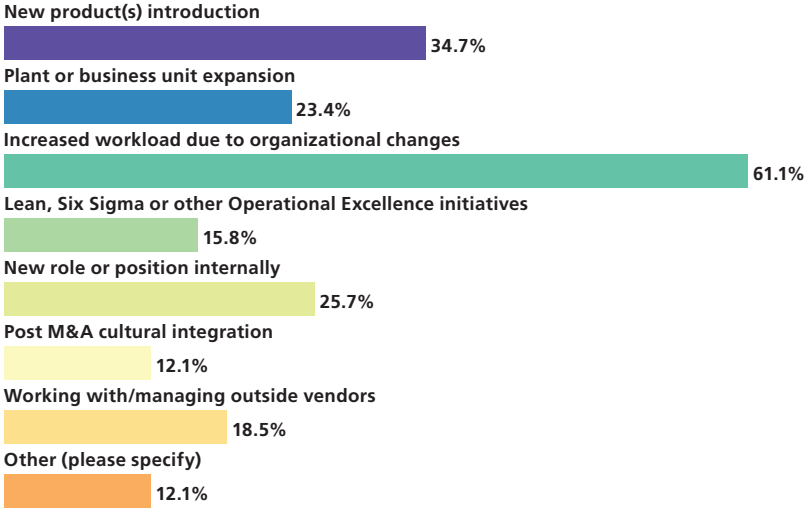
While the sudden surge in job confidence might seem misplaced during time where scrutiny of drug pricing has become commonplace amongst policymakers, there are several viable theories explaining a decline in job security fears. It is possible that much of it is tied to the demographics of survey respondents. At a recent That's Nice OSD Symposium, several industry panels predicted that the industry will see a declining emphasis on manufacturing, countered by an increased focus on outsourcing and R&D. It might follow that those working in those departments would find greater job security. In our survey, 17 percent of respondents indicated R&D job titles and 10.5 percent worked for contract manufacturers.

According to Randstad's annual "hot jobs 2017" prediction study[3], the highest in-demand positions for life sciences are related to regulatory, clinical research and drug safety. More than 42 of respondents fell into one of these three categories.

A feeling of competency is also contributing to readers' increasing confidence levels. When asked how they would rate the suitability of their skills to manage current responsibilities, 67 percent felt their skills and background were well suited. Conversely, just 6.4 percent indicated that the diminishing relevance of their skills due to changing technologies and industry focuses are the biggest threat to their job security.

Of those who are wary of job security, the majority (53.8 percent) were most concerned with internal cost-cutting measures. This concern was followed by 25.6 percent noting external financial pressure on their companies, such as expiring patents, failed product development or failure to obtain regulatory approval. Interestingly enough, our surveys have revealed a shift from concerns about external financial pressure to internal cost cutting, starting in 2012. This shift is possibly a reflection of an industry that is becoming less reliant on the success of blockbusters and is altering its business model accordingly.

What were the biggest challenges you had to face in the past year? Check all that apply.



MARKET FORCES

While our new president's specific plans for the pharmaceutical industry have not been clearly laid out yet, there is little doubt that pharma is moving in some new and interesting directions. Major business unit or operations restructuring continue to lead in terms of what market and competitive forces respondents felt have affected their company, with 46 percent noting this as applicable.

Merger and acquisition remains a constant within the pharmaceutical industry. The pharma industry spent $98.7 billion on acquisitions in 2016[4]. Yet, 2016 featured only one mega-merger — Shire's acquisition of Baxter's Baxalta. Historically, the mega merger has been a popular means of growing presence globally; but the last few years have seen a concentration on smaller acquisitions, mostly aimed at building R&D pipelines. Accordingly, close to 40 percent of respondents indicated that their company had been recently affected by M&A activity. This is surprisingly on target with numbers from years past, despite 2016's M&A totals having dropped substantially from 2014 and 2015.

KEEPING IT REAL

Saving lives isn't easy, and with that responsibility comes hard work and long hours. According to the survey, more than 58 percent of readers feel overly stressed some of the time at

What is the greatest threat to your job security?

	EXTERNAL FINANCIAL PRESSURE ON COMPANY DUE TO CURRENT ECONOMIC CRISIS	CONTINUED INTERNAL COST-CUTTING MEASURES	POSSIBLE PLANT CLOSING	THE TREND TOWARD OUTSOURCING	THE DIMINISHED RELEVANCE OF MY SKILLS DUE TO THE CHANGING TECHNOLOGIES AND INDUSTRY FOCUSES	PERSONAL ISSUES WITH COWORKERS OR SUPERVISORS
2016	25.6%	53.8%	11.5%	2.6%	6.4%	n/a
2015	21.20%	41.1%	16.6%	13.3%	8%	n/a
2014	20.2%	50%	11%	6.6%	4%	8.3%
2013	30.4%	42.8%	8.7%	4.8%	6.3%	6.9%
2012	29.9%	39.8%	8.3%	7.9%	6.6%	7.5%
2011	47.1%	21.3%	14.2%	8%	3.1%	6.2%
2010	30.3%	31.6%	13.9%	7.4%	4.3%	12.6%
2009	39.6%	32.6%	11.7%	7.8%	2.2%	6.1%

work, while 19 percent feel overly stressed most of the time. More than half of respondents failed to take all of their allotted vacation time last year, which is not unusual for American workers, who chronically under-vacation. Most national surveys report that about 55 percent of workers across all industries leave vacation time unused.

While the survey results overall were very positive, when put on the spot to describe what made them least satisfied about their current position, readers responded with honestly. Management and senior leadership bore the brunt of the criticism with readers noting lacking and poor communication, lack of direction and lack of support from above. In fact, almost 43 percent of respondents said they do not receive meaningful feedback on job performance on a yearly basis.

Understandably, many readers were also frustrated with corporate bureaucracy and internal politics, which many said have resulted in delays and inefficiencies. Others mentioned a disconnect due to their company's global nature, which included post-merger cultural struggles and well as cultural clashes between U.S. workers and colleagues abroad.

STUDY DEMOGRAPHICS

Examining demographic profiles revealed by *Pharmaceutical Manufacturing*'s respondents, participants were predominately North American-based (71 percent), with the remainder of respondents dispersed in Europe (7 percent), Asia (7 percent), India (6 percent), the Middle East, Africa and Latin America. More than 80 percent of survey respondents were male, despite data compiled by the National Center for Science and Engineering Statistics reporting that percentages of women employed in the biological and life sciences are on the rise, reaching 48.3 percent in 2015.

The majority of respondents (74 percent) were 40 and older, with most possessing a bachelor's or master's degree in either chemistry, chemical engineering or pharmaceutics, and the remainder with engineering degrees or specialties like biochemistry. Most fill operational roles (60 percent of 238 responses) across manufacturing, quality assessment, plant engineering and R&D categories. Industry longevity reigned supreme, with close to 86 percent of responding readers having 7 or more years of industry experience — with an impressive 41.6 percent of total respondents boasting more than 20 years of experience.

Responding readers represented the panoply that is the pharma industry, with 20 percent from Big Pharma, 16 percent from small and mid-sized specialty manufacturers, 15 percent from generic pharma and 10.5 percent from contract pharma. Biopharma manufacturers followed with 10 percent. The remainder, including consultancies, vendor/solution providers and all others, accounted for about 28 percent of the total pie.

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DON'T GET STRANDED:

Derisk the Supply Chain

Identify the top risks and uncertainties, and then optimize manufacturing and supply networks

By Martin Lösch and Venu Nagali, McKinsey & Company

TO INCREASE the agility of their end-to-end supply chains, pharmacos can apply a systematic approach to identify the top risks and uncertainties, and then optimize manufacturing and supply networks. This helps them ensure the availability of supply, achieve greater cost savings and encounter fewer quality and compliance issues. Coordinating risk management activities among functions is critical to success.

THE INCREASING COSTS OF FRAGILE SUPPLY CHAINS

Supply chains have become increasingly fragile for pharmacos, which has taken a toll on the availability of certain drugs. For example, recent reports indicate that there is a shortage of some cancer drugs, especially certain low-margin generics, forcing doctors to delay treatment. The Food and Drug Administration (FDA) lists a range of supply chain risk issues that are currently causing drug shortages, including greater-than-expected demand, manufacturing delays, commodity shortages and supply issues.

Drug shortages stemming from demand-and-supply issues are only part of the story. Manufacturers have also experienced a surge in quality problems that have resulted in recalls, regulatory settlements, lost revenues and diminished brand equity. A reliance on single sourcing has exacerbated these quality issues for some manufacturers. For example, a large diversified health care company in the United States has been losing about a billion dollars of revenue annually as a consequence of quality issues for certain over-the-counter medicines produced at manufacturing plants that rely on single sources.

Despite the apparent and growing cost associated with fragile supply chains, most pharmacos still do not have a systematic approach for assessing and managing the risks arising from supply chain shortcomings.

To help pharmacos address this critical issue, we have developed and implemented a comprehensive approach to improving supply chain agility and risk management. The approach addresses the following questions:

- Which sources of supply chain risk and uncertainty at the enterprise, sector and product levels are the most important to address? How can the company identify its more important products that require a robust supply chain?
- How can the company determine the optimal manufacturing, sourcing and inventory strategies for each product, and mitigate its top-priority risks efficiently? What are the optimal levels of single versus dual sourcing and

risk inventory for the different product segments?
- What governance structure is best suited to embedding risk management throughout the organization?

By delving into the issues raised by these questions and taking the necessary actions in response, companies can significantly increase the sophistication of their efforts to manage supply chain risks.

IDENTIFYING TOP RISKS AND UNCERTAINTIES IN THE END-TO-END SUPPLY CHAIN

All parts of the healthcare supply chain are exposed to risks: suppliers can raise prices or deliver products that are inadequate or insufficient, in-house manufacturing capabilities can fail to produce sufficient quantities to meet demand, and regulators can delay manufacturing or stop delivery.

Managing risks in the supply chain entails a cross-functional effort to comprehensively identify the most important risks, understand their potential impact on the organization's objectives and mitigate them as necessary. The fullest picture of risks will come from a combination of sources, including the knowledge of executives in different functions, the company's past experience, the lessons learned from competitors' experiences and insights into external trends (such as rising commodity prices or regional political instability).

This cross-functional effort to manage supply chain risk has three major steps:

STEP 1: Create product groupings based on risk. The company should start by identifying all of the top risks (those with the highest expected impact) that could impair its ability to supply a product to the end customer, result in higher production costs, or cause regulatory issues with respect to quality or compliance. Some risks may affect a combination of supply, cost and regulatory objectives. To efficiently identify the top risks across the enterprise, we recommend a three-part approach focusing on products and functions: First, a company should identify and assess the risks individually for a select set of its most important products; then, it should identify and assess the risks for individual functions such as procurement, manufacturing and distribution; and, finally, it should combine the findings of the two assessments.

To identify its most important products for purposes of this analysis, a company needs to consider its risk appetite — that is, the extent to which it will accept a particular risk rather than actively mitigating it. The appetite for risk will vary dramatically from one company to another and even from one product to another within a company's offerings. A company may have a substantially lower risk appetite for products that can adversely impact public health. That said, given the complexity of many companies' portfolios, management should specify risk appetite not by individual products but by product groupings. These groupings can be based on products' importance to one or more enterprise objectives, such as financials, public health, reputation and brand name.

For example, a major health care company recently categorized its entire product portfolio into three groups with regard to risk appetite. It based these groupings on a

Exhibit 1

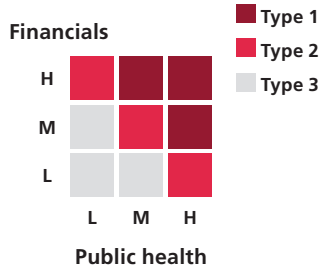
Define the risk appetite for products

Ascertain a product's importance to key enterprise objectives

- Public health
- Financials
- Brand name

Consider a product's enterprise objectives around financials, public health, and brand name

... to risk categorize all products ...



Use the importance of a product to key enterprise objectives to risk-categorize all products

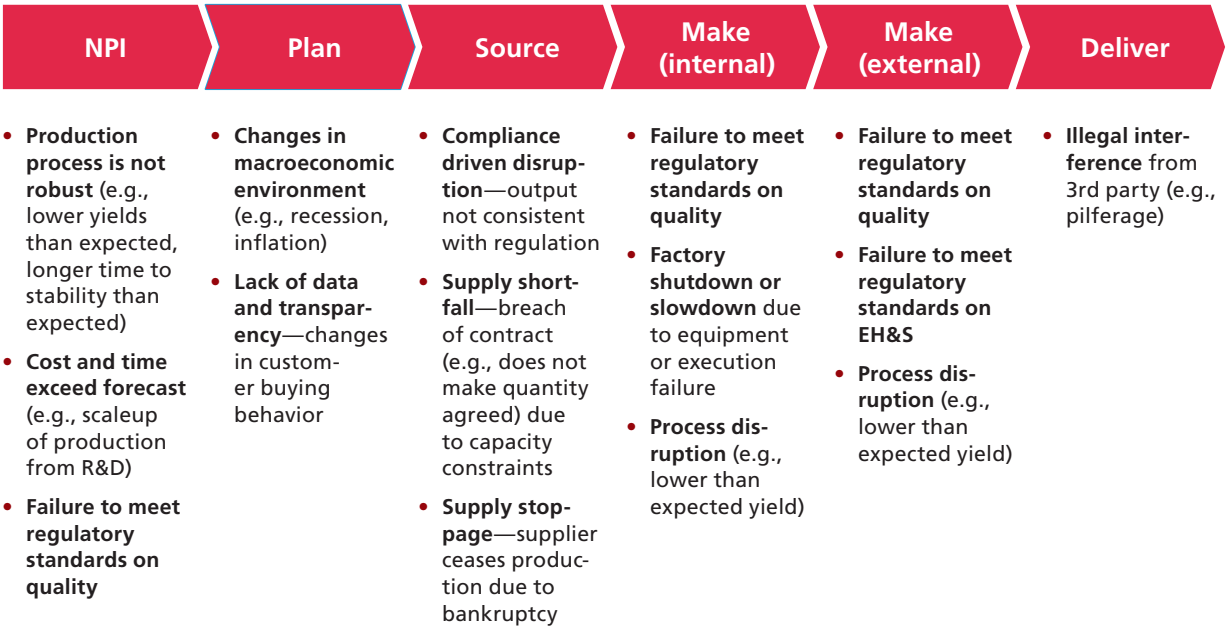
... and define risk appetite by product risk category

- Regulatory
- Demand fill rate
- Cost

Set thresholds around risk appetite for key supply chain objectives based on product category

Exhibit 2

Assessing risks from the end-to-end supply chain for products



product's financial, public-health and brand characteristics, as illustrated in Exhibit 1. The company also categorized its production facilities into risk segments based on the type of products they manufactured. The site segmentation enabled the company to prioritize investments, properly allocate management attention among multiple facilities, more accurately determine the frequency and duration of quality audits, and better assess its overall business continuity preparedness.

STEP 2: Set exposure thresholds. Next, each company should define its risk appetite by setting exposure thresholds for each product grouping. These exposure thresholds can be pegged, by product grouping, to supply chain metrics such as meeting demand (fill rate or service level), cost-saving targets or quality and compliance levels (Exhibit 1 illustrates an example of a process that concludes with setting exposure thresholds). Defining risk appetite will enable managers throughout the organization to make quantitative and consistent decisions when faced with trade-offs between risk levels and investment.

Companies must estimate each identified risk's potential impact on supply, cost and regulatory objectives. They can determine this impact on the basis of the risk's size and likely duration and the company's preparedness for it. For example, a commodity-packaging supplier's failure to deliver its materials might disrupt production for several weeks or months while an alternative is found. If the company has six months of finished goods in its warehouses, then such a disruption is unlikely to affect customer supply. The same failure by a single-source supplier of critical APIs, by contrast, might threaten supply for several months, creating the real potential for lost sales.

For example, delays in the qualification and approvals process for a new API supplier caused an 18-month shortage in the supply outside North America of one important drug for a common neurological condition. FDA action to fix quality problems at a United States plant also led to yearlong shortages of important drugs for two different genetic disorders.

Companies should also estimate the probability that a particular risk event will occur in a given year. This estimate can be based on a statistical analysis of internal data sources (such as historical deviations and rejection rates, to assess quality risks in manufacturing and sourcing), and external data sources (such as credit scores from Dun & Bradstreet and Standard & Poor's, to assess a supplier's financial strength).

STEP 3: Quantify exposure. By analyzing impact, preparedness and likelihood with respect to a

risk, companies can quantify their risk exposure and prioritize their supply chain risks. This typically allows them to reduce an initial list of several hundred risks to a few dozen top-priority risks that require immediate attention. A standard evaluation approach will enable management to make an apples-to-apples comparison of risks across products, functions and sites in order to identify the most immediate potential disruptions facing the company.

To conduct the assessment comprehensively and efficiently, companies can identify risks individually from each of the functions in the end-to-end supply chain: new-product introduction, plan, source, make and deliver (see Exhibit 2 for an illustrative set of risks from each of the functions). The range of risks assessed should include event-driven risks, which are low-likelihood but high-impact risks that may or may not have occurred at any point in time (such as regulatory and compliance incidents or earthquakes), as well as continuous risks, which materialize as a range of values at any point in time (such as uncertainty in demand, supply and cost).

After the company has identified all the risks, it can categorize them as either strategic or operational based on the level of investment required to mitigate them:

- The top strategic risks typically arise from high levels of single sourcing; significant investment is required to mitigate these risks, through dual sourcing maintaining higher inventory levels, or both.
- Typical operational risks can stem from several factors: insufficient manufacturing capacity in cases where the company would benefit from more capacity to address greater uncertainty; an insufficiently robust production process, resulting in significant yield issues; or inadequate quality and compliance practices. These operational risks can be mitigated by small, targeted investments (see Exhibit 3 for a representative list of the operational risks at a pharmaco).

OPTIMIZING MANUFACTURING AND SUPPLY NETWORKS TO INCREASE AGILITY

Companies can employ a range of measures to mitigate specific risks. Some measures (such as process and component standardization and upgrading of production machinery) decrease the likelihood that a risk will occur. Other measures (maintaining higher inventories of components, works in process and finished goods, for example) increase preparedness. And others (such as dual sourcing) reduce the impact if risks do occur.

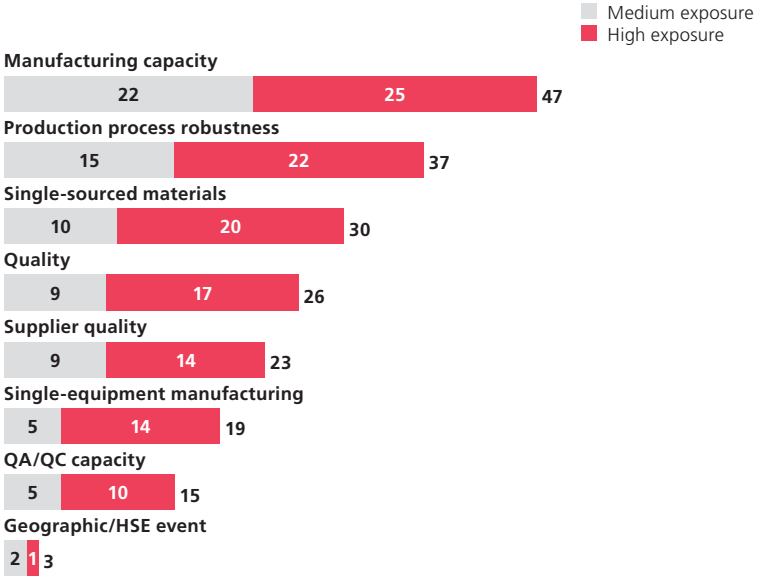
Small, targeted investments (for example, upgrading or repairing production machinery) can address specific sources of risks. Measures such as dual sourcing and maintaining additional inventory can systematically address several sources of risk at once. Because these measures can be expensive, it is critical to determine the optimal levels with respect to top products. Further, companies may be able to more efficiently mitigate a source of risk within a particular function by taking steps within another function. For example, they can manage a potential raw-material shortage by increasing the inventory of the finished product.

As opposed to safety stock, which companies use to manage day-to-day uncertainty in demand, "risk inventory" is used to manage low-likelihood, but potentially high-impact disruptions in the supply of raw materials or production.

Exhibit 3

Sanitized list of operational risks for a pharmaco

Number of risks



SOURCE: McKinsey analysis, sanitized example

Companies can determine the optimal combination of risk inventory and dual sourcing for each top product through a careful calculation that accounts for the incremental cost of these measures, the current inventory level and its shelf life, and the required risk protection level. A higher level of risk inventory may be needed in cases where the cost of dual sourcing is prohibitive, such as for production of biologic-drug substances and certain APIs. In other cases, such as for finished-product production and packaging, dual sourcing may be cheaper and more effective than maintaining risk inventory (see Exhibit 4). In addition to mitigating downside risks, optimal levels of dual sourcing and risk inventory will also address upside opportunities.

To determine the optimal manufacturing and supply network across all of its top products, a company should make this calculation for each major production step for each product, and then combine the individual product-specific strategies.

We recommend using similar risk-informed approaches to make other supply chain decisions. These include network optimization, manufacturing footprint, supplier contracts, inventory policies, level of outsourcing and offshoring, and level of flexibility for a manufacturing plant. This broad application increases the complexity of making such decisions, because it introduces additional factors that are difficult to quantify. Yet we find that the additional effort yields useful results. Companies can reach vastly different outcomes by going beyond traditional practices to explicitly account for risk in certain supply chain decisions — such as the level of risk inventory and dual sourcing and the size of backup manufacturing facilities. This is particularly true in the health care sector, where rigorous supply chain risk management programs are still relatively rare. Only by adopting a risk-informed approach will management be able to make more robust decisions that can withstand the future's inherent uncertainties.

Finally, while companies most commonly seek to reduce their exposure to risk by determining the optimal set of mitigating actions, this is not always the right response.

In some cases, a company may find itself able to tolerate greater exposure for certain products, processes and facilities. In this way, a rigorous risk-based approach can not only mitigate threats but also unlock incremental value, by freeing time and attention that had been devoted to keeping certain risks unnecessarily low.

GOVERNANCE STRUCTURE TO EMBED RISK MANAGEMENT

Although most companies in the pharmaceutical sector have risk management programs in place, those programs are typically confined to particular organization units or functions. For example, companies may have business continuity management (BCM) programs for individual manufacturing sites that focus on recovering from disruptive events, measures within the procurement organization to mitigate sourcing risks from suppliers, or compliance and audit management initiatives in the quality organization. Yet there is little, if any, coordination of these efforts. Furthermore, most BCM plans typically specify similar time-to-recover goals for each manufacturing site without explicitly considering the relative importance of the products being produced or the likelihood of bad events. They also often fail to include proactive steps to mitigate the risks from such events.

Exhibit 4

Determining the optimal combination of dual sourcing and risk inventory

	Current status	Option 1: Single-sourced Build up inventory with current sourcing status	Recommended Option 2: Dual-sourced Build up inventory with current sourcing status Activate second source producing 4 tons/year[1]
Risk protection level Weeks	10.5	20	20
Date of protection achievement	Now	Q2 2013	Q2 2013
DS risk inventory requirement **Holding cost[2]** $ millions **Inventory level** Weeks	0.5 4	1.8 13.5	1.1 8.5
Capex $ millions	…	…	0.3 (registration of site)

1 Accounts for 2/3 of EU volume (20% of total), but capacity is available to back up the remaining 1/3 (9 weeks for ramp-up required)
2 Inventory value x WACC
SOURCE: McKinsey analysis, sanitized example

Companies should recognize that risk management is inherently a cross-functional activity, because different functions within the supply chain can identify and manage the sources of risks only within their own domain. This interconnectedness makes establishing a cross-functional risk management process critical to success.

The process must explicitly define roles and responsibilities of the different supply chain functions, with clear lines of demarcation. A dedicated supply chain risk management team may be needed to facilitate this cross-functional process.

Its responsibilities should include the following:

- Developing standard taxonomy, analytics and tools that all functions will use to measure and manage risks
- Working with senior management to define the risk appetite, and translating it into operational metrics
- Providing independent oversight of the risk management strategies implemented by the different functions
- Consulting, as needed, with the operational teams to make risk-informed strategic supply chain decisions
- Facilitating cross-divisional risk management strategies
- Aggregating risk exposure across functions and divisions and reporting on it to different management levels.

In addition, the company must periodically reassess risks to ensure that its mitigation strategies remain appropriate for the market's changing dynamics.

Given the scope and complexity of most companies in the sector, managing the sheer volume of information from this process is a challenge. A set of customized risk reports and dashboards can help. One major health care company is implementing a series of dashboards that can be customized to specific levels within the management structure. For example, the company compiles all of the top risks for a particular product and displays them on a single dashboard for the product's manager. It displays information for multiple products, functions and sites on a division level dashboard for risk officers and other senior leaders. Furthermore, the BCM plans for an individual manufacturing site should be explicitly tied to the specific set of top risks affecting that site. These risks should be determined through a detailed assessment and aligned with the established risk appetite associated with the products manufactured there.

Finally, developing the right culture is a key element of managing risk in any organization. Management should foster an open environment in which individuals feel empowered to discuss risks and potential disruptions and even to challenge line managers on specific decisions where appropriate. Individuals should be as candid in discussing bad news as they are when sharing good news. And workers within the different supply chain functions should share actions and best practices across functional boundaries. For example, an employee in manufacturing should be aware of and able to leverage a mitigation action that has worked well in procurement. Establishing this culture requires a high degree of communication, in which management establishes the right set of incentives for individuals to respect rules and procedures and to work for the organization's greater good.

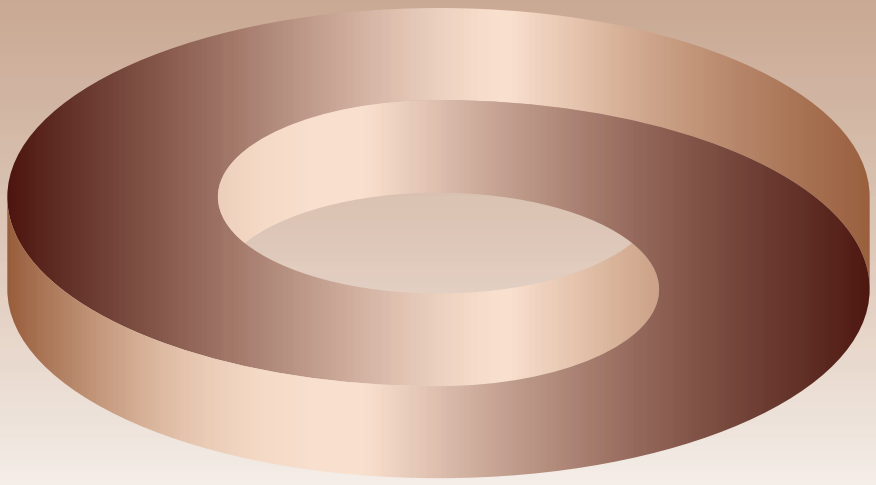
GETTING STARTED

Pharmacos' senior executives can start the process of improving risk management by asking the supply chain organization to identify the greatest sources of risk to the enterprise. This information can be provided through specific deliverables, such as a "heat map" that describes where the top sources of risk are concentrated across various supply chain functions. It could also include an analysis of strategic investments that includes both conventional metrics, such as expected net present value (NPV) and return on invested capital (ROIC), along with risk-adjusted measures like standard deviation or worst-case NPV and ROIC.

This information will help catalyze a set of initial activities that ideally constitute the first two components of the framework we have described. Companies should categorize all products into a few types and then define the risk appetite for each type. This should lead to an assessment of supply chain risks for the top products that determines the greatest sources of risk and the specific mitigation actions for each. With this as a foundation, risk organizations can become progressively more sophisticated in implementing risk management across the supply chain.

By implementing a comprehensive supply chain risk management program, companies can capture a wide range of benefits.

They will be well positioned to understand the likelihood of certain risks, proactively and cost-efficiently mitigate those risks, and obtain incremental value by making risk-informed strategic supply chain decisions. However, management must understand that risk management is not a one-time activity. To capture the wide range of benefits, companies must embed risk management within their operations.



NEXT GENERATION
True Continuous Manufacturing

It's time to replace the pharma industry's conventional batch-based processing with efficient, true continuous manufacturing

By Babu Padmanabhan, Ph.D., managing director & chief knowledge officer, STEER*Life*

CONSIDER THESE STATISTICS:

- Drug recalls have grown at an alarming rate. The last three years have seen almost as many recalls as the previous nine years combined[1]. Contamination during the manufacturing process being one of the biggest contributors.
- $50 billion/year losses in manufacturing costs from inefficient processes.[2]
- According to the FDA, ~300 drugs are currently in short supply.[3]

The pharmaceutical manufacturing industry has remained with batch processes, backed by rigorous testing at each stage (Figure 1), for well over 50 years, especially when it comes to the preparation of solid oral dosage forms. It has relied heavily on standard operating procedures and process control without being able to solve the fundamental issue — variability in end-point of a typical batch process that can only be controlled by the subjective intervention of a human operator. Statistics, like the ones listed above, indicate that pharmaceutical manufacturing cannot afford to have any controls that are subjective and variable.

Continuous processing could lend itself to solve the end-point variability and free the "process" from operator dependence. That said, continuous process can be exploited by the pharma industry if and only if certain prerequisites are maintained.

Continuous manufacturing practiced in several industries (not related to pharmaceuticals) is typically associated with wide Residence Time Distribution (RTD) due to back flow and stagnation, with inherent risk of quality and control. As such, continuous manufacturing is employed to achieve economics — as in gourmet vs. mass production of food products.

In the pharmaceutical industry, some manufacturers employ highly automated batch processing in lieu of continuous manufacturing considering it as a superior option. In such instances, there continues

Figure 1: Batch Manufacturing[4]

to be multiple batch operations such as fluid bed drying linked via automatic transfer systems with these unit operations still needing individual control and monitoring at each stage (Figure 2). Operator intervention is tried to be replaced by on-line measurements for determination of end-point. However, neither automated batch processing nor wide RTD continuous manufacturing or a combination of the two is suitable for wide-scale adoption in the field of pharmaceutical manufacturing. The high degree of control required for maintaining product quality can only be realized in a steady state and in the event control is lost, the ability to deal intelligently with the product in stream has severely restricted the application of continuous processing in the pharmaceutical industry.

In other words, the pharmaceutical industry needs Next Generation (21st Century) true continuous manufacturing that has certain unique attributes that satisfy all of the requirements — regulatory and quality, amongst others.

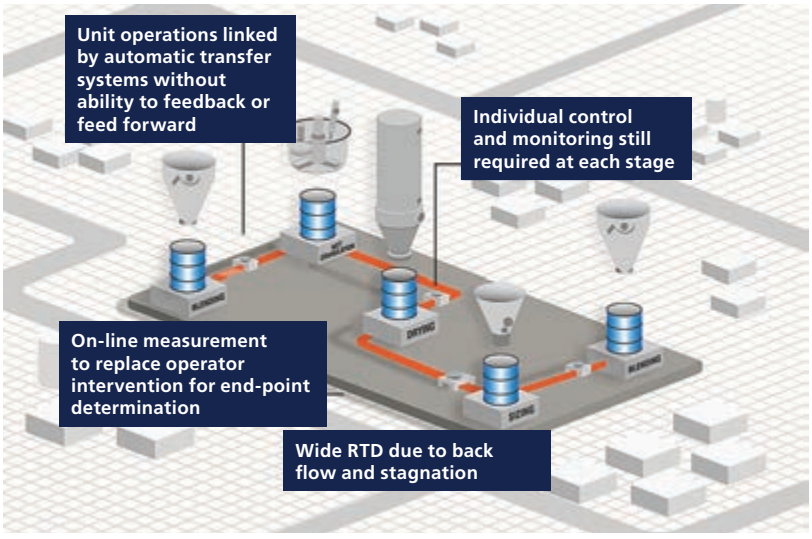


Figure 2: Automated Batch Processing

A PARADIGM SHIFT: TRUE CONTINUOUS, SINGLE POT MANUFACTURING

True continuous, single pot manufacturing is built on the principle of a "flow stream in continuity." Utilizing a twin screw processor, that has a unique ability to clean itself, true continuous manufacturing relies on keeping the input, process material and output in a continuous flow, with particles moving as a highly stratified process stream.

The energy transfer is made effective using thermal, mechanical or chemical means at wide-ranging magnitudes with minimal shear or pressure peaks providing specific advantages in handling sensitive input materials that may or may not rely on the use of water or vapor. Granulation process can typically be achieved with residence time as little as 5-15 seconds (including granulating, drying and sizing), and the optimized granules obtained are ready to be compressed into tablets or filled into capsules (Figure 3).

True continuous, single pot processing provides significant improvement in building both temporal and spatial control in process engineering through removal of hot spots and dead zones, while maintaining higher level of process continuity. Another key aspect is the principle of integration. All operations are integrated into a single piece of equipment, hence the term 'single-pot,' minimizing the need for human intervention.

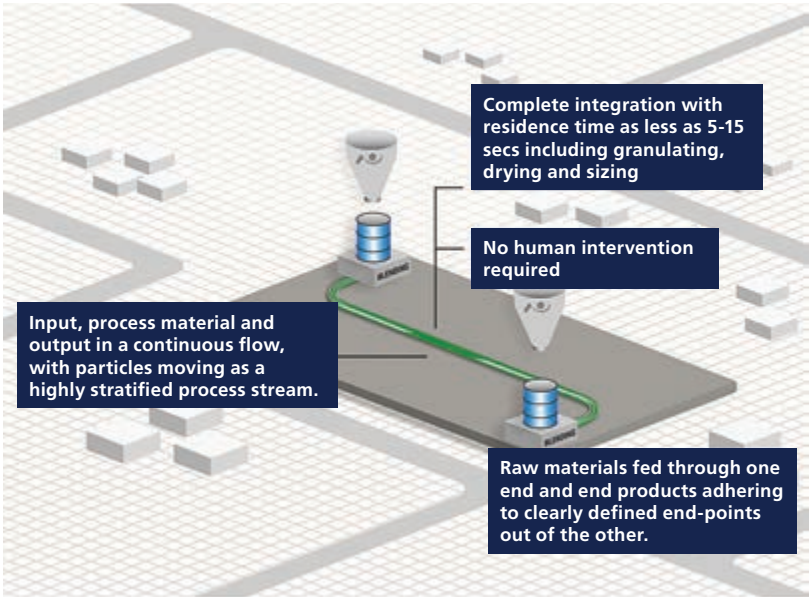


Figure 3: Next Generation (21st Century) True Continuous, Single Pot Processing).

Raw materials are fed through one end and end products adhering to clearly defined end-points come out of the other.

Moreover, true continuous processing allows for a significantly smaller footprint (due to integration), is flexible and versatile, and can significantly reduce capital costs and wastage besides minimizing the burden on the environment.

IT'S TIME TO CHANGE

The FDA is, in fact, urging manufacturers to shift to continuous processing for its numerous advantages, including flexibility, reliability and scalability. But above all, the pharmaceutical manufacturing industry faces a dire need to reduce its burden and shift its focus onto quality manufacturing (QbD via well-established risk and product quality). True continuous processing not only addresses the most fundamental concerns relating to regulatory requirements and quality, but also provides manufacturers with a significant reduction in capital and operating costs, manufacturing footprint, wastage and downtime, while significantly increasing the speed to market.

SPECIFIC ADVANTAGES OF TRUE CONTINUOUS PROCESSING

- Elimination of hot spots and dead zones
- Traceability (stratified continuous stream)
- The ability to maintain steady state of control
- Near complete delivery
- Versatility (easily adaptable to meet differentiated needs during process development)
- Quality by Design (well established risk and product quality)
- Economical development
- Ease of scalability (linear and non-linear)
- No metal dust contamination

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ABOUT THE AUTHOR

Babu Padmanabhan, Ph.D., has made significant contributions to the field of polymer processing. His work in designing processing section components has led to the development of intelligent compounding technology that has redefined pharmaceutical manufacturing. The fractional lobed processor invented by him provides critical break-through in enabling novel true continuous technologies and solutions. For more information about STEER*Life*, visit www.steerlife.com.

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Pallet Type MATTERS

Are your pallet choices aiding or thwarting your facility's sanitation efforts?

By Peter Connors, founder, Remcon Plastics Inc.

IN NO OTHER INDUSTRY is the demand for sanitation higher than it is in pharmaceuticals. Companies making everything from over-the-counter pain remedies to life-saving cancer drugs are expected by the public to manufacture products with 100% quality. As a result, we see manufacturing built around robust processes, which lend themselves to frequent, thorough cleaning and disinfection.

Inventory controls have become more sophisticated, diminishing the risk of using wrong or out-of-date raw materials. Equipment cleaning and disinfection is minimizing cross contamination between batches.

In every continuous improvement process, you eliminate the largest obstacles to quality first and work your way down the list. Often nearing the bottom of this list are pallets. Pallets are one of the most universal components of our distribution network and, as such, they became almost invisible. That is, until the culprit of some costly product recalls turned out to be the facility's material handling equipment and pallets. Before such product integrity problems were traced back to these workhorses, manufacturers didn't give pallets much thought beyond making sure they had the right size and strength.

PALLET BASICS FOR PHARMA FACILITIES

The purpose of a pallet is to enable the rapid, inexpensive movement of goods by making them easily accessible to mechanical handling, i.e., forklifts and pallet jacks. The three primary materials used to make pallets are wood, plastic and metal. Each material comes with its own set of benefits and challenges, making certain pallet types more suitable than others for drug manufacturing environments. Pharmaceutical manufacturers must understand how these different pallet materials can impact their facility and the quality of their final product.

WOOD PALLETS

When comparing pallet materials, wood pallets pose the most challenges to sanitation. The first and most obvious challenge is that of housekeeping. It is not uncommon for wood pallets to be damaged by handling equipment. Wood particles and nails can be broken loose, causing unsightly litter on the floor. These loose fragments pose significant contamination risks in pharmaceutical manufacturing facilities, especially if the pallets are being used with any lifting and dumping equipment that would place them above processing machinery.

In addition, exposed nails are a physical risk to employees as a source of cuts or punctures. The flooring in pharmaceutical facilities can also be damaged by the nails and jagged edges characteristic of wood pallets.

However, as has been shown by huge product recalls, it is the absorptive nature of wood that presents the greatest risk to product integrity. Water absorbed into a wooden pallet can become a breeding ground for bacteria and microorganisms.

A 2010 report from ABC News citing a study of wooden pallets in the food industry found that a significant portion of the pallets were contaminated with E.coli, salmonella or listeria. Moisture in the wood allowed for the growth of these pathogens. To combat the issue, wood pallet manufacturers have used the absorptive nature of wood to their advantage by applying pesticides and fungicides to prevent the pallets from becoming breeding grounds for contaminants. However, multiple incidents from 2009 to 2011 have shown how the treatment of wood pallets can backfire into tremendously costly product recalls.

Wood Pallets at the Root of Drug Recalls

Following consumer reports of pills having an unusual mildew-like odor that was associated with nausea, stomach pain, vomiting and diarrhea, FDA investigations determined that 2,4,6-tribromophenol (TBP), a fungicide/flame retardant chemical, was the primary cause of product recalls for three different pharmaceutical manufacturers. The initial cases took place from 2009 to 2011 with Johnson and Johnson, Depomed and Pfizer — each having consumer complaints and subsequent recalls that were traced back to wooden pallets treated with TBP.

Analysis revealed that the pallet moisture content exceeded the 13 percent limit, which allowed for fungal growth. The reaction of the fungi with the TBP resulted in the production of 2,4,6-Tribromoanisole (TBA), a highly volatile chemical that gives off a moldy, foul odor and is associated with nausea, vomiting and diarrhea. Including additional cases in 2011, it is likely that the industry cost of pallet contamination exceeded $1 billion, not to mention the loss of reputation. These incidents led to the following statement from the FDA:

"FDA recommends that manufacturers and distributors take precautions to prevent the use of wood products treated with or exposed to a halogenated phenolic preservative [such as TBP] anywhere in the supply chain. This includes all facilities that manufacture, hold or distribute drug products, components or packaging materials. We recommend that manufacturers not store drug products, components or packaging materials near wood or wood-derived storage materials unless there is assurance that the wood material has not been treated with a halogenated phenolic preservative."

PLASTIC PALLETS

Plastic provides a stark contrast to wood from a sanitation perspective. Polyethylene is the primary material used to manufacture plastic pallets. Since this material is inert, very little sticks to it. Plastic pallets can be readily washed and disinfected, making them ideal for the support of a clean, contaminant-free manufacturing environment.

The inherent resilience of plastic pallets makes them ideal for multiple-use applications where they provide both sanitary conditions and long-term cost savings. The relative softness of the plastic means that damage to floors and equipment is virtually eliminated. And typically, plastic pallets are the lightest option with the lowest probability of causing employee injuries.

Safety Measures for Using Plastic Pallets

The downside of this material is the reduced friction it provides between the pallet and the product it is carrying. Care needs to be exercised by forklift operators to avoid sharp turns that can destabilize the load and cause spills. Some plastic pallet manufacturers have addressed this issue through the application of traction media on the pallet deck, or by molding ribs on the face of their pallet to physically locate and secure the load.

Additional safety consideration should be given to plastics in the event of fire. Although it takes higher temperatures to ignite plastic over wood, the resultant fire burns hotter. Some plastic manufacturers have integrated flame-retardant additives to their products, but these additives have led to contamination problems similar to those caused by the pesticide and fungicide chemical treatments used on wood pallets. Depending on a facility's insurance requirements, changing out fire sprinkler heads to allow higher water flow may be an acceptable safety measure for pharmaceutical plants using plastic pallets.

METAL PALLETS

Pallets constructed from metals such as aluminum and stainless steel offer sanitary advantages like those provided by plastic pallets. In fact, since pharma manufacturers have cleaning protocols for metals based on their machinery cleaning processes, the sanitization of metal pallets falls within well-known procedures.

Although metal pallets do not share the characteristic of softness with their plastic counterparts, metal's strength makes it unlikely that aluminum or steel

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fragments will result from normal material handling operations.

Two primary downsides of metal pallets are typically weight and hardness. Metal pallets can be damaging to the pristine, expensive flooring found in most pharmaceutical facilities. Scratched floor surfaces can be a constant source of maintenance costs and can increase sanitation needs.

EVALUATING PALLET COSTS

Wood represents the lowest up-front cost for the mass handling of goods, with more than 95 percent of pallets in use worldwide being constructed of wood. Plastic and metal represent a significant jump in initial price, but usually end up saving manufacturers money in the long run because of the longevity these materials provide. Durable plastic and metal pallets typically outlast wood by a factor of 10-15 times.

From a pharmaceutical perspective, the true cost of pallets must take into account a material's potential for contamination issues and resultant product recalls. To date, drug recalls due to contamination originating from pallets have only been traced back to wood. The loss of both revenue and reputation associated with such recalls creates a choice between plastic pallets and metal pallets for many pharmaceutical facility operators.

Several pharma manufacturers receive raw materials on wood pallets and immediately transfer the loads over to plastic pallets, which are sanitized before bringing goods into the manufacturing facility. On the other end of the production process, once their pharmaceuticals have been securely packaged, these manufacturers bring finished goods out of their plant on plastic pallets and then transfer the products to wood pallets for final shipment to the customer. This allows the manufacturer to have maximum control over the sanitation of their processing environment while receiving long-term value from their plastic pallets.

Choosing the right pallet type for your pharmaceutical facility requires more than an evaluation of black-and-white figures. It requires an understanding of the role material-handling equipment plays in your sanitation efforts throughout the production process. The increased risk of contamination that comes with lower upfront costs is something all plant operators should evaluate before introducing wood pallets to their facility. The reduced surface friction of plastic pallets and the maintenance needs often associated with metal pallets are concerns that should factor into an operator's decision as well. Ultimately, the safety and well-being of your end-users should be your guide in choosing the right pallet type for your pharmaceutical facility.

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Bridging the Communication Gap Between QC and Production

An electronic environmental monitoring system that can seamlessly integrate with the LIMS used by different teams can improve organizational efficiency

By Sinéad Cowman, EU business development manager, Informatics, Lonza

MANUFACTURERS OF biotherapeutics and medical devices must perform a wide range of quality control-microbiology tests to ensure both products and clean room manufacturing facilities meet strict regulatory guidelines on contaminant control. The recent rapid growth in the number of these sterile products entering the market means that increased regulatory attention is now being paid to how QC data is collected, managed and stored. Many laboratories still rely on paper-based environmental monitoring approaches, however, these are prone to human error and often require considerable amounts of time to collect and interpret this information. In this article, we look at how the latest paperless systems are improving the reliability and effectiveness of environmental monitoring from a QC microbiology perspective, and how this technology can seamlessly integrate with laboratory information management systems (LIMS) to bridge the communication gap between QC and product manufacture.

THE NEED FOR STERILE MANUFACTURING ENVIRONMENTS

Microorganisms such as bacteria, fungi and mold can be found everywhere: in the air, in water, on surfaces, and on our clothes, hair and skin. But the presence of even trace amounts of these biological contaminants in biotechnology products, such as biological medicines and medical devices, can significantly impact drug efficacy and device performance and can have serious consequences for patient health. Bacterial endotoxin contamination in parenteral pharmaceuticals and implantable devices, for instance, can result in life-threatening conditions such as septic shock if accidentally introduced into a patient's cardiovascular or lymphatic systems. Even endotoxins from

dead bacterial cells introduced to the product during the manufacturing process can compromise patient safety when used clinically.

To minimize the risk of contamination, the FDA requires manufacturers to demonstrate that production and packaging facilities and representative product samples are free from these types of contaminants. To do this, regular sampling of the laboratory environment must be undertaken. And because microorganisms can contaminate a wide variety of surfaces and environments, an extensive range of samples must be collected, from air and water specimens through to surface swabs of benchtops, instruments and personal protective equipment. These samples — often numbering in the thousands per month — are incubated on agar plates and analyzed for microbial growth.

Many laboratories still use paper-based systems to schedule the sampling process and manage the collection of this environmental data. However, with such a large volume of samples to be taken, organizing, retrieving and interpreting this information can be challenging.

Paper-based systems are inherently inefficient and not ideally suited to the demands of sterile manufacturing environments. All materials, including paper, must first be sterilized before entering the clean room, adding additional, time-consuming stages to data-collection workflows. When you also consider that paper records and worksheets must often be manually logged into spreadsheets for data to be shared or analyzed, it becomes clear that paper-based systems unnecessarily burden laboratory workloads and are more prone to errors. And with an increased regulatory focus on data integrity, paper-based workflows simply don't provide the level of accuracy, traceability and completeness that regulatory authorities demand.

PAPERLESS SOLUTIONS OFFER ENHANCED DATA INTEGRITY

Purpose-built electronic environmental monitoring systems overcome many of the limitations associated with paper-based approaches. The latest paperless environmental monitoring systems possess a number of features that make QC testing more convenient for users, while helping laboratories reach the highest levels of data integrity and meeting regulatory guidelines.

Using paperless systems, measurements of incubation temperature or pH can be taken directly using probes that can be connected to the device, minimizing the potential for human error and ensuring data collection is always accurate. Electronic systems can further reduce errors by guiding users through data-collection protocols, preventing process deviations and prompting users to complete missing information prior to submission in ways that paper-based approaches cannot enforce. These systems can help ensure laboratories comply with regulatory guidelines by recording all necessary measurements according to standard operating procedures.

With a wide range of locations and samples to test, environmental monitoring systems for QC microbiology must be mobile. Lonza's MODA-EM system, for instance, is built using robust hardware that can withstand regular sterilization, while allowing users to move between data collection points around the clean room. Systems based on printed barcode labeling — made possible through the use of easily sterilized label printers and portable barcode readers — can help make data collection quick and convenient for users, while ensuring data is accurate, organized and traceable.

REAL TIME DATA ANALYSIS FOR A RAPID RESPONSE

With patient safety of primary concern for biotechnology manufacturers, the discovery of laboratory or batch contamination can cause significant and costly disruption to production workflows — not to mention possible regulatory action or reputational damage. By combining environmental monitoring systems with LIMS, such technology enables QC microbiology laboratories to analyze and share test results in real time, allowing manufacturers to take corrective and preventative action (CAPA) at the earliest opportunity.

Through powerful data analysis and visualization software, electronic environmental monitoring systems can help laboratories identify the source of potential contamination more quickly. Systems are available that can track and trend data such as microorganism levels based on a range of sampling parameters, including location, employee, batch or any combination thereof. The results of subsets of tests can be quickly correlated over specified time periods, facilitating rapid investigation of non-standard results.

Automated, electronic monitoring systems also ensure CAPA workflows are enforced when expected operating parameters are breached. For instance, the detection of bacteria on a laboratory surface or in a particular product can automatically trigger a new workflow to investigate and resolve the issue. Such systems ensure issues are investigated according to standard procedures and are properly documented. Not only does this prevent affected products reaching patients, it can also prevent similar incidents from occurring in the future. With regulatory

authorities increasingly looking at the way in which laboratory data is collected and stored, paperless monitoring systems that enforce user compliance ensure that the necessary data is always available at the click of a button.

BRIDGING THE GAP BETWEEN QC AND PRODUCTION WORKFLOWS

Whether production and QC teams are located at a single manufacturing site or collaborate between multiple facilities, it's vital that decision makers have access to the information needed to safeguard product quality. By sharing QC data on representative batch samples, users from all parts of the value chain can gain timely access to relevant information on product or environmental QC in advance of batch release. Using a monitoring system that can seamlessly integrate with the often disparate LIMS used by different teams can therefore help to bridge the communication gap between manufacturing and QC and improve organizational efficiency.

In bacterial endotoxin testing, for example, LIMS can schedule the testing of product batches by the QC microbiology laboratory, and alert the manufacturer to the outcome or status of these tests prior to product release. With real-time QC tracking, changes in the production process that affect product quality or sources of contamination can be rapidly identified and corrected. Comparisons of product quality between manufacturing sites can also be made, ensuring consistency across the organization.

MEETING MICROBIOLOGISTS' NEEDS

While there are many advantages to integrating electronic environmental monitoring systems with LIMS, many off-the-shelf LIMS packages are built with batch-control chemistry rather than QC microbiology in mind. These systems often cannot meet the business requirements for managing the entire microbiological workflow, the frequency of sample collection or the volume of testing required. Additionally, batch-focused LIMS are not well suited to interpreting the location-based sampling approaches that form an essential component of QC microbiology testing. Many commercially available LIMS packages therefore often require considerable and costly customization in order to meet the needs of microbiologists.

Some systems designed specifically for microbiologists include user interfaces that can actually map the clean room and the data collection points within it. These interfaces more clearly visualize the status and outcomes of tests, helping to pinpoint the source of any potential contamination more rapidly and make identifying outstanding tests easier. Additional features, such as conditional logic-based limits that can alert users or perform actions depending on whether a limit has been reached a specified number of times over a certain time period, are also very useful for microbiology applications.

Combining environmental monitoring systems with LIMS enables QC microbiology labs to analyze and share test results in real time, allowing manufacturers to take corrective and preventative action at the earliest opportunity.

Photo © Lonza, Basel, Switzerland

Being able to perform offline data collection is also an advantage for microbiologists who use clean room laboratories where Wi-Fi connectivity is not necessarily available. This feature gives users the freedom to collect data contemporaneously in a range of sampling locations, unlike many off-the-shelf LIMS that require online connectivity at all times.

AN INTEGRATED FUTURE

Electronic environmental monitoring systems offer a more accurate, convenient and efficient way for manufacturers of medical devices and biotherapeutics to perform QC microbiology testing than conventional paper-based approaches. The incorporation of such systems into QC microbiology workflows allows manufacturers to demonstrate their products and sterile production environments comply with regulatory guidelines, and ensure that corrective and preventative action is automatically taken when expected operating parameters are breached. Integrating these monitoring systems with LIMS can give manufacturers timely access to information relating to batches undergoing QC microbiology testing, helping to bridge the communication gap between QC and production. These paperless workflows can improve process efficiency and save valuable time and resources, and help manufacturers ensure patient safety is never compromised.

GLITTERING INSIGHT FROM INSIDE THE INDUSTRY...

Pumps, Valves, and Fluid Control

Innovations include smart flow instruments, new valve body sealing, heavy-duty hygienic diaphragm valves, peristaltic cased pump for upstream/downstream bioprocessing and dual-duty pumps

BY KATIE WEILER, MANAGING EDITOR

SMARTER FLOW MEASUREMENT

Endress+Hauser's Proline 300/500 smart Coriolis mass and electromagnetic flow instruments simplify installation, speed commissioning, and streamline operation and maintenance. Proline Promass Coriolis mass flowmeters are available in 11 models from 1/24 to 14 inches in diameter for measuring flows up to 100,000 tons/day. Proline Promag flowmeters are available in sizes from 1/12 to 78 inches for volume flows up to 634 mgd. Equipped with aluminum, hygienic stainless-steel or cast stainless-steel housings, Proline offers flexibility for environments including high temperatures, corrosive fluids, hygienic and sterile. The 300 series is compact with the transmitter mounted integrally to the sensor, while 500 series provides remote accessibility of the transmitter from sensors. Proline 300/500 features new Heartbeat Technology.

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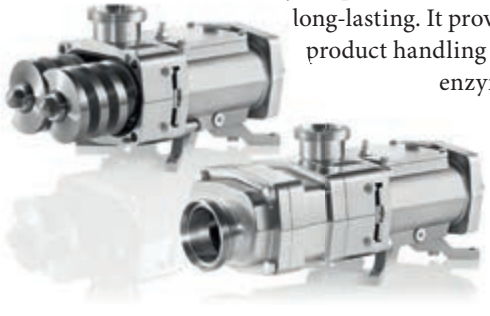

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Viega introduced its line of ProPress Zero Lead Ball Valve press x hose thread for copper fittings. The bronze ball valves are full port and designed for potable water applications. They are available in 1/2" and 3/4" press sizes and 3/4" hose sizes. Other features include a lockable metal handle, stainless-steel ball and EPDM sealing element. The Viega ProPress for copper system is available in more than 600 fitting configurations, in sizes ranging from 1/2" to 4". The Smart Connect feature ensures the integrity of connections.

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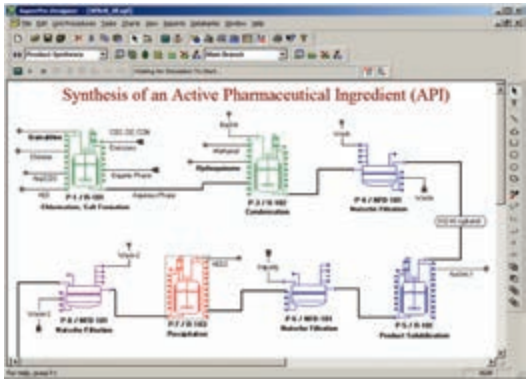

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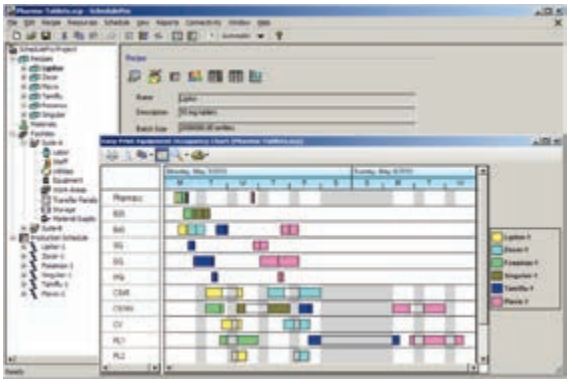
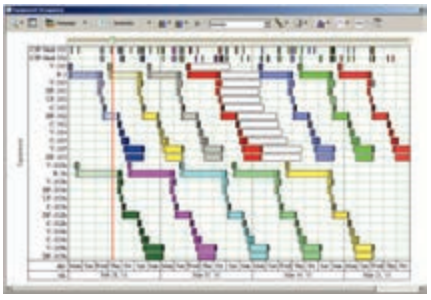
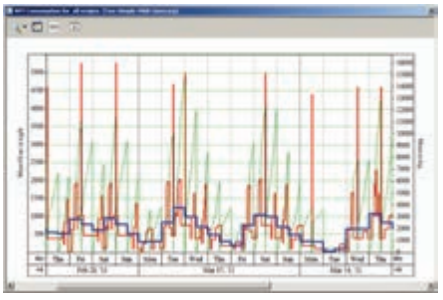


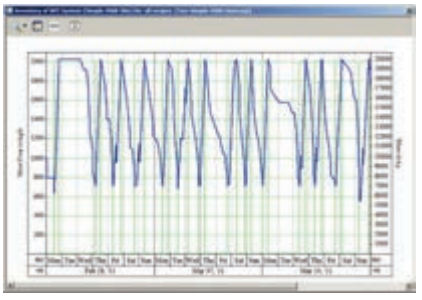
Migrate to SchedulePro to model, schedule, and debottleneck multi-product facilities



Easy production tracking, conflict resolution and rescheduling



Tracking demand for resources (e.g., labor, materials, utilities, etc.)



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SuperPro Designer is a comprehensive process simulator that facilitates modeling, cost analysis, debottlenecking, cycle time reduction, and environmental impact assessment of integrated biochemical, bio-fuel, fine chemical, pharmaceutical (bulk & fine), food, consumer product, mineral processing, water purification, wastewater treatment, and related processes. Its development was initiated at the Massachusetts Institute of Technology (MIT). SuperPro is already in use at more than 500 companies and 900 universities around the globe (including 18 of the top 20 pharmaceutical companies and 9 of the top 10 biopharmaceutical companies).

SchedulePro is a versatile production planning, scheduling, and resource management tool. It generates feasible production schedules for multi-product facilities that do not violate constraints related to the limited availability of equipment, labor, utilities, and inventories of materials. It can be used in conjunction with SuperPro (by importing its recipes) or independently (by creating recipes directly in SchedulePro). Any industry that manufactures multiple products by sharing production lines and resources can benefit from the use of SchedulePro. Engineering companies use it as a modeling tool to size shared utilities, determine equipment requirements, reduce cycle times, and debottleneck facilities.

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No Easy Answers for Drug Pricing

Improving manufacturing efficiencies offers most concrete possibilities for cost reduction

BY JERRY MARTIN, PHARMACEUTICAL AND LIFE SCIENCES CONSULTANT, PMMI

DRUG PRICING is a complex and controversial topic that does not have an easy or particularly straightforward remedy. The cost of medicine is a function of R&D and process development/validation costs, the cost of regulatory approval and manufacturing costs — with manufacturing costs accounting for the smallest portion of the burden.

Today the average estimated cost of discovery and development for a new molecular entity is $1.4 billion, a sharp increase from 2010, when that estimated cost was $830 million. A single clinical trial can cost well over $100 million, and a new drug can require multiple trials before approval.

Perhaps the most significant part of this equation for research-based drug manufacturers, however, is the cost of failure. When comparing total R&D spending to revenue of approved drugs per company, the cost per drug balloons to between $4-11 billion. Rather than assessing individual drug case studies, this estimate accounts for each failure a respective drug company sustained and the dollars spent on every drug that did not make it to market. With only one to two drugs per 10,000 new molecular entities ever making it to market, this consideration becomes significant.

Any macro changes to this system will require difficult choices and political impetus. Cost controls in other countries, for instance, deliver savings to the domestic patient population, but do so at the expense of a pharmaceutical company's R&D budget. Thus, for new drugs, these companies are more dependent on research funded by approved drugs sold in the United States.

The other end of the cost equation — manufacturing — offers more concrete possibilities to reduce costs, and potentially pricing when those cost savings are passed on the patients, or to better subsidize R&D for new, better drugs. Suppliers of pharmaceutical machinery and equipment are constantly at work looking to improve drug manufacturing efficiency:

- In biotech, moving to single-use systems can reduce operational and utility costs by eliminating the need for cleaning and cleaning validation, sterilization and sterilization validation, and significantly reducing changeover time. Single-use also reduces costs associated with supply and shortage issues, as manufacturing drugs on a local level is made more tenable.
- The move from batch to continuous manufacturing with automated process controls also offers manufacturers the promise of a more efficient line by integrating processing with fewer steps and eliminating downtime for cleaning and re-setup.
- Processing and packaging equipment is becoming increasing modular and flexible, streamlining changeover of components and therefore reducing downtime.

MANUFACTURING OFFERS MORE CONCRETE POSSIBILITIES TO REDUCE COSTS, AND POTENTIALLY PRICING.

- New software and sensors that monitor and make adjustments to equipment, known as the Industrial Internet of Things (IIoT), will likely become more widely adopted in drug manufacturing in the future and offer a host of benefits that can improve efficiencies and reduce costs.

In addition to employing their technical innovations, close collaboration with suppliers can help manufacturers mitigate process development, validation and regulatory costs. Even though the onus is on the drug manufacturer to assess the risk of its equipment from a regulatory perspective, suppliers are increasingly assisting customers in the validation of equipment by providing technical support, testing data and documentation for regulatory submissions.

Single-use suppliers, for instance, are now providing testing data on extractables and potential leachables to their customers. Providing this type of testing data is particularly valuable for the drug manufacturer, as it eliminates the cost of conducting the test themselves and, more importantly, reduces the time to market for the drug. Each day that FDA approval is delayed while testing data is gathered, represents a significant cost to the manufacturer. This type of collaboration is compounded when accounting for the fact that a supplier can share testing data with multiple customers, whereas previously, each of those companies would have undergone their own testing and incurred that cost separately.

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