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VOLUME 17, ISSUE 6

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The Apples of Pharma's Eyes

Pharma Innovation Awards applaud the fruits of suppliers' labor

AS A SCIENTIST, Sir Isaac Newton accomplished quite a bit: His three laws of motion formed the basic principles of modern physics, he developed a new theory of light and color, he designed the first reflecting telescope, he discovered and quantified gravitation, and his invention of calculus lead to countless historic breakthroughs in mathematics. Not surprisingly, many consider Newton one of the most influential men in scientific history.

And yet, what's the very first thing most people associate with Newton? An apple. Newton's iconic discovery of gravity is perhaps the most recognizable anecdote about the birth of an innovative idea in history.

It's very likely that Newton's apple story has been greatly embellished; in fact, it's even possible that Newton himself made it up. But you have to admit, no one knows how to pitch science like Sir Isaac.

Walk the halls of any tradeshow or event in the pharmaceutical industry and you will find no shortage of equipment and technologies. But take the time to stop and start a conversation, and you will inevitably hear a great story. Over the course of a year's worth of events, our editorial team has amassed quite a collection of winning technologies.

Just a few examples: The FlowCam Nano from Fluid Imaging is the first imaging flow microscope that automatically detects, images and characterizes both micron- and submicron-sized particles in a fluid sample at the same time. The AXF-1 from Micropore Technologies managed to scale up membrane emulsification to be usable for mass production. Antares Vision's LYO-CHECK is the first visual inspection machine on the market specifically dedicated to the lyophilization process. Vanrx's Microcell Vial Filler successfully fills an unmet need early in the drug product supply chain by enabling drug development activities to happen earlier in a drug product's lifecycle. And these are just a mere taste of accomplishments from our innovators.

It's true that most of these technologies have stories that are not as easily digestible as Newton's apple legend. The reality is, most innovation is the result of an elaborate and collaborative process. And that's why the Pharma Innovation Awards are so important — our conversations with hundreds of respected and talented equipment suppliers throughout the year have helped us truly appreciate the time and investment these pharmaceutical suppliers put into their technologies. We want to tell their stories and recognize their contributions to the industry.

As such, this month's cover story highlights and applauds those who have distinguished themselves as leaders in pharmaceutical equipment innovation. This year, we have an incredible 18 winners, spanning across five different categories. Please take the time to read through our annual Pharma Innovation Award cover story in this issue. We promise that our picks are innovative to the core.

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

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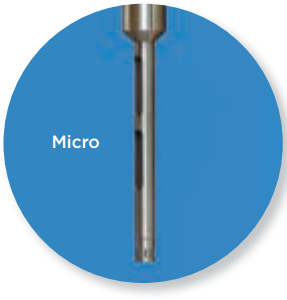

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Industry Travel Log

This summer, *Pharmaceutical Manufaturing* editors escaped their offices and brought back insights from these note-worthy events

EMBRACING DISRUPTION

Adents Serialization Innovation Summit illustrates how serialization mandates are driving pharma's digital transformation

Forward-thinking companies are realizing that meeting global serialization mandates is about more than just compliance. Serialization regulations have opened the door to industry-wide transformation.

Adents' recent Serialization Innovation Summit in Philadelphia brought together key players from all areas of the supply chain — including pharmacists, distributors, manufacturers and solution providers — to discuss in detail the true impact of serialization regulations on the industry and offer insights into the latest technologies available to help solve, and go beyond, these challenges.

Cloud serialization solutions offer pharma incredible benefits in terms of connectivity, scalability and data security, integrity and compliance. Technologies such as blockchain, digital twins, AI and mixed reality go hand-in-hand with these solutions and offer endless promise in terms of aiding pharma on its transformative journey.

"Digitalization is everywhere," said Todd Lybrook, Siemens Life Science Director. Its impact on our personal lives and businesses is massive and irrefutable. Des Creary, Microsoft's Health Business Leader of the Americas, pointed out that pharma business leaders are all talking about digital transformation – each with their own specific definition of what exactly digital transformation involves — but most agree that reaping the benefits of digitalization requires a holistic approach.

Despite the variations in defining digital transformation, pharma companies have the same end goal driving them to innovate: getting quality products to market as quickly as possible. What it comes down to is empowering the industry — and the people within it — to embrace digital disruption. True digital transformation involves envisioning new ways of bringing together people, data and technology — and events like the Adents summit are helping facilitate these powerful new partnerships.

EXPANDING API PRODUCTION ON HOME SOIL

Alcami shows off its newest production facility in Wisconsin

China and India may be the world's biggest countries for API production, but that doesn't mean America doesn't have a few leading companies in the game. Recently, Alcami Corporation, a contract manufacturer, hosted an open house and tour of its Center for Excellence for API development, located in the sprawling farmlands of Germantown, Wis.

The event allowed Alcami to tout its accomplishments at the Center, which was opened last year, including its expanded ability to service potential rising stars in the pharma world. During our tour, we got an up-close look at the Center's R&D capabilities and its ability to manufacture a wide range of API batch sizes.

About 62 percent of Alcami's end-to-end projects originate from its Germantown site — and it's these kinds of projects the company would like to do more of. Although Alcami services big players in pharma, their target is the little guy. The goal, company representatives said during a presentation, is to be the CDMO with the most successful product launches per year in the industry. And with its expanded capabilities, Alcami is successfully carving out its niche in the API world.

North Carolina-based Alcami has seven facilities scattered throughout the U.S. and in the Netherlands. The company's revenue hits about $250 million a year, and it has around 1,000 employees.

DON'T MISS ONLINE

Empty Chamber Studies (aka Much Ado About Nothing)

Despite its regulatory origins and prevalence within the healthcare industry, there is currently no "official" means to conduct an empty chamber study. This article, from expert and *Pharmaceutical Manufacturing* advisory board member James Agalloco, endeavors to present some recommendations for their execution based on Agalloco's more than 40 years of experience with sterilization processes.
bit.ly/EmptyChamber

The Clock is Ticking: How to Speed up Efforts to Meet Traceability Deadlines

Digitization will require significant investment but will pay off in protection from counterfeits, cheaper recalls, and improved production and inventory management. This article discusses why a multi-pronged approach should be adopted when developing serialization and traceability solutions. *bit.ly/DSCSAClock*

How Data is Changing the Pharma Operations World

Why is it so difficult to implement digital tools to scale? You need visionaries — and not just pragmatists — to see the full potential of digital. At the same time, organizations need to manage expectations and understand the impact will come in successive horizons. This article provides key insights into how to turn the buzzword into a strategy with exponential impact.
bit.ly/DataChangingPharma

*Data collected from attendee survey following our webinar, "Navigating Data Management Challenges."

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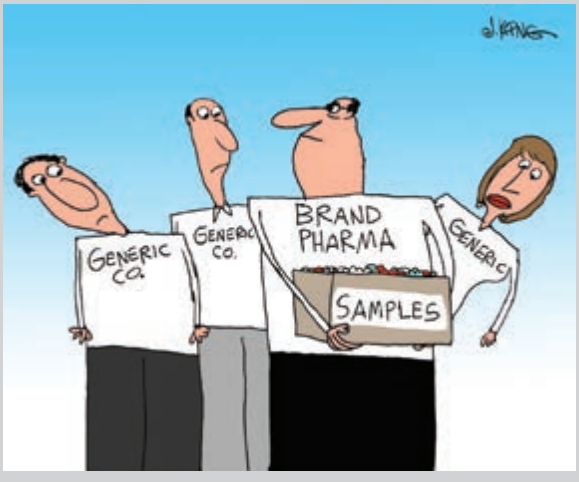

"These are part of a safety program. My money is safe... as long as you can't copy my drugs."
— Bill Russo

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

PHARMA HAPPENINGS

Join members of the *Pharmaceutical Manufacturing* team at these notable industry events:

GRX+BIOSIMS

SEPT. 5-7 | BALTIMORE, MD

Two industry conferences have merged into one, providing an opportunity to hear directly from government officials, learn best practices and connect with peers in the generics and biosimilars industry. The program will be comprehensive and the speakers are the top in their field.

SMART INDUSTRY

SEPT. 24-26 | CHICAGO, ILL.

Take your lean/continuous-improvement efforts to the next level with this informative conference focused on business, operations and technology strategies for digital initiatives. Pharma professionals can also network with industry leaders reaping real rewards from digital transformation.

CPHI WORLDWIDE

OCT. 9-11 | MADRID, SPAIN

CPhI Worldwide hosts more than 45,000 visiting pharma professionals over three days and brings together every sector of the pharmaceutical market under one roof. Over 2,500 exhibitors from 153 countries will also be on hand at the event alongside more than 150 industry seminars.

PACK EXPO

OCT. 14-17 | CHICAGO, ILL.

Over 50,000 attendees will gather to check out more than 2,500 exhibitors and see the latest packaging innovations in a variety of industries — from food to pharm. The massive event also features seminars and networking opportunities.

ON DEMAND WEBINARS

Missed a *Pharmaceutical Manufacturing* webinar? All of our recent live events are now available for download. Gain solutions to emerging issues with these informative events on topics such as next generation CMC management, ensuring data integrity and facilitiating compliance with ISO 17025, and navigating data management challenges in the pharma life cycle.

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Innovation Gets Regulatory Backing

The FDA is working to facilitate the uptake of emerging manufacturing technologies

BY SAU (LARRY) LEE, PH.D. AND AHMED ZIDAN, PH.D., OFFICE OF PHARMACEUTICAL QUALITY, CDER

THE EMERGENCE of advanced manufacturing technologies offers positive changes for the pharmaceutical industry. The FDA's Center for Drug Evaluation and Research (CDER) is taking steps to facilitate the uptake of emerging technologies to improve product quality, address many underlying causes of drug shortages and recalls, and support accelerated clinical development.

CONTINUOUS MANUFACTURING

We recognize that a transition to continuous manufacturing may seem daunting. However, economic analyses have shown potential significant long-term savings. For small molecule drugs, the FDA has approved applications for drugs made by continuous processes. For other types of drugs, such as biological products, technology is being developed to produce them continuously, but these efforts are still in their infancy. Research is underway at CDER's Office of Testing and Research (OTR) to address challenges, including any regulatory uncertainties that may delay product approval if an emerging technology is used.

OTR is developing continuous manufacturing platforms (e.g., continuous crystallization, loss-in-weight feeding, continuous wet granulation) that are integrated with advanced control strategy approaches such as process analytical technology, and feedback and feedforward controls. These platforms allow the FDA to investigate the impact of material and process disturbances and system dynamics on product quality, and to identify methods for validating advanced control strategy approaches.

The FDA also is providing resources to help facilitate the transition to continuous manufacturing. For example, the agency has partnered with the Biomedical Advanced Research and Development Authority, another program within the U.S. Department of Health and Human Services, to help fund and support research. We are also training our application assessment staff and conducting internal research on risk areas associated with continuous manufacturing, so we can better assess related technologies.

3D PRINTING

3D printing of drugs allows for the manufacture of solid drug products in various shapes, geometric designs, strengths and spatial distributions of the active and inactive ingredients. The release profile of the active ingredients can be tailored to meet the needs of specific patients or groups with special requirements — a tantalizing step toward more personalized medicines. 3D printing could also be used to produce complex dosage forms with characteristics that cannot be achieved in conventional dosage forms, such as instantaneous disintegration of an active ingredient or other complex drug release profiles.

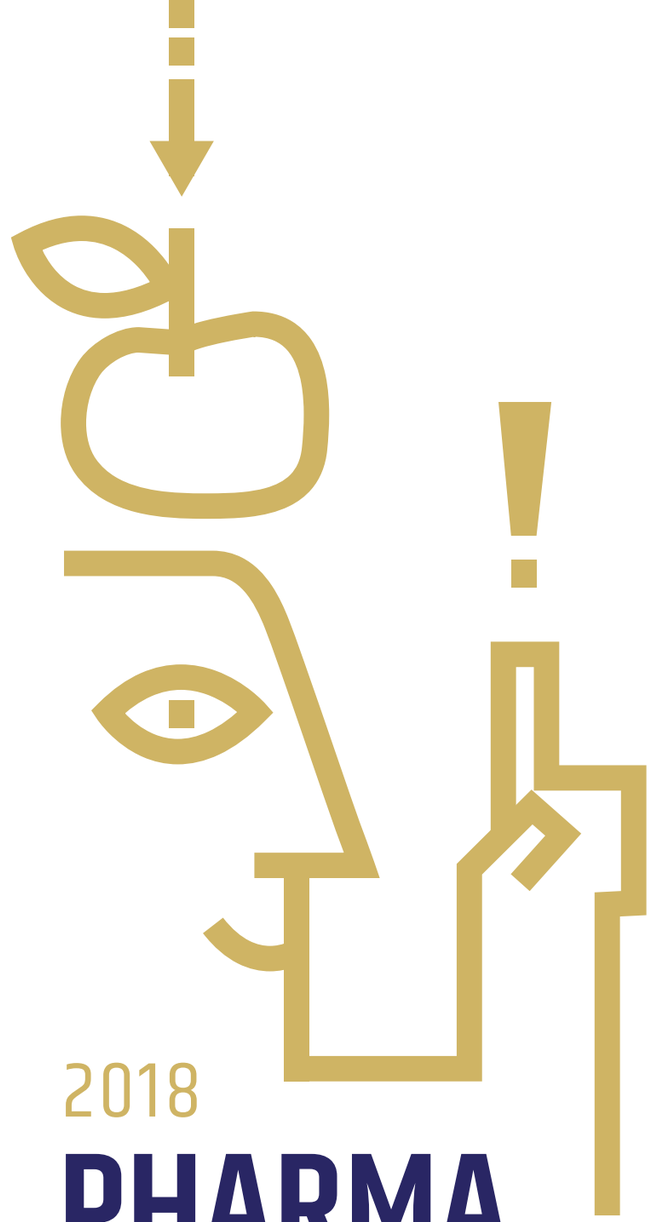
OTR is working to understand the effects of material and process parameters on the performance of 3D-printed drugs. OTR is also studying roles and functions of common inactive ingredients in 3D-printed products because the functions of these ingredients may not be applicable for 3D printing processes. We're looking to better understand these differences, and developing a "risk map" that can describe how variations in material attributes and how they are processed may impact a drug's quality, safety and efficacy.

This research will enable the FDA to answer key regulatory questions, such as, what are the critical parameters affecting the printability of different materials into drug products? How can we best assess the performance of 3D-printed drug products? In what situations might a certain 3D geometric design not perform as it should? We are working with our colleagues at FDA's Center for Devices and Radiological Health to determine the best ways to approach these questions.

EMERGING TECHNOLOGY ASSISTANCE

Our Emerging Technology Program is engaging with industry early in the process of developing new technology, and discussing any anticipated regulatory or scientific issues that may be part of a future application. Read the *Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base Guidance for Industry* on the FDA website to get more information and advice about how to work with the agency early in the development process.

Sau (Larry) Lee is the Deputy Director of the Office of Testing and Research, and Chair of the Emerging Technology Team, Office of Pharmaceutical Quality, CDER; and Ahmed Zidan, Ph.D., is a senior staff fellow at the Division of Product Quality Research, Office of Testing and Research, Office of Pharmaceutical Quality, CDER



2018

PHARMA INNOVATION AWARDS

By **Karen Langhauser**, Chief Content Director

A much-deserved celebration of manufacturing technologies, hand-picked by *Pharmaceutical Manufacturing*

WHEN IT comes to famous "eureka" tales of innovation, Isaac Newton taking an apple to the head and suddenly coming up with the theory of gravity is perhaps the most famous. It's inspiring to think that at any moment, a brilliant idea can literally hit you on the head. But while it's tempting to condense historical stories of innovation into quick anecdotes, more often, innovation is the result of an elaborate and collaborative process.

Here at *Pharmaceutical Manufacturing*, we understand the time and investment pharmaceutical equipment suppliers put into their products. And we feel that this type of innovation should be recognized. As such, this month's cover story highlights and applauds those who have distinguished themselves as leaders in pharmaceutical equipment innovation.

With that said, we are proud to introduce this year's Pharma Innovation Award winners: recently launched or updated technologies and systems that, based on their relative practical and technical merits, were selected by *Pharmaceutical Manufacturing*'s editors and reviewers.

BIOPROCESSING

As the market demand for biopharmaceuticals grows, drug manufacturers are looking for new strategies to meet global needs. Modern therapies are proving more difficult to sterilize and handle and require faster speed to market — further emphasizing the need to take advantage of new technologies and explore new ways of addressing process control and efficiency.

Our bioprocessing category encompasses the broad range of equipment and technologies needed to maintain a sterile, streamlined reaction from the lab to the plant floor. This year's winners include everything from a vial filler for clinical trials to a single-use component recycling program.

Starting on the clinical side, our first winner — from a company making its second consecutive appearance on our innovator list — is the Vanrx **Microcell Vial Filler**. The Microcell is a fully integrated gloveless robotic isolator for pharmaceutical vial filling that can be used to make clinical trial supplies and develop new products — including autologous cell therapies and personalized medicines.

Traditional manual filling and small-volume filling machines that combine with biosafety cabinets, RABS or isolators are often costly, difficult and time-consuming to integrate. This Microcell can be used as a replacement for these machines.

Small but mighty (under 6' wide and just over 7' high), the compact unit is extremely agile, giving operators the ability to fill up to four products in a single day. As a gloveless isolator, the unit eliminates operator error and shields them from contact with potentially dangerous drug products. By providing cost-effective, flexible filling capacity, the isolator has the potential to help drugmakers bring drug products to market faster.

Panacea Technologies' OpenBIO Benchtop Bioreactor

Speaking of small but mighty, our next winner is a six-inch manufacturing game-changer. Micropore Technologies' **AXF-1** is an innovative new design of in-line mixer, providing the ability to produce a high-quality emulsion, with a tightly controlled particle size distribution, at high throughputs. Capable of processing up to 1,400 tonnes of product per year, the device uses a process called membrane emulsification, where one substance is passed continuously through a tube laser-drilled with microscopic holes while a second substance passes around the tube shearing off droplets as they form through the tiny pores. These droplets can be turned into microcapsules and controlled release systems of precision-controlled size.

Easy to assemble, operate, dissemble and clean, the stand-alone membrane emulsification device can produce near mono-dispersed droplets. In pharma, the economic benefits of producing droplets that are all the same size in a low energy process include a tremendous reduction in unwanted product destruction and energy usage. While membrane emulsification has existed for years on a laboratory scale, the AXF-1 scales this process up to be usable for mass production — which is truly unique.

Next up is the **OpenBIO Benchtop Bioreactor** from Panacea Technologies — an impressive addition to modern laboratory systems.

Designed to be the "centerpiece" of your laboratory operations, the fermenter platform can be controlled from anywhere

with a tablet, phone or computer — a truly mobile experience for staff. Remote notification and an alarm system keeps batches and experiments running by informing staff of critical events, even when they are off-site.

Scalability is also easy — whether your application requires a single bioreactor or several hundred, the configuration is straightforward. Hybrid-cloud based architecture makes adding bioreactors as easy as plugging in a network cable.

The platform is designed for immediate deployment in most lab settings. In order to avoid downtime that could occur when parts need to be replaced, the platform is built with standard hardware — enabling greater lab productivity. As an added bonus, Panacea is a member of the Control System Integrators Association (CSIA) — a not-for-profit, global trade association — which adds an additional layer of assurance for plant managers looking for reliable partners in industrial automation.

Wrapping up our bioprocessing category is MilliporeSigma's **Biopharma Product Recycling Program**. The increase in single-use plastics waste is pushing biopharma manufacturers to address the environmental impact of currently utilized methods of disposal, such as landfilling and incineration, and question whether there is a better option.

In an exclusive partnership with Triumvirate Environmental, MilliporeSigma has developed this better option — a program that enables bioprocess manufacturing customers to fully recycle plastic single-use and disposable products, including bio-hazardous classified material, without requiring segregation or disassembly.

MilliporeSigma is the only company that has partnered with a waste management company to address these unique and challenging disposal issues that come with single-use products.

ANALYTICAL AND MONITORING DEVICES

Analytical and monitoring devices are essential in an industry that requires accuracy, reliability and repeatability. When it comes to pharmaceutical products, quality is paramount. The right analytical tools are needed to not only obtain, but validate and maintain that quality.

Kicking off the category is Thermo Fisher Scientific's **Applied Biosystems MycoSEQ Mycoplasma Detection Kit**. Mycoplasmas, the smallest known free-living organisms, are a common bacterial contaminant of mammalian cell cultures. Regulatory guidance requires that all products derived from mammalian cell culture be free of Mycoplasma. But Mycoplasmas present particular challenges because they are difficult to detect using traditional microbiological techniques — the most commonly used Mycoplasma test is a costly, 28-day culture-based method.

Thermo Fisher's kit uses a patented multiplexed primer design and innovative discriminatory positive control, which enable highly sensitive, specific, and comprehensive Mycoplasma species detection. This system integrates real-time PCR assays, instruments, and software with optimized and automated sample preparation. The biggest selling point? Rapid results in less than five hours, which makes possible in-process monitoring for the presence of Mycoplasma during cell culture manufacturing; this enables the earliest possible detection of a contamination event, protecting against the spread of contamination to downstream equipment, processes, and resin.

Our next winner is B&W Tek's **STRam** portable Raman analyzer. Raman spectroscopy is an important analysis tool in the pharma

Thermo Fisher Scientific's Applied Biosystems MycoSEQ Mycoplasma Detection Kit

industry because of its ability to identify chemical species quickly and non-invasively through transparent packaging material. However, traditional Raman spectroscopy faces challenges when it comes to identifying materials inside visually opaque and diffusely scattering media.

B&W Tek's system allows users to collect Raman spectra for material identification through a variety of barrier layers and visually opaque packaging. The comprehensive instrumentation technology consists of advanced algorithms, a high throughput spectrometer and a specialized probe which increases sampling depth and area, all packed in a portable system.

An excellent identification tool for industries with the need for quick and nondestructive analysis, the technology eliminates the need to open containers and come into contact with substances, maintaining sample integrity in the lab or the field.

Our final winner in this important category hails from Fluid Imaging Technologies. Touted as the "industry's first ever flow imaging nano particle analyzer," the **FlowCam Nano** provides digital images of particles ranging in size from 300nm to 10+ µm using patented, oil immersion technology for enhanced optical resolution.

Single-use plastic devices used for drug delivery bring an increased risk of shedding microparticulates. The FlowCam Nano reveals protein agglomerates, silicon oil droplets, glass shards and other opaque, transparent and translucent sub-visible particles with the high-resolution imagery needed for identification. Traditional particle analyzers based on light obscuration, dynamic light scatter, Brownian motion or Coulter Principle are unable to image these particles and allow for their identification.

Additionally, the FlowCam Nano may serve as an invaluable companion to USP<788> compliance testing methods for particulate matter.

PLANT FLOOR OPERATIONS

Today's plant floor is growing exponentially in its complexity. Managing the modern plant floor demands the skills and technology to optimize every process, asset and resource — giving the plant every opportunity to gain a competitive edge. Newly added as a Pharma Innovation Awards category this year, this category's three winners each offer unique approaches to operational reliability, efficiency and control.

Starting off the category is Honeywell's **Experion Batch** — an automation solution that promises to increase operational efficiencies, bridge operator skill gaps, and ensure repeatable quality. The interface combines distributed control, batch automation, and innovative visualization technology in one solution, ultimately providing users with ways to squeeze more out of plant assets, deliver higher quality, and reduce production costs.

Experion Batch's distributed control system moves batch programming and recipe structure out of the dedicated server and into the controller, which means no need for the upkeep and patching associated with Windows systems.

Honeywell's visualization technology leverages an intuitive visual interface, presenting the current and future state of operations which means operators to anticipate more, plan their work, and maintain unit uptime and speed. This visual intelligence can also be accessed by engineers working in the field via mobile device — keeping personnel connected wherever they are.

Our next winner comes to you from across the Atlantic from IMA Active. Crafted with Italian style, the **PREXIMA 300** rotary tablet press machine ensures complete separation between processing and mechanical areas, thanks to the use of purposely designed seals and

Honeywell's Experion Batch

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‹ MODEL **C-CS**

The Model C-CS is a pressure-reducing regulator used to control downstream pressure. This regulator is primarily designed for steam service at temperatures equal to or less than 366°F, however the unit may also be used for clean gaseous or liquid applications.

MODEL **5381** ›

The Model 5381 is a sanitary pressure-reducing regulator used to control downstream pressure. The 5381 incorporates a stainless steel body.

‹ MODEL **1088**

The Model 1088 is a perfect blanketing regulator for small batch tanks with lower volume requirements.

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IMA Active's PREXIMA 300 rotary tablet press

protections. The design also improves accessibility: the processing area is fully accessible once the external doors are opened, while entrance to the machine basement is required only for maintenance.

Our editors were fortunate enough to see the brand new tablet press in action during a Techceuticals training course at the Federal Equipment Company facility and were particularly amazed at how sturdy and quiet the unit was during operation. The cast-iron structure guarantees main compression forces up to 100 kN with maximum reliability. Tested in an anechoic chamber at the University of Ferrara in Italy, the unit is fitted with sealing on the machine doors, and sound proof panels and anti-vibration feet at the bottom.

Last but not least is Veeva's **Vault Training**, a new cloud application designed to simplify role-based training and help quality teams remain audit-ready and compliant.

Changing regulations in pharma means quality teams are constantly revisiting their SOPs. As a result, training manufacturing and quality employees at a pharma company (and proving to regulators that training happened) requires hundreds of hours of resources and effort. Veeva's Vault Training application offers a centralized view of training across the organization — providing full visibility into what content exists and who has achieved qualification to ensure job-readiness.

Vault Training allows users to collaboratively manage the complete lifecycle of training content — from authoring, to approval through assignment and completion — in one application. Users can easily track and complete tasks, or monitor statuses with a role-based home page for trainees, training coordinators, managers and compliance officers.

In an industry where quality and efficiency are paramount, this compliance-related training system ultimately has the potential to reduce validation times from months to days.

PACKAGING AND HANDLING

Changing patient demands are giving rise to new drug formulations — especially complex biologicals and biosimilars. At the same time, regulators are pushing for new levels of quality and traceability. Fortunately, suppliers of packaging and packaging equipment have stepped up to these new challenges, and this category demonstrates just a sampling of the groundbreaking results of these efforts.

Our first winners come from the primary packaging side of the category. Another exciting Italian import, our editors got their first glimpse of Bormioli Pharma's **AccuRec** at CPhI in Germany. This cutting-edge dual-chamber packaging enables end-users to reconstitute a range of oral drugs in a few steps. Pre-dosed solvent and drug powder are stored in separate chambers in a tamper-evident and child-proof package; a simple twist releases the powder into the solvent at time of dosing. Reconstitution

Ompi's LDP Vials

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Bormioli Pharma's AccuRec

is traditionally a complex procedure for patients, but the AccuRec system helps eliminate the chance for human error by providing guided self-administration and effective mixing.

And, because the chambers prevent active ingredients from interacting with the solvent until the moment of administration, the system eliminates the need to include excipients, maximizing drug stability and reducing potential adverse side effects.

Italy isn't quite done offering innovation gems. Our next winner, the **LDP (Low Delamination Propensity) Vials** from Ompi (part of Italian multinational company, Stevanato Group), offer the advantage of a minimized delamination propensity, reducing the risk of drug product recalls.

Often a consequence of aggressive drug formulations, terminal sterilization or thermal exposure, delamination of pharmaceutical glass is a serious issue, potentially causing glass particles to appear in vials. After an extensive investigation by SG Lab on the chemical performance of the inner surface of vials and on the process parameters that influence the final delamination propensity of vials, Ompi launched their product in both bulk and ready-to-use configuration.

A result of an optimized forming process that minimizes the surface inhomogeneity formation (homogeneity describes the variation of index of refraction in a glass) the vials are comparable to the raw material in terms of release of glass elements, ensuring patient safety and product quality. Vials are produced with Type I Borosilicate glass and have no coating applied which means users do not need to re-file with regulatory agencies.

Our next innovator is a drug delivery device, hailing from CSP Technologies — another repeat winner. CSP's new **XHaler** dry powder inhaler incorporates moisture protection, dose counting, and key safety features along with a sleek design to create a sophisticated inhaler platform for drug formulations. The innovative 30-dose inhaler is capable of delivering a wide range of drugs to the respiratory tract.

Together with Simplified Solutions, a Swedish dry powder inhaler developer, CSP designed the inhaler utilizing a patented technique that opens the protective seal covering the dose to be inhaled. This solution eliminates the need to puncture the protective seal — which in turn eliminates the risk of contaminating the medical substance with foreign debris. As an added bonus, the low component count design reduces complexity and production costs.

Our last two winners come to you from the packaging equipment side of the category. Making its debut at INTERPHEX, Antares Vision's **LYO-CHECK** is the first machine on the market specifically dedicated to the lyophilization process, rather than designed initially for liquid inspections and then later adapted to lyophilization.

It is becoming more common for injectable drug products to come in lyophilized form, which is not surprising due to the numerous

Antares Vision's LYO-CHECK

benefits. Lyophilized drugs preserve the original product features, can be stored and transported easily, and can be rapidly reconstituted for patient use.

However, the quality control inspection of products in lyophilized form poses unusual challenges, requiring a dedicated system which is totally different from the one so far applied to inspect parenteral products in liquid form.

Antares Vision was awarded a European Commission Grant to develop its new technology, which offers fully automated, 100 percent inspection of lyophiles. It features a floating carousel that allows the performance of precise inspections without any electronic or mechanical parts on the underside of the vials, along with other inspections involving capping.

Rounding out this robust category is the **TX2** line of collaborative robots, coming to us from Swiss global mechatronics solution provider, Stäubli. Being touted as the "world's fastest safe robots," the six-axis generation offers a combination of speed and precision while adhering to high safety standards.

The new TX2 now allows direct human-robot interaction and integration into Industry 4.0 environments. Stäubli has defined five levels of man-robot collaboration (MRC), estimating that 98 percent of industrial robot use still falls within the stage one spectrum, in which a process is performed by a non-contact robot separated from its operator by a cage. In stage five, however, the robot is collaborating with a human while in motion, with the robot and operator moving simultaneously.

The TX2 robot is prepared to act as a stage one robot as needed by most companies today, but is versatile enough to make its way up through stage five. The robot can be customized to accommodate the diverse needs of specific sectors, including pharma and biopharma production, cleanrooms and laboratories.

SMART PHARMA

Digital innovations such as cloud computing, the Industrial Internet of Things (IIoT), big data, and artificial intelligence are opening exciting new possibilities for drugmakers looking to transform their operations. The concept of "smart pharma" is broad, but ultimately comes down to the use of real-time data and technology by people and machines. Quickly proving to be the category with the biggest "that's so cool" factor, it was difficult to narrow these winners down to three.

First brought to our editors' attention on the INTERPHEX show floor, the KORSCH **PharmaView** leverages advanced HoloLens technology to enable equipment maintenance augmented by digital content, technical holograms, and real-time support — enhancing the service experience and redefining the concept of technical support.

KORSCH PharmaView

The virtual reality headset's hands-free, interactive capabilities include access to multimedia such as videos, photos, mechanical drawings, and electrical schematics in the field of view, which can support virtually any aspect of the machine setup, operation, changeover, or maintenance. And if the user needs help, the HoloLens platform supports a secure video call capability which connects a remote KORSCH expert and a customer user to permit a collaborative service experience.

The headset truly brings data to life, taking efficiency and safety in machine operation to the next level.

Complex infrastructures like those on a pharma manufacturing production line make changing authentication solutions such as usernames and passwords, smart cards, and PINs, prohibitive. Another INTERPHEX find, the **Nymi Enterprise Edition** authentication solution features a complete enterprise system for administration, management a new multi-factor authenticator called the Nymi Band, a biometrically authenticated wearable that simplifies log attempts across the manufacturing process, from raw material R&D through to finalizing batches. The Nymi Band, worn on the user's wrist, looks to replace the point-in-time authentication model so often used in pharmaceutical manufacturing environments with one that sees its users in a continuously authenticated state throughout their workday.

Pharmaceutical manufacturers deploying Nymi Enterprise Edition provide employees with a simple way to achieve compliance and security standards without compromising productivity. The solution ultimately makes audits simpler and less intrusive by ensuring uncompromised data integrity, traceability, and non-repudiation of a company's electronic records.

Our final winner in this exciting category is Petasense's **Asset Reliability & Optimization (ARO) System**, a simple IIoT system that combines wireless sensors and cloud software to optimize equipment health and performance.

This end-to-end, wireless predictive maintenance system gauges the health of critical equipment such as reactor tank motors and feed pumps, volumetric and pressure fill pumps, and granulator drive motors. The system includes a patent-pending wireless vibration sensor, cloud software and machine learning-based pattern analysis of multiple parameters such as vibration, temperature, pressure, ultrasound, current, and more. By analyzing these characteristics, Petasense software is able to predict common defects like pump cavitation, bearing wear and misalignment. These algorithms generate a numerical health score of the machine in real-time, enabling plant managers to make informed maintenance and operation decisions. Through integrations with data historians and other plant systems, users can move beyond predicting failures to optimizing equipment performance.

This system promises to be a key tool for any pharma manufacturer's reliability-centered maintenance efforts, helping to ensure quality, efficiency and speed.

And there you have it: The 2018 Pharma Innovation Award winners. Congratulations and thank you for the role you play in improving and saving lives around the world.

Achieving Sustainability in an Evolving Pharma Sector

Life sciences companies look to utility savings, collaborative product development and serialization to go green

By Tom Egan, Vice President, Industry Services, PMMI, The Association for Packaging and Processing Technologies

AN AGING world population and improved healthcare availability in emerging markets are driving demand in the pharmaceutical industry while creating new norms throughout the marketplace. As a result, manufacturers must cater to demands for a wider variety of pharmaceutical products. This can require changes to production that conflict with sustainability objectives.

Notably, a shift toward smaller batch runs that enable product diversity but require more frequent changeovers can create significant obstacles for pharma companies looking to reduce energy consumption and overall environmental impact. Additionally, advancements in drug delivery add to growing variety. Accurate dosing is of the utmost importance, so when patients and consumers achieve better results with oral, injectable or nasal sprays versus other formats, companies have strong incentives to offer those new delivery mechanisms.

The resulting challenge to the industry is accommodating even more demanding production schedules and product variety in the most sustainable way possible. Pharmaceutical manufacturers must implement packaging solutions that minimize the environmental impact of expanding product lines, build sustainability practices into the development of new delivery systems, seek utility savings in new automation strategies and leverage serialization.

FUNCTIONALITY FIRST

In a sustainability strategy, it's important to remember that any packaging which falls short of serving its purpose is never sustainable — no matter the material reduction, recyclability or use of recycled materials. In pharma manufacturing, the patient needs are the most important considerations. The goal is to achieve a safe delivery to the patient along with all necessary components and instructions for an effective application.

When considering the packaging operations of a pharmaceutical company, the patient, efficacy and sterility are always the most important elements. For example, a pain relief product must maintain its promised levels of effectiveness while that drug travels throughout the supply chain. Failure of the packaging to protect against elements like light and air that could jeopardize product effectiveness is not characteristic of a sustainable solution. Neither is any packaging that fails to protect the product against contaminants.

Lightweighting of blister pack materials, for example, may leave a product vulnerable to contamination; therefore, manufacturers must look to other areas where savings are possible. More plausible strides could be made with technology as more efficient sealing has the potential to reduce material usage and wastage. However, given the tight parameters enforced by regulators, it can be a challenging balance to achieve.

In a **sustainability strategy**, it's important to remember that any packaging which falls short of serving its purpose is never sustainable.

Packaging also plays an essential role in providing the track-and-trace and authentication measures that guard against counterfeiters and tampering. Packaging that cannot support these functions is no longer part of a sustainability-enhancing strategy and only contributes to fully costed waste.

BUILD WASTE REDUCTION INTO PRODUCT DEVELOPMENT

Although the high efficacy, sterility and safety standards of the pharmaceutical and medical device industries provide some barriers to traditional avenues of material savings, these two sectors have seen a rise in collaborative problem solving to drive innovation in many areas, including sustainability. Combining pharmaceutical products with medical device delivery systems means overall products become simpler and more convenient, ultimately requiring less packaging. An example of this collaboration in action is the work carried out by both pharmaceutical and medical device manufacturers in the implantable devices space. Pill bottles, for example, can now be equipped with digital timestamp readouts that remind patients to take their medication, and are able to be monitored remotely by a doctor to ensure patients take the correct dosages.

As healthcare treatments become more complex, the pharmaceutical and medical device industries will continue to merge their technologies and expertise to deliver patient solutions that combine pharmaceuticals and medical devices into one simple and convenient product — ultimately presenting opportunities to become more sustainable through consolidation. The approach is a win-win, enabling innovation to address better patient compliance, to utilize unique drug delivery methods and to improve package integrity and product safety.

INVEST IN ENERGY- AND UTILITY-SAVING SOLUTIONS

Medication for patients is becoming more personalized and specific. As a result, the concept of million-bottle runs for a particular dosage is becoming a thing of the past for many companies.

To meet the demand for more personalized products, driven largely by the decline of blockbuster drugs, the explosion of biologics and the growing use of generics, so-called micro runs are now commonplace. These require lines to be stopped often for small tweaks (more tablets or different dosages), and during that time the lights are on, the line is operational but not producing. The additional energy required for all of that changeover presents a challenge on the sustainability front, prompting manufacturers to re-evaluate their operations for opportunities to gain back efficiencies, energy and utility savings.

Pharmaceutical companies work tirelessly to reduce the amount of power, air or water used on a line. For example, reducing the amount of heat used to shrink a lid is sustainable, as is looking at ways to reduce water consumption, or to optimize utility usage such as heating, ventilation and air conditioning (HVAC). Some are also giving serious consideration to clean technologies, such as solar, wind or power generated by biofuels, which is a huge step forward.

SUSTAINABILITY THROUGH SERIALIZATION

A new need that can be related to sustainability is serialization. The serialization of pharmaceutical products has been mandated for six years now and asks that pharmaceutical products are tracked from their point of manufacture to when they reach the patient. Where serialization is concerned, manufacturers need to make sure the information used to track products is readable throughout the supply chain — including human readable codes. The package therefore needs to be big enough to carry that information.

Sustainability also enters the equation because serialization provides a much better window to the manufacturer as to a product's location and eventual distribution. This allows them to create the correct number of products, which saves on production and therefore elements such as material and energy usage, and even distribution. While it is not designed to be more sustainable, serialization increases supply chain visibility and therefore adds to the overall control and sustainability of a product.

SHARING IDEAS AND EXPERIENCES IS VITAL

For pharma manufacturers, sustainability will always be a challenging area to address, but a multifaceted approach can provide the most effective results. Operating amid a strict regulatory environment that governs patient safety and product effectiveness, these companies must often look beyond the more traditional paths to achieving strides in environmental responsibility. Through collaboration, innovation and thoroughly evaluating existing operations and practices, life science companies can implement sustainable initiatives with impact.

Companies can get a head start by exploring the latest sustainable solutions at Healthcare Packaging EXPO, co-located with PACK EXPO International Oct. 14-17, 2018; McCormick Place, Chicago.

Choosing advanced solutions rather than manual data analysis helps improve quality insights

Dealing with Disparate Data

By Lisa J. Graham, Ph.D., P.E.,
CEO and Founder, Alkemy Innovation

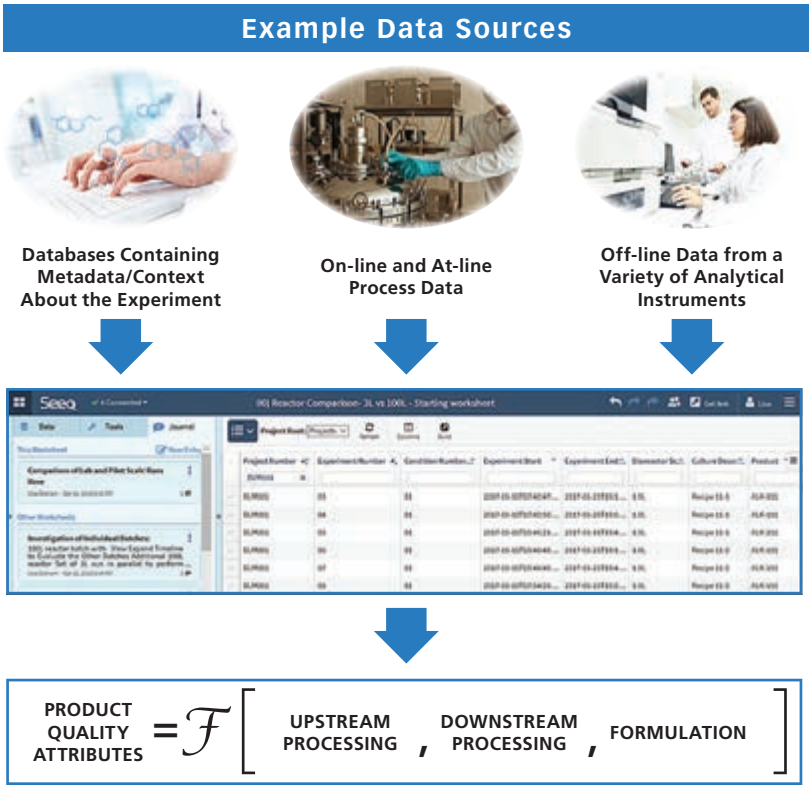
WHILE THE definition of quality is unique for every situation, the spirit of ensuring it is universal, as is the desire to ensure a safe and effective production process. Whether responsible for a clean water process, the overall productivity of a lab or pursuing continuous improvement/manufacturing excellence — an effective data analytics solution provides a lasting foundation.

In a pharmaceutical environment, having enough data is typically not the issue. Having the right data at the right time is, as is the ability to have the best tools on hand to quickly investigate key quality metrics. It can also be a challenge to prioritize the following requirements when implementing an advanced analytics solution:

- Easy access to old and new data sources without requiring significant IT investment
- Simplified analysis and visualization tools to be used by the majority of the scientists and engineers
- Flexibility to support a spectrum of model development needs without requiring IT resources
- Centralized access to results by teams along with long-term knowledge management
- A user-friendly utility for real-time action using boundary management and alarm notifications

The advancement of user-friendly advanced analytics software, along with growing computational power and inexpensive data storage, has provided options to meet each of these needs.

Exhibit 1



In this article, we review several considerations for implementing an advanced analytics solution to provide the appropriate level of control over quality metrics. Case studies will provide real-world examples of how an advanced analytics solution can be successfully implemented by providing:

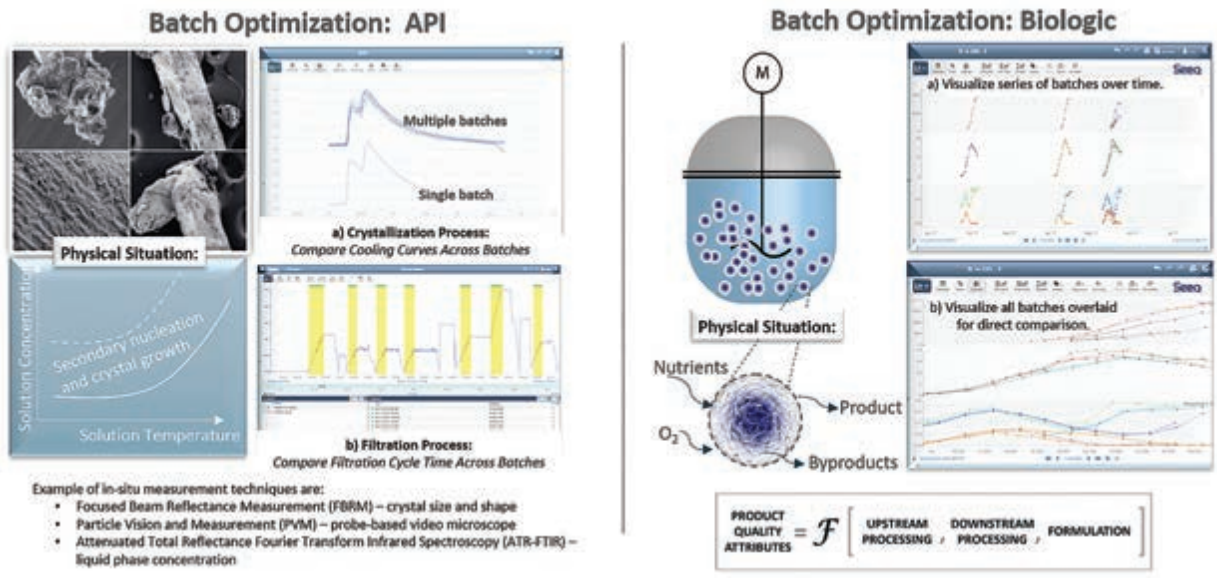
- Data source integration to drive quality in batch processing,
- Flexibility to support a spectrum of model development needs without requiring IT resources, and
- Centralized team access to results for short and long-term knowledge management.

The right solution will deliver what is needed to assemble, cleanse, search, visualize, contextualize, investigate and share insights from disparate data sources (Exhibit 1).

APPROACH: QUALITY TIED TO THE PROCESS

Beginning with strong stakeholder engagement, an assessment of a company's needs will quickly identify the gaps in the current data analytics environment that are making quality control overly challenging. A solution may then be implemented to provide flexibility to those trying to understand the correlations required to predict and control quality. In other words, innovative advanced

Exhibit 2



analytics combined with data-focused technologies is crucial to transforming process and analytical data from sensors and instrument systems into useful information and actionable intelligence.

Actionable intelligence, as related to quality metrics, must be generated to deliver value to the organization. The following case studies illustrate how to use advanced analytics software to:

- Assess a process to gain an understanding of cause and effect relationships critical for maintaining quality,
- Analyze and then optimize a process step for consistent operation, and
- Receive early warning that a process may be moving away from desired parameters, while there is still time to assess and react in a meaningful way.

Using advanced analytics software to execute these steps results in faster, smarter insights that improve execution, drive down costs and increase earnings. It is also a better approach than traditional reliance on spreadsheets — which typically requires time-consuming, manual gymnastics to transform data into whatever format is required to link with useful tools like multi-variate analysis programs, modeling applications and visualization software.

In contrast, an advanced analytics solution is a better approach because it provides easy access to disparate data sets, while streamlining the connectivity to these other tools. With the right solution, it will be simple to add new data sources, and to customize the views of the data to efficiently extract the desired information — as will be shown in the following examples.

CASE STUDY EXAMPLES

Implementing an Advanced Analytics Strategy to Optimize Quality in the Batch Production of a Biotherapeutic or Active Pharmaceutical Ingredient

Effective control over the production of a biotherapeutic or active pharmaceutical ingredient (API) is critical for achieving target product quality attributes. However, batch-to-batch variability during the upstream process can have profound impacts on the efficacy of the final product, with direct process and cost implications for downstream partners.

In this first example, the data analytics strategy discussed above was applied to optimize the quality of a batch operation for both a chemically defined API and a biotherapeutic (Exhibit 2). For the API example, both the cooling step and the filtration processes were analyzed for consistency, and the process was tuned for optimized crystal properties.

Since key product quality attributes affecting downstream processing and product performance — such as purity, particle size distribution, polymorphic form and crystal habit — are defined by how a process is run, it is important to correlate these metrics with process conditions.

Seeq, an advanced analytics solution, was used to couple on-line process data, off-line analytical data and

batch context data to rapidly identify opportunities for process improvement. This yielded tighter control of the anti-solvent addition step and an optimized filtration process, resulting in higher yield and purity, more consistent batches, optimized powder properties, reduced cycle times and lower cost of goods.

For the biologic example producing a biotherapeutic, bioreactor batches were compared across multiple equipment scales (100L and 3L) to develop an effective scale-down model. In this example, correlations were developed among metabolites, oxygen concentrations, viable cell density and protein titer — ultimately enabling robust scale-up to meet key clinical timelines. Cost savings were realized by providing users with enough time to reconfigure the process to meet clinical timeline, which saved the cost of a clinical batch.

Implementing an Advanced Analytics Strategy to Monitor and Maintain Consistent Water Quality

With both upstream or downstream processing in pharma or biotech, ensuring consistent water quality requires utilization of PAT to provide on-line particle count and bioburden monitoring in real time. Also required is access to current and historical data from the water system and other disparate data sources. With the data sources accessible and tools available to analyze it, this strategy provides a good foundation for process understanding.

For this water system quality example, calculating biologic particle counts in real-time was the goal, which would reduce the use of the existing off-line standard method of measuring Colony Forming Units (CFUs), a multi-day process (Exhibit 3). With current off-line CFU measurements, it was not possible to tie in the important quality metric, total particle and bio particle counts, into the current process as it was occurring, which meant there was no way to correlate bioburden with other metrics.

By gathering real-time particle and biologic count data, and analyzing it with Seeq, real-time measurements were presented visually, allowing users to:

- Observe transient changes impacting performance with insight on a per-second basis,
- Trend totalized particle and microbial counts over time,
- Identify repeating patterns impacting water loop performance, opening the door to insights about how particle counts are related to overall water system operation,
- Provide handles for process monitoring with boundary management and alarm notifications.

With the large amount of data signals available, users also wanted a way to be notified when a process was moving away from defined parameters. This would provide them with an opportunity to react before losses occurred, as opposed to doing a post mortem on a contaminated run. As part of this advanced analytics solution, users needed to use historical data to define operating boundaries and alarm limits, and to create notifications.

Using an advanced analytics solution, the water system is now tested for biological and total particle counts in real time, and then analyzed in concert with process data about the system and the external environment. A system containing real-time bio and total particle counts from an IMD-W system, coupled with a data historian system, gives users the power to:

- Leverage all the best data sources: Connect IMD-W, data historian and MES data sources together for access by a data analytics program,

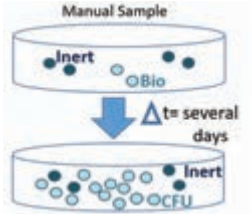
Exhibit 3

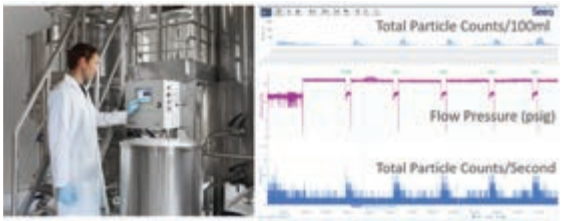
Off-Line Method:
Slow process requiring significant numbers of trained personnel; Takes several days to receive results

VS.

Real Time Method:
Instantaneous bio and total particle counts for real-time water system management and optimization

Laboratory technician analyzing petri dish bacterial cultures.





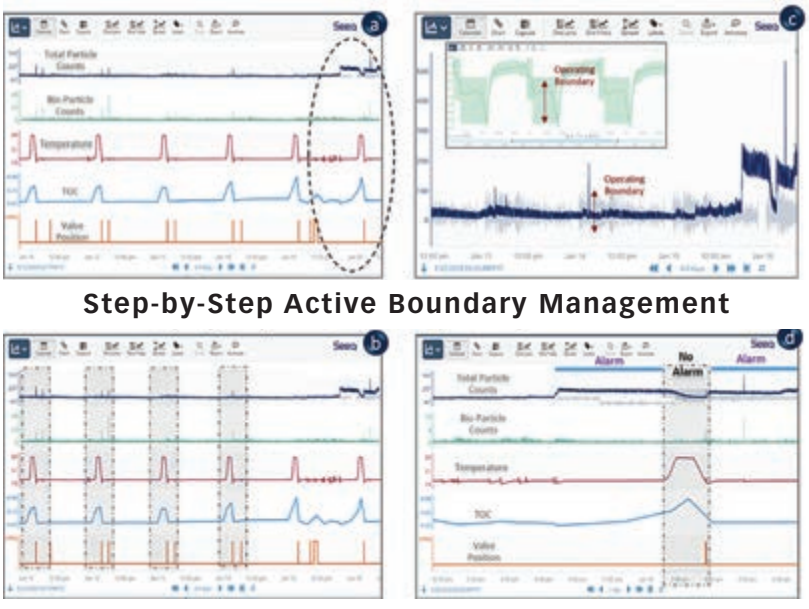
Engineer assessing and reacting to bioburden risks in real time.

Photography courtesy Azbil North America, Inc.

- Analyze using historical context: Perform calculations using ability to look at historical data,
- Develop understanding: Develop models connecting the water system operation with particle count data to define cause and effect relationships,
- Create structure: Define operating boundaries and management logic,
- Implement, review and improve: Define an alarm strategy and read outputs back into data historian system alarm notification software.

To enable real-time notifications, boundaries of normal operation required definition, along with logic for how and when to be notified. Starting with the simplest rule, a small number of scenarios were

Exhibit 4



Water system health monitoring was improved by: a) viewing total particle and bio-particle counts alongside system operation b) identifying correlations between system operation and particle counts, c) defining operating boundary, and d) implementing a proactive alert strategy during normal operation.

added, and then a work process was developed.

With this strategy developed, iteration is now key for refining boundary definitions where it matters (i.e. level of importance related to quality), then repairing false positives and negatives as they occur. This immediate workflow is essential and allows the user to modify the boundary to more accurately reflect the desired control of that quality metric, with results depicted in Exhibit 4.

EMPOWERING FOCUS

An effective advanced analytics solution provides a lasting foundation essential to long-term success in quality management and metrics. Giving scientists, engineers and managers the tools to extract and analyze only the data needed is imperative — as is enabling data focus.

As demonstrated in the case studies provided, a flexible, self-service advanced analytics strategy enables a robust method of selecting the data needed for analysis and decision-making for both process scale-up and real-time process monitoring.

These are key factors in meeting clinical timelines. In other words, well-defined process boundaries and monitoring reduce mistakes and improve process quality and ultimately product quality. Through the implementation of these solutions to combine disparate data sources and make the analytics process user-friendly, it is much easier to realize effective work processes to support workflow execution through analysis and reporting; optimized use of time and key resources to avoid unnecessary experimentation; and knowledge creation and management to streamline cross-group access to existing data and share results.

The key to achieving quality is empowering internal resources by giving them the right advanced analytics solutions for their specific needs, and empowering them to focus on just the data of interest.

Acknowledgements: *The author wishes to thank Brian Crandall and Brian Parsonnet at Seeq; and Dr. Allison Scott, Aric Meares and Mary Parsons from Azbil- BioVigilant Division.*

THE Art OF THE Science

Mastering the complexity of PLGA microsphere manufacturing

By Daniel Leblanc, Senior Vice President of CMC Operations, Flexion Therapeutics, Inc.

SINCE THE approval of Zoladex and Lupron Depot for the treatment of prostate cancer in 1989, the use of polylactide (PLA)/poly lactic-co-glycolic acid (PLGA)-based delivery systems has enabled the development of extended-release formulations that can reduce dosing frequency and minimize drug side effects.

For example, Risperdal Consta, the first long-acting injectable atypical antipsychotic approved by the U.S. Food and Drug Administration and indicated for the maintenance treatment of bipolar I disorder as monotherapy, has been shown to provide superior efficacy compared with oral atypical antipsychotics, with a low level of treatment-emergent side effects and favorable patient acceptance. Its prominent role in the treatment paradigm is largely attributed to improved compliance with treatment derived from the administration of the long-acting, injectable PLGA microsphere formulation every two weeks in a physician's office — compared with self-administration of the oral formulation on a daily or every-other-day basis.[1]

PLA/PLGA microspheres have been incorporated into a multitude of pharmaceutical products used for the treatment of a wide array of indications, including cancer, psychiatric disorders, endocrine disorders and periodontal disease. In fact, to date, the FDA has approved 16 PLA/PLGA-based products, of which 12 are formulated as microspheres. Many of these products have become leading medicines in their respective categories due to enhanced safety, efficacy and dosing profiles.

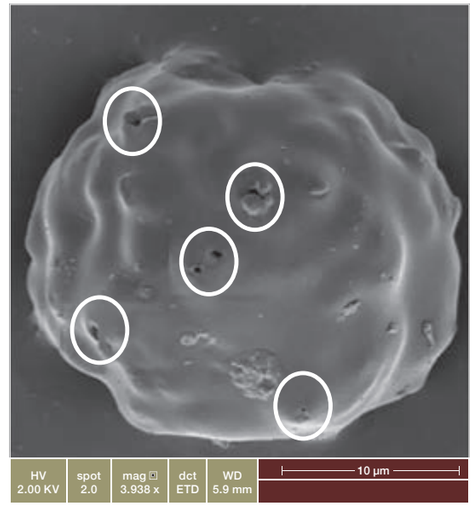
Despite this market potential, there are no generic versions of PLA/PLGA products, even for those products for which patent protection has expired. This highlights the inherent complexity of manufacturing a PLA/PLGA-microsphere product under the reproducible and exacting standards of the Good Manufacturing Practices (GMP) that are required to achieve FDA approval while also meeting desired parameters for drug loading, dose-release profiles, route of administration and cost-effective drug development.

THE COMPLEXITY OF MANUFACTURING PLGA MICROSPHERES

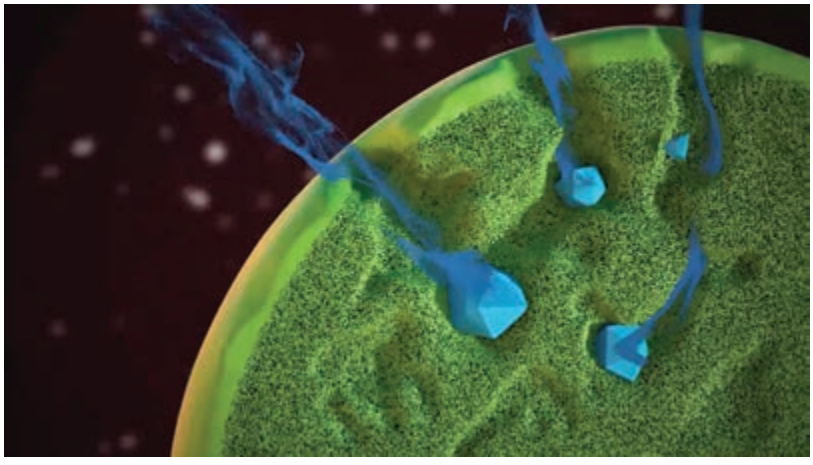
The complex and proprietary nature of the biologics manufacturing process creates a high bar when it comes to the development of biosimilars, because even a small change to the process can have a substantial impact on the safety, efficacy, activity or stability of the final product.

As a result, although 18 biologics are off patent, only seven of these products have FDA-approved biosimilars.[2,3] Products with multi-billion-dollar U.S. sales in 2017, such as Rituxan, Xolair, and Tysabri have no generic competition despite the absence of patent protection and the large market.

The complexity of manufacturing PLA/PLGA microspheres creates a similar challenge when planning to develop new extended-release therapies



Representative scanning electron image of a Zilretta microsphere showing surface characteristics as well as channels for drug release.



Drug release from Zilretta microspheres demonstrating the mechanism of release.

or generic versions of branded products. The challenges stem from several factors, including local drug diffusion and polymer degradation in vivo. PLA/PLGA begins to degrade following administration, resulting in an increase in the amount of water-accessible space leading to the interior of the particle, and accumulation of lactic and glycolic acid that may substantially lower the pH within the interior of the particle. The decreased pH can further accelerate particle degradation, and the composition of the polymer and its inactive ingredients have a significant impact on the time-release properties of the product.[4]

The challenges of manufacturing a PLGA microsphere in particular are highlighted by a study in which multiple formulations of microparticles containing risperidone yielded statistically significant differences in drug loading.[4] This study also highlighted the challenge in finding manufacturing assays that even enable comparative evaluation of in vitro drug release profiles for establishing equivalence among various microsphere formulations. The extent to which the complexity of PLA/PLGA manufacturing raises the bar for the development of generic forms of branded PLA/PLGA products is underscored by the fact that the FDA's Office of Generic Drugs has awarded a variety of grants and contracts to support research in five areas that are critical for expanding development of PLA/PLGA-based drug products: development of in vitro-in vivo correlations (IVIVC); development of in vitro release testing (IVRT) methods; understanding of the impact of properties of PLGA polymers on product performance; modeling and simulation of PLA/PLGA-based drug products; and investigating potential peptide PLGA interactions during product manufacturing and use.[5]

Despite these challenges, innovation in PLGA manufacturing continues. In October 2017, the FDA approved the 16th PLGA microsphere product, Zilretta, for the treatment of osteoarthritis (OA) knee pain. This approval demonstrates that adapting PLGA manufacturing methods to meet the clinical needs of specific disease indications can be a powerful driver for bringing new therapies to market.

The following case study outlines the design and manufacturing approach undertaken to leverage PLGA microsphere technology into a new treatment option for patients with OA knee pain.

A CASE STUDY IN INNOVATION

Zilretta was developed by Flexion Therapeutics, Inc., a biopharmaceutical company in Massachusetts, as a novel PLGA formulation that was designed to enable a long-acting, non-opioid treatment for OA knee pain. The FDA approved Zilretta as an intra-articular injection for the management of OA pain of the knee. Flexion's approach to developing Zilretta serves as an example of how the design and manufacturing of a microsphere formulation can be tailored to meet the clinical needs of a specific patient population.

In developing an extended-release therapy for the treatment of knee osteoarthritis, Flexion was seeking to address an unmet clinical need for patients living with this chronic painful condition. Non-opioid therapies include the injection of immediate-release (IR) corticosteroids, such as triamcinolone acetonide crystalline suspension (TAcs). While the analgesic effect of immediate-release steroid injections typically lasts two to four weeks, by medical convention, these drugs are not administered any more frequently than once every three months.

We set out to develop a TA formulation that enabled an extended-release dose of the medicine at the source of a patient's OA pain, and could provide pain relief for the entire duration of the dosing period. While other therapies administered by intra-articular injection to the knee rapidly leave the joint, we sought to develop a formulation that would remain in the knee joint to optimize persistent drug concentrations within the target tissue while minimizing systemic exposure to TA. This is an important

consideration when delivering a drug that could potentially have off-target effects if administered systemically, as such effects can have a negative impact on safety profiles and are associated with product development failure. Based on the success of currently approved PLGA-based products that provide sustained efficacy, Flexion chose to develop a PLGA formulation of TA for the treatment of knee OA pain.

Thinking Outside the Box

Before creating a new PLGA microsphere formulation, Flexion had to start by addressing the limitations of existing PLGA technologies, such as the typical emulsion-based process used to commercialize a majority of the approved microspheres. First, these technologies can exhibit a high burst release, which means that a large fraction of the dose is immediately released upon injection. This may result in excessive drug concentrations at the administration site while reducing the amount of drug within the microsphere that is delivered over a longer period of time.

Second, the manufacturing process needed to be completely sterile. And third, every active pharmaceutical ingredient has a different set of attributes that needed to be taken into consideration in the PLGA formulation. In other words, each PLGA formulation is a completely customized product based on the drug being delivered, the desired time-release profile and the location and route of administration.

Rather than adapting the profile of a new drug to the constraints of current PLGA technologies, Flexion took a step back and identified a set of defined clinical objectives that the PLGA product needed to achieve: (1) an extended-release to provide sustained pain relief following a single dose; (2) a quick onset of action but a low burst after injection to minimize systemic exposure to drug; (3) ease of administration; (4) simple packaging into the volume needed for an intra-articular injection.

With these objectives in mind, the team identified and implemented innovative PLGA manufacturing processes. First, they used a scalable, non-aqueous process that allowed the product to be terminally sterilized by irradiation. This enables a high level of sterility assurance while maintaining cost-effective manufacturing.

Second, the team developed a formulation with a release mechanism that would maintain concentrations of the drug in the knee joint for at least 12 weeks. Release mechanisms differ depending on the route of administration, and may vary across intramuscular, subcutaneous or intra-articular injection. Therefore, it's important to understand the desired release profile of the product, as well as the way in which the route of administration will affect this profile. Environmental and physical conditions of local delivery are critical factors to consider when designing a microsphere product, and the structure of the knee joint requires a different set of design criteria compared with other routes of administration due to the higher volume of drug injected into the knee compared with other sites. Our formulation took these factors into account and resulted in a novel product with an extended-release profile optimized for intra-articular injection that met the company's product design objectives: prolonged residence within the knee joint, long duration of action, and minimal systemic side effects.

SCIENTIFIC AND TECHNOLOGICAL DISCOVERY IS A CRITICAL DRIVER FOR IMPROVING CLINICAL CARE.

Scale Matters

Scalability is essential to the success of any new manufacturing process. The team designed scale-up processes for Flexion's proprietary PLGA microsphere technology when Zilretta was still in Phase 2 clinical development. This allowed larger amounts of product to be manufactured by increasing the run time of the existing process — rather than requiring the development of a new process that could operate at a higher scale. The ability to retain the same process eliminated development and regulatory risks that might have resulted from changes to equipment or critical aspects of the process. This allowed Flexion to submit a package on manufacturing and product stability to the FDA based on Phase III product manufacturing. They were then well-positioned for a full commercial launch within weeks of the FDA approving Zilretta — a significant accomplishment for a small company launching its first product.

Commercial-scale manufacturing for Zilretta was established at Patheon, a contract manufacturing organization. Flexion chose Patheon, a Thermo Fisher company, for its "condo model" in which each client company has a dedicated

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suite for manufacturing. Flexion retains control of the manufacturing process knowledge while the CMO controls the GMP environment in Flexion's suite.

This type of arrangement gives Flexion access to a commercial-scale infrastructure without having to invest in a proprietary manufacturing facility, while enabling the company to maintain control over manufacturing cadence. It avoids the potential for scheduling challenges that often exist with traditional CMOs that routinely require manufacturing runs to be booked six to 12 months in advance. This type of model could be especially attractive to companies developing innovative technologies that may not easily fit into the existing manufacturing process that CMOs typically offer.

CREATING CLINICAL VALUE WITH PLGA

Scientific and technologic discovery is a critical driver for improving clinical care. Flexion's experience with Zilretta underscores how critical drug delivery innovation is, and highlights how continued advances in the development of novel PLGA microsphere formulations can provide significant clinical benefits. The ability to innovate additional microsphere formulations could facilitate the development of new classes of therapies that hold the potential to address real clinical need, especially in chronic diseases that require long-term treatment (i.e. OA or autoimmune diseases). Continued development of novel drug formulations and drug delivery approaches will play a critical role in catalyzing therapeutic advances that improve patient care and outcomes. Realizing the clinical potential of PLGA microsphere technology requires that the pharmaceutical industry rise to — and overcome — the real but solvable challenges of PLGA product design and manufacturing.

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From Laggard to Leader: A Formula for Lean Success

How pharma can address its lack of progress and ensure lean efforts are successful and sustainable

By Robert Spector, Director, Clarkston Consulting

LEAN MANAGEMENT continues to be one of the most prevalent business improvement approaches in the pharmaceutical industry. Successful application of lean leads to shorter lead times with improved quality and customer responsiveness, resulting in enhanced revenues, reduced investment and costs. Unfortunately, as evidenced by the lack of significant improvement industry-wide in the inventory turns metric (the measure of a company's "leaness") over the course of over a decade,[1] the industry has not been successful in ensuring sustainable improvements from lean.

WHY LEAN FAILS

What can pharma companies do to address this lack of progress and ensure their lean efforts are successful and sustainable over the long term? The place to start is identifying the root causes holding back progress. These consist of a lack of senior management commitment and involvement; an emphasis on driving cost reduction benefits (primarily in labor force reduction) over revenue enhancement and strategic benefits; and the siloed focus on application to manufacturing rather than across the enterprise.[2]

ADDRESSING THE CHALLENGES

Addressing these challenges begins with gaining a clear understanding that lean is not just a "set of tools," but a holistic operating system as illustrated by the Toyota Production System "house."[3]

The TPS House is a simple visual representation of the Toyota Production System to show that TPS is a structural operating system, not just a set of techniques. The analogy is of a house that is strong only if the roof, pillars and foundations are strong; all elements of the house reinforce each other — a weak link threatens the whole system. For lean to be successful, all elements must be implemented starting with defining clear goals, developing a solid foundation, implementing process improvement tools, and ensuring that people — who are at the center of the system — are fully engaged and driving continuous improvement.

SUCCESS STARTS WITH LEADERSHIP

Over 90 percent of successful lean implementations have a strong leader who understands and lives lean.[4] This must be an individual at the senior level who has strong leadership skills, understands the concept of lean needing to be employed as an operating system, and is committed to driving the change no matter what. The role of this lean leader is to drive the change through all levels of the organization, starting at the senior levels. In many cases, companies do not have the internal capacity and/or lean implementation expertise in-house and thus employ external consulting partners. It is important to vet potential consulting partners to ensure they have successful track records with lean implementations that include all aspects of lean — not just the technical tools, but also with driving the human elements (work center and problem-solving teams, Gemba walks, leadership training).

The first step for the lean leader is to build buy-in at the senior levels of the organization by ensuring that the implementation will directly impact the company financials. Results are needed in a reasonable period of time to build momentum and ensure buy-in via proof of concept. This is done by building a business case that is tracked throughout the lifetime of the implementation. Benefits should be determined by conducting an assessment to understand where the opportunities lie in terms of both financial and operational metrics, e.g., revenue by product line, production cycle times, inventory turns, right-first-time quality metrics, etc. Lean initially is counter-intuitive to standard accounting metrics, so education and buy-in with finance is crucial to ensure success.

LINKING LEAN WITH VALUE

There is a reasonable expectation amongst senior leaders that lean will produce significant financial and operational results, and that results will be achieved in short order. This leads to the expectation to "see results quickly," which many times results in labor cost reduction. Labor costs are easy to measure while the strategic benefits of improved speed, quality, flexibility, customer satisfaction are more challenging to quantify.

Further, moving beyond cost reduction to benefits in areas such as revenue enhancement requires collaboration across the various functions. For example: marketing, sales and operations working collaboratively to increase market share by capitalizing on enhanced speed and increase capacity, or operations and product development collaborating on building quality into new treatments. Unfortunately, functions, divisions, and geographic units at most pharma companies remain strongly independent with the silo mentality deeply entrenched. This lack of collaboration is another contributing factor to lean implementation being isolated to "the four walls" of manufacturing versus the entire supply chain or product development.

Overcoming this challenge requires two things: the ability to identify financial benefits that are attainable within a reasonable period of time; and changing the culture to drive collaboration between individuals,

departments and function. For the first element, companies need to understand where the "levers" are in their organization that can drive the most improvement quickly. For this task, one can look to an improvement approach known as the Theory of Constraints (TOC).[5] TOC looks at businesses as systems — a collection of interrelated, interdependent components or processes which act in concert to turn inputs into a set of outputs in pursuit of some goal.

TOC likens systems to chains, or networks of chains of dependent events. What factor determines the strength of the chain? Clearly, a chain is only as strong as its weakest link. TOC defines the weakest link as the constraint to the system, i.e., it is the limiting factor.

TOC posits that the greatest improvements come from addressing issues at the weakest links in the chain. Improvements at non-constraints have very little positive impact on the overall system and can even be detrimental.

Translating this analogy to a pharmaceutical manufacturing business, the "chain" is the supply chain which consists of a sequence of dependent events to buy things, convert them to something else (usually), and finally ship things to customers (or distributors) with a resulting sale. The strength of the chain is measured by the rate at which the supply chain generates money for the business through sales. All manufacturing companies have one of two possible locations for the constraint either internal or external. The question is: Can you meet existing customer demand with your existing processes and capacity vs. having excess capacity and not enough demand in the marketplace? This is a fundamentally important question for companies to be able to answer.

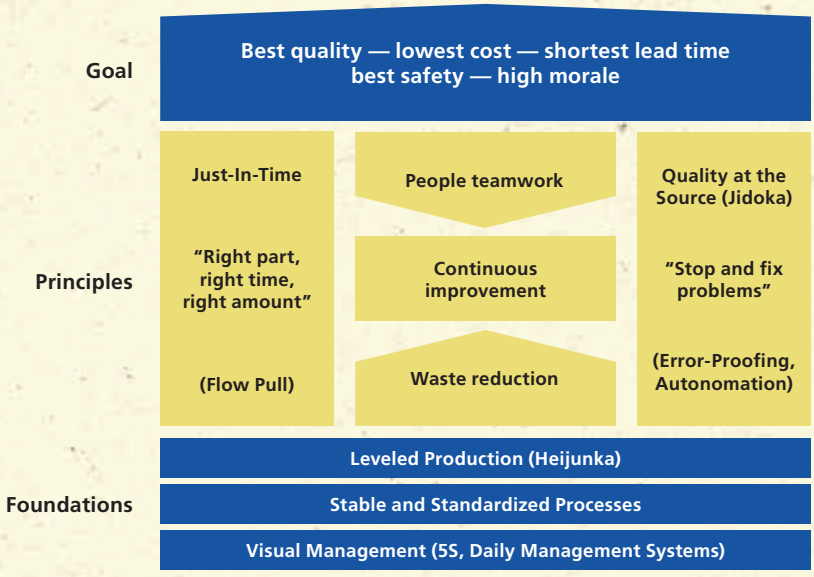
By identifying and eliminating waste, lean primarily frees up capacity. If the company has an internal constraint that's located in manufacturing, then lean implementation will free up capacity and increase the speed at which companies can fulfill both existing and unsatisfied market demand, thus resulting in immediate improvements to both top and bottom line financials via additional sales.

However, if a company chooses to begin lean at a manufacturing site that does not have any capacity constraints, i.e., external market demand is the limiting factor, that freed up capacity cannot be used for additional sales. So what will happen to the additional capacity? With the pressure to "see results quickly" there will be a high likelihood of layoffs. Recall that the cost reduction viewpoint is one of the root causes of lean failures. Thus, there is a need to ensure that the right areas are chosen to implement lean.

Breaking a capacity constraint results in immediate benefits in terms of revenue enhancement — an area with far larger profit potential than labor cost reduction. It may be that there is a capacity constraint with some product lines, but not others, for example, life-savings treatments vs. less common treatments with limited market demand. Once these product lines are identified, the next step is determining the potential revenue enhancement benefits from implementing lean in these areas. Doing this requires determining the drivers of the capacity constraint(s), e.g., downtime of equipment, long setup-times, etc., and estimating the potential improvements from lean implementation to resolve these issues.

Lean implementation also results in a significant reduction in inventories, which frees up working capital and results in improved cash flow and reduced costs associated with holding inventory. Both revenue enhancement and

The TPS House
The Toyota Production System



BY IDENTIFYING AND ELIMINATING WASTE, LEAN FREES UP CAPACITY.

reduced inventories are significant opportunity areas that need to be assessed to develop a business case resulting in improvement initiatives that impact company financials in a relatively short period of time.

In the situation where the constraint is external, then it should first be evaluated which area of the business has the most opportunity for financial improvement in a relatively short period of time. This process starts with a thorough understanding of the nature of the competitive landscape for the company's products. Do the company's products compete on price, quality, speed (areas that are most impacted by lean implementations)? For example, if a customer is willing to switch suppliers to the one that can provide the fastest, most reliable delivery, then application of lean to the relevant production lines can provide the improvement needed to capture more business.

OVERCOMING CULTURAL CHALLENGES

Developing a culture that supports collaboration is a great challenge — one that many pharma companies have not been able to successfully resolve. Companies that successfully incorporate lean as an operating system have common cultural attributes of engagement, empowerment and accountability. To develop a culture that embodies these culture attributes, an assessment (culture polls, surveys, etc.) should be conducted, followed by leaders defining, aligning, and communicating a clear vision of the desired state, then leading the way.

Leading companies have driven culture change by conducting cross-company training programs for all managers to change their role from the traditional "command-and-control" model to that of "manager-as-coach." Command-and-control culture is characterized by managers whose roles primarily consist of enforcing rules (attendance, making sure that operators follow SOPs, instructions, etc., while doing their work), dealing with interpersonal conflicts, solving problems and making decisions regarding any irregularities during daily work. In this environment, managers have the minimum skills and accountability required to perform at current levels with little or no ownership of work center performance, process improvement, or people development. As a result, the environment is typically one of being in constant "firefighting mode" — lack of collaboration, potential for adversarial "us vs. them," and the lack of utilization of shop floor employees to their full potential — which lean would label as a waste.

By contrast, in the "manager-as-coach" model, the people manager takes on the role of coach. A coach develops the abilities of his/her employees to independently solve problems and implement improvements of ever-increasing levels of complexity and risk. The coach empowers people, drives accountability, sets the performance standard, collaborates and energizes people, enables the high-performance team culture, and develops their people's capabilities. The end-result is dramatic performance improvement across KPIs, increased employee engagement, increased productive use of leadership time, collaboration, increased retention of high-performing employees, and the creation of successful leaders. Coaching builds systemic strength in an organization and enables a high-performance culture — ensuring that lean efforts are successful and sustainable. The lean operating model then provides the mechanisms to utilize coaching and collaborative teamwork via the self-directed worker team's concept and cross functional "focused factories."

BRINGING IT ALL TOGETHER

Key elements to ensure successful lean implementations include: top management commitment and involvement, building a business case that incorporates an understanding of the "levers" (constraints) to drive financial benefits in the areas of revenue enhancement and inventory reduction, and breaking down cross-functional silos by changing the role of the manager to a coach.

By incorporating these elements, pharma companies can ensure they can maximize their performance in the competitive edge factors of speed, quality and cost, while ensuring sustainability and continuous improvement for the long term.

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Going With the Flow

How new fluid control technology is keeping drug innovation in motion

By Meagan Parrish, Senior Editor

THERE'S NO part of the manufacturing process that hasn't been impacted by techy advances related to Industry 4.0, the Internet of Things (IoT), artificial intelligence, automation and the like — including fluid control.

As with other areas of operation, these kinds of innovations can help reduce human error, increase quality, lead to meaningful data collection, help with regulatory compliance and speed up the manufacturing process.

"As the drug industry matures, the demand for increased quality and innovations has been coupled with an even bigger demand to decrease time to market and the cost of development for manufacturers," Peter Levison, executive director of business development at Pall Biotech, says. "The industry has recently responded with a call for automated integrated processes and we are starting to see a lot of progress in finding new approaches."

REMOTE CONTROLS

With many pharma plants operating around the clock, the need to keep tabs on every part of operations is a never-ending endeavor. Remote monitoring has made this task much less labor intensive.

"The industry has been looking for new solutions, and we will continue to see and develop advanced technology that will allow technicians to remotely monitor and control pumps securely 24/7 from their smartphone, tablet or computer," Gregg Johnson, global senior product manager, Masterflex and Ismatec, at Cole-Parmer says. "We will see less personnel working around the clock onsite physically checking and monitoring pumps. More offsite and off-hour technicians will be able to verify pump operational status and respond to status and error alerts."

One of this year's Pharma Innovation award winners (read our cover story on page 14) is Petasense's Asset Reliability & Optimization System, an end-to-end, wireless predictive maintenance system that gauges the health of critical equipment such as reactor tank motors and feed pumps, and volumetric and pressure fill pumps. The key features in this system are the web and mobile applications that make it possible for operators to visualize asset health and performance, and receive real-time alerts from anywhere at any time.

As Johnson notes, remote monitoring also increases safety.

"This technology allows pumps to be used in applications where runs may need to be initiated during 'off' hours, and allows for remote control of pumps operating in cleanrooms, glove boxes or isolation chambers to distance technicians from harmful chemicals and situations," Johnson says.

As is the case with Cole-Parmer's Masterflex cloud-enabled pumps featuring its MasterflexLive platform, data collection is often a byproduct of these new tools, giving manufacturers useful insights for analytics and quality improvement.

"We are seeing a drive to paperless compliance which fits very well with connected fluid handling products that deliver performance

Sierra's line of flow meters for pharma manufacturing are equipped with software and digital protocol integration.

Cole-Parmer's MasterflexLive is a secure, cloud-based platform for controlling and monitoring select Masterflex L/S and I/P pumps. The smart technology, a first-of-its-kind for peristaltic pumps, provides real-time control of all pump parameters, including speed, flow rate, dispense volume, and more.

data directly to the cloud. The use of big data and analytics collected from the fluid handling path can drive efficiences in workflow, predictive maintenance, and ease compliance with federal regulations," Johnson says.

FUTURE-PROOF FLOW METERS

Although equipment vendors are continuously improving the technology of their products, manufacturers are not always keeping up. When it comes to flow meters, many are still investing in products that aren't compatible with the latest Industry 4.0 updates — which can lead to costly updates.

"To be Industry 4.0 ready, flow meters and controllers must have the ability to connect and communicate with pharma manufacturing processes and immediately provide trustworthy flow data," Scott Rouse, vice president of product management at Sierra, says. "Flow measurement devices that fit the bill must offer precision flow accuracy, reliable repeatability, offer a full suite of digital communication protocols, and be flexible to change in the applications — and do all this without having to shut down the manufacturing process."

Many of the newer flow meters are bringing fluid control into the Industry 4.0 era by offering the ability to measure and control gas flow, and communicate that information to operators to help them make informed decisions about the process.

"Since all chemical reactions are mass-based, direct mass flow is an indispensable requirement," Rouse says.

Pall Biotech has also begun to re-think its portfolio and how it can offer total, integrated solutions.

"As we continue to refine the portfolio via product updates or additions, we are paying closer attention to how we can automate and integrate unit operations to build flexibility into each piece of equipment," Levison notes.

The company's Cadence Virus Inactivation system, for example, has been designed for integrated unit operation — the single-use fully automated system consists of two mixers that can work in continuous or batch mode. It also allows low pH virus inactivation of an incoming elution stream continuously by automating elution collection, titration to low pH, hold, titration to high pH, and then transfer out steps — for 24 hours, if needed.

SEALING THE DEAL

Seals may not seem like the most tech-intensive components in fluid control, but there is a lot of work going into the R&D of new products.

As manufacturers work with a higher range of temperatures and look to speed up their processes with higher pressures, vendors for fluid control seals are finding new ways to meet these evolving needs. The R&D team at Saint-Gobain, for example, has been working on innovating a new line of OmniSeal spring-energized seals made with high-performance materials that can handle more diverse demands.

"Our global R&D teams are focusing on material formulation, characterization and processing to create new sealing solutions to keep pace with increasing demands for pressure, temperature and life cycle requirements for pharmaceutical applications," Ronelle Decker, the market manager for Life Sciences at Saint-Gobain, says.

Whether it's with updated components or innovative tech, equipment vendors are developing new ways to keep up to speed with fluid control in manufacturing.

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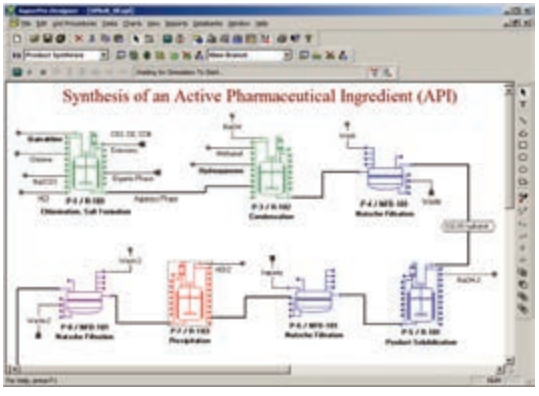

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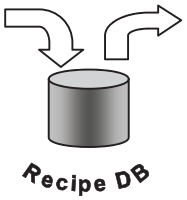

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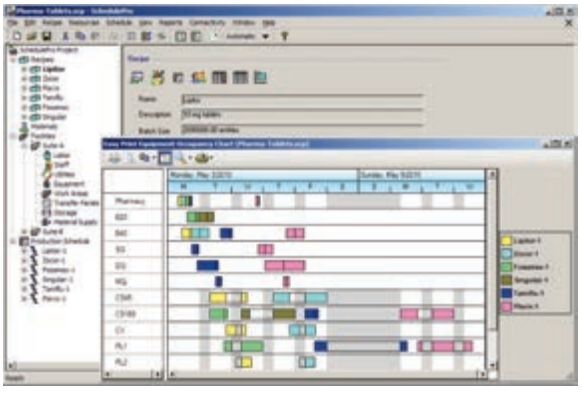

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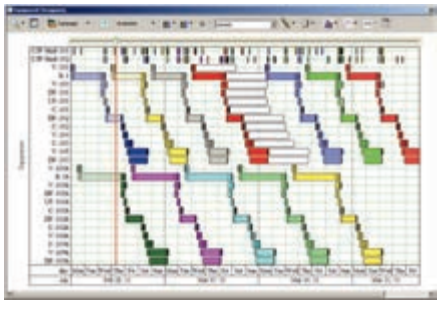

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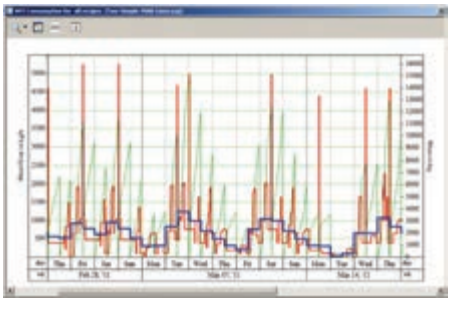
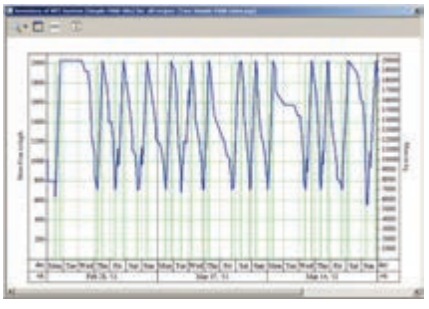


Tracking demand for resources (e.g., labor, materials, utilities, etc.)



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Developing an Appetite for Change

Is your culture correct for digital transformation? (Hint: it should be)

BY CHRIS MCNAMARA, SMART INDUSTRY CONTENT DIRECTOR

IT'S OFTEN said that company culture eats strategy for breakfast. And when it comes to strategy intended to advance an organization's evolution into Industry 4.0, pharmaceutical companies have not historically embraced the seismic cultural, talent and process shifts that digital transformation represents.

That's holding all of us back. (But don't feel too bad. Other industries are having their own struggles stepping into the digital future.)

So what's the fix? For answers, we turned to Suzanne Burns, member of the global industrial, infrastructure and digital practices for Spencer Stuart. Our goal was to find out how to optimize the change needed within corporate culture to accelerate digital innovation. Is it a cultural shift? Is it a strategic shift?

Burns responded with an all-around "yes."

"The answer is both. You can have the best-laid strategy, but if your culture is not right it can derail best-laid plans," said Burns.

Burns stressed that in order for manufacturers to be successful, they must take a different path than they have historically chosen. The culture that made them successful in the past was likely results-oriented, process-oriented, operating within a narrow discipline. And this culture persisted for good reason: to deliver stable, predictable outputs and economic performance. The common line of thinking has been: "That's what we're known for, so why change it?"

But even if these cultural attributes served the pharmaceutical industry well in the past, they're often diametrically opposed to the agile, collaborative and learning-oriented attitudes embodied by leading digital organizations.

"As industrial companies want to become more customer-centric, innovative and agile, they are recruiting executives from B-to-C companies to help them in those areas," explained Burns.

And the reverse is true where industrial companies are infusing talent in B-to-C companies to help with operating discipline and productivity improvements.

Of course, disruption for the sake of disruption is not necessarily a good thing. But in order to gain long-term competitive advantages, manufacturers must accept change as a business imperative. "We're witnessing that with an Amazon or Uber coming up with different business models that change the landscape," she noted. "For a business to compete in the long-term they must have strategies that are able to address these changes straight on and, hopefully, be ahead of the curve."

Is that your business? Perhaps more importantly, is that where you'd like your business to be?

A critical component is personnel. Specifically, change-agents who spearhead the (occasionally difficult) process of shifting mindsets and tactics. And it comes from top down. While digital transformation is a technology-dependent shift in business model, people are at the heart of it. Go figure.

TO GAIN LONG-TERM ADVANTAGES, MANUFACTURERS MUST ACCEPT CHANGE **AS A BUSINESS IMPERATIVE.**

"The signal for the necessary changes has to come from the top of the organization," Burns said. "That executive sets the tone that ripples through an organization. But in no way is change successful without having every level in an organization embrace it along the way. You must have that buy-in throughout an organization, aligned with the strategy."

Or, more specifically, you must have that buy-in throughout an organization that wants its digital transformation to succeed. Ultimately, you need a culture that balances the need to deliver consistent, profitable growth against the ability to absorb and capitalize on often disruptive digital innovations.

Want to network with Suzanne Burns? Burns is a featured speaker at the 2018 Smart Industry Conference, where she'll deliver a presentation titled, "Change Your Culture, Accelerate Digital Innovation," sharing how industry leaders at all levels can serve as change agents within their organizations. Learn more about the conference here: Event.SmartIndustry.com

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