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Modern aseptic performance demands new flexibility in both mindset and technology

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BY KAREN LANGHAUSER, CHIEF CONTENT DIRECTOR

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Elephant in the Cleanroom

Finding value in small-volume aseptic processing means confronting pharma's fear of change

SAYING GOODBYE to the Ringling Brothers and Barnum & Bailey circus was a tough thing for me to do. As a child, I was mesmerized by the magic of the circus. As an adult, I was awed by the talent of the performers and wooed by the nostalgia of one of the most iconic forms of American entertainment.

The circus industry is one largely built on tradition, experience, and credibility. Trying to stay profitable in that space is tough — and trying to break into that market is even tougher. Cirque du Soleil, however, pulled it off.

Ringling Bros. set a grand standard for circuses — a massive caravan rolling into town carrying every type of performer from motorcycle-riding daredevils to elephants. In the early '80s, despite getting off to a tough start, Cirque du Soleil evaluated market demands and realized that rather than trying to do things the way they were always done, a newer, leaner way of thinking was necessary.

So Cirque du Soleil scaled back: no lions, no elephants, no grandeur — just a tent, clowns and acrobats.

Today's modern drug therapies — complex, targeted approaches to treatment that are resulting in small-batch aseptic products — require that manufacturers step away from tradition, taking advantage of new technologies and exploring new ways of addressing process control and efficiency.

Traditional drug manufacturing required heavy investments in large manufacturing facilities and equipment. The "tried and true" approach to aseptic design and process control, geared toward mass production, may not be optimal, or in some case even feasible, with modern therapies.

I recently read an article by two INSEAD professors about how Cirque du Soleil reinvented the circus. In an attempt explain what Cirque du Soleil achieved, the authors gave the example of a market composed of two oceans: red and blue.

"In the red oceans, industry boundaries are defined and accepted, and the competitive rules of the game are known. Here, companies try to outperform their rivals to grab a greater share of existing demand. As the market space gets crowded, prospects for profits and growth are reduced. Products become commodities, and cut-throat competition turns the red ocean bloody. Blue oceans, in contrast, are defined by untapped market space, demand creation, and the opportunity for highly profitable growth."

This rings true of modern aseptic processing as well. An industry accustomed to large-scale processing is being challenged to shift its mindset — something that is not always easy for pharma — but the rewards for patients and profits can make it worth it.

As America's entertainment preferences changed, Ringling Bros. suffered from slumping ticket sales that ultimately made the business unsustainable. The sophisticated eloquence and simplicity of the Cirque du Soleil model seemingly paid off, however. They pushed the boundaries of tradition and consequently, customers were willing to pay a price several times that of traditional circuses.

Today's aseptic performance demands new flexibility in mindset, and if the industry can overcome that hurdle, I think we are in for a grand performance.

BY KAREN LANGHAUSER, CHIEF CONTENT DIRECTOR
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ET Phone Home, Then Call the FDA

In FDA's world, ET does not refer to The Extra-Terrestrial as made famous by the movie, but rather Emerging Technologies, and it set up a special task force to facilitate pharmaceutical innovation

ALTHOUGH ET may be alien to some, emerging technologies has become a buzzword in the pharma space. But those are not just words to the FDA. The agency put those words into action when it launched its Emerging Technology Team (ETT) — aimed at providing early engagement and additional meeting opportunities for companies interested in implementing emerging manufacturing technologies into their production process. The ETT program helps the FDA address a long-standing concern that the Agency is a roadblock to new technology adoption.

The first question that comes to mind is what exactly constitutes emerging technologies? In a recent presentation at the 2017 PDA annual meeting, Laurie Graham, FDA Acting Director, DIPAP, defined ET as "technology with the potential to modernize the body of knowledge associated with pharma development to support more robust, predictable, and/or cost-effective processes or novel products and with which the FDA has limited review or inspection experiences."

For example, emerging technologies for small molecules include continuous manufacturing, 3D drug printing and continuous aseptic spray drying. For biological molecules, ETT has been involved with controlled ice nucleation for lyophilization processes, advanced process control and next generation sequencing. On the equipment side, innovations include closed aseptic filling systems, isolator and robotic arms for aseptic filling, and novel container/closure systems for injectables.

The FDA believes emerging technologies have made it possible for drug manufacturers to remedy a variety of problems that have traditionally plagued operations. Advanced automation equipment, for example, has led to less operator error while isolators and other separation technologies have lessened contamination on the processing line.

But the FDA admits that its inability to keep up with emerging technologies has made pharmaceuticals hesitant to use them despite the benefits. "Pharma companies may have concerns that using such technologies could result in delays while FDA reviewers familiarize themselves with the technologies and determine how they fit within existing regulatory approaches," FDA says.

Hence, ETT was created — to promote pharmaceutical innovation. Of course, emerging technologies still need to meet regulatory pathway requirements for approval, including manufacturing per cGMPs.

The ETT not only serves as the primary point of contact for companies interested in implementing emerging manufacturing technology and relevant quality assessment team, but also performs other functions:

- Answers an applicant/sponsor's submission questions;
- Identifies and helps facilitate regulatory review;

THE ETT PROGRAM HELPS THE FDA ADDRESS A LONG-STANDING CONCERN **THAT THE AGENCY IS A ROADBLOCK.**

- Serves as the lead on the quality assessment team, in partnership with relevant CDER pharma quality offices, to make the final quality recommendation; and
- Identifies and captures resolution to policy issues that may inform FDA approaches and recommendations regarding future submissions with the same technology.

The FDA says it aims to work with participants on a one-to-one basis, including coordination with FDA staff involved in the review of CMC sections of the application and facility evaluation.

Given this rationale, this program could encourage companies to adopt emerging technologies faster than they otherwise would by granting easier access to resources within the FDA that deal directly with submissions involving emerging technologies.

This month's cover story addresses how recent emerging technologies in aseptic processing, such as advanced isolators, robotics and increased automation, have advanced the industry and markedly reduced contamination risks for sterile products. Aseptic experts agree that as we enter a new era of smaller batch aseptic products, the acceptance of new technologies is critical.

So now when you think of ET, emerging technologies might just replace the cute little alien image in your head.

KATIE WEILER, MANAGING EDITOR
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CPhI NA: Spreading Brotherly Love Throughout the Pharma Eco-System

THE *PHARMACEUTICAL MANUFACTURING* staff was fortunate enough to be part of the very first CPhI North America in Philadelphia, Pa. There is no better backdrop to make history than America's birthplace!

The diversity of exhibitors accurately reflected the show's mission to serve the full pharmaceutical value chain — an undertaking unique to the CPhI brand.

A notable theme throughout the show was that of quality; appropriate as quality is something that needs to be applied to every step in the pharmaceutical value chain. A keynote discussion from USP CEO Ronald Piervincenzi focused on pharma's new era of quality, including the challenging task of understanding and attaching value to quality. As the pharma supply chain has grown increasingly complex and global, establishing a common definition of quality — one that can be used throughout the entire pharmaceutical value chain — remains a challenge. USP is working with industry and regulators to establish this umbrella definition of quality.

PhM editors meet a legend at CPhI.
Photo: Oceanic Pharmachem

Piervincenzi also pointed out that it is important to consider how trends in the pharma industry — such as new manufacturing practices, digital health monitoring, biosimilars and personalized medicines — are impacting quality. This insight was echoed by various contract manufacturers on the show floor, many of whom are offering services surrounding emerging technologies.

Show floor discussions leaned toward the expanding role of contract manufacturers at all stages of the pharmaceutical process. Several recent expansions reflect the healthy outsourcing market. A few notable ones:

- WuXi AppTec subsidiary STA Pharmaceutical continues to expand its integrated R&D and commercial site in Changzhou, China.
- Catalent will increase spray-drying capacity for APIs at its newly acquired Pharmatek San Diego site as well as add advanced spectroscopy and mass spectroscopy instrumentation to several sites.
- Cambrex has expanded large-scale manufacturing capacity and introduced continuous flow production at its Karlskoga, Sweden, facility.
- Hovione will more than double its New Jersey manufacturing site capacity, introducing new drug substance capacity, a new spray dryer able to handle potent compounds and analytical chemistry labs.

Positioned close to the heart of the world's largest pharma market, the CPhI debut was not only a good indication of what's in store for future North American tradeshows, but also of how we can collectively help the industry move forward into the future of medicine.

FUNNY PHARM

"We will cut down that wall — and Pharma will pay! Pharma will pay!"

— Peter Clark

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

CONTROLLING CONVENTION

Modern aseptic performance demands new flexibility in both mindset and technology

By Karen Langhauser, Chief Content Director

THERE'S A QUOTE I once saw framed in the lobby of a pharmaceutical company: "Be stubborn about your goals, and flexible about your methods."

The pressing need to take advantage of new technologies and explore new ways of addressing process control and efficiency is ubiquitous to all areas of pharmaceutical manufacturing.

However, today's modern therapies — new, targeted approaches to treatment that are resulting in small-batch aseptic products, proving more difficult to sterilize and handle, and requiring faster speeds to market — add further emphasis to this industry-wide need.

"If you look at where we are today with the effects of genomics-based tools and genetics understanding, that's all having an effect on making much more specific and smaller patient population therapies. And the effect is that we are not all going to take a blockbuster — we are going to take a very specific therapy for our condition, which will most likely be a smaller batch injectable with a higher price tag," says Chris Procyshyn, aseptic subject matter expert and CEO at Vanrx, a company at the cutting-edge of aseptic filling.

This shift in market demand means that manufacturers are now able to recognize previously unattainable value in small-volume aseptic processing. With this shift not only comes the opportunity, but the *need* to refocus on available technologies.

"Traditional methods and approaches to aseptic design and process control that were geared toward mass production may not be optimal, or in some case even feasible, with some of the new therapies we are seeing," says Hal Baseman, chief operations officer, ValSource. "Rather than take needs of these new therapies and try to fit them into the ideas and approaches that have worked for large-scale manufacturing, maybe we should be looking at this a different way, instead asking what are the new approaches that we should be considering that would better fit these new therapies."

THE DEMANDS OF SMALLER BATCHES

Smaller batch sizes mean that manufacturers are looking at facilities very differently, and re-assessing capex spending.

"The industry is starting to see a lot more products being manufactured in each facility, and a lot more specific process requirements. This is a different scenario for drug manufacturing — one that is really demanding a rethink on how facilities are put together and where priorities are placed," says Procyshyn.

Drug manufacturing of the past required heavy investments in large manufacturing facilities and equipment, but this may not be the case with modern aseptic processing. Some biologics manufacturers are even using their clinical manufacturing facilities to launch, enabling them to determine how well the product performs before making bigger investments into manufacturing technology, points out Barry Starkman, a 30-year veteran in biopharma facility design and principal consultant, parenteral manufacturing, for DPS Engineering.

Speed to market is also more important than ever before, which means facilities of the future need to be operational a lot faster than facilities of the past. Equipment standardization is a great enabler when it comes to bringing products to market quickly. Conventional, custom-built fill-finish lines are expensive and time-consuming to build and offer

Vanrx's SA25 Aseptic Filling Workcell is the first gloveless robotic isolator for making sterile injectables. The machine is designed for flexible production of multi-therapy portfolios, with new technologies that provide superior aseptic assurance and process repeatability.

limited flexibility. Equipment leaders, such as Vanrx, are recognizing this new challenge.

"We are talking about an equipment market where 'custom' used to be the rule. But today's drug manufacturers don't have time to be the guinea pigs for what's never been tested before. Customers are looking for something that is predictable. At Vanrx, we build very consistent, standardized offerings, and consequently we can develop and refine and test at a very deep level," says Procyshyn.

Standardization needs aren't limited to filling lines. Aseptic component designs also can benefit from standardization.

"The machine is just a vector for the components to flow through. Standardizing component offerings would be an important move forward for the industry. If you get too many different component designs it becomes difficult to design machines that can be everything to everybody. If the goal is maximizing flexibility while minimizing costs, the implementation of standardized, ready-to-use components allows for more flexible facilities, capable of handling a wide variety of products in a single facility," says Starkman.

EMBRACING EMERGING TECHNOLOGY

The U.S. FDA defines emerging technologies as, "Technology with the potential to modernize the body of knowledge associated with pharmaceutical development to support more robust, predictable, and/or cost-effective processes or novel products and with which the FDA has limited review or inspection experiences, due to its relative novelty."

The industry's migration away from standard cleanroom filling in favor of isolators (close to 30 years ago) brought with it dramatically improved product safety and environmental compliance. This, according to Starkman, helped open the industry's eyes to the incredible benefits of emerging technologies. "There was an increase in willingness to look at the data and make changes accordingly," notes Starkman. "And I'm hoping this continues, because acceptance of new technologies is the only way the industry is going to move forward."

Recent emerging technologies in aseptic processing, such as advanced isolators, robotics and increased automation, have indeed changed the industry and markedly reduced contamination risks for sterile products.

"Equipment manufacturers are definitely moving in the right direction and end-users are getting better at defining what they want, but ultimately there needs to be a lot more consorting and collaboration between equipment manufacturers, end-users and regulators. We are getting there, but there is still a ways to go," says Starkman.

An often-used reason for the drug industry's reticence when it comes to the use of new, emerging technologies in the drug manufacturing process is regulatory hurdles. And yet, most experts agree that regulatory agencies are no longer impeding progress when it comes to technology.

"We are in a really interesting time. Global health authorities are recognizing that these new therapies don't quite fit large-scale manufacturing methods, and consequently, I believe they are open to considering changes," says Baseman. Baseman is also the committee co-chair of PDA's Manufacturing Science and Operations Program, which, among numerous goals, seeks to identify and encourage use of new manufacturing technology and methods.

In late 2015, CDER's Office of Pharmaceutical Quality (OPQ) established its Emerging Technology Team (ETT) to serve as a primary point of contact for companies that are interested in implementing emerging

manufacturing technology in the manufacture of their drug products. The group is focused on establishing open communication between the FDA and drug companies who want to introduce modernizing technologies. Participating in this program will grant a drug company a face-to-face meeting with the FDA as well as an onsite meeting at the participant's plant in order to show the Agency the technology in action.

Encouragingly, the Agency noted last year that aseptic innovations were one of the dominating submission types for participation in the FDA emerging technology program.

Vanrx, who has met with the ETT to discuss the company's gloveless isolator technology, reports that the team is very positive and ready to work with industry.

"Ultimately, regulators have the obligation to make sure there is a supply of safe and effective medication. They are pushing for technology advancements. Keep in mind that they see everyone's filing and everyone's plant, so they know what best-in-class looks like. Consequently, they push for advances once they see what's possible," notes Procyshyn.

RISE OF RISK-BASED APPROACH

Regulator's shifting attitude in terms of emerging technologies can partially be attributed to the adoption of a risk-based approach to manufacturing.

Adoption of a true risk-based approach to process design and process control involves drug manufacturers defining the quality attributes of their products, and how to best assure those quality attributes are established and maintained. As a result of this reverse engineering approach, manufacturers can look at each step along the way and determine the risk of failure.

Taking a risk-based approach means pharma can better articulate its processes to regulators. Having good data and analyzing that data means manufacturers can better understand — and articulate — the risk of failure.

"The idea of the risk-based approach has really driven regulators to look at things differently. With manufacturers now able to demonstrate that they understand the critical quality attributes of their products and what drives them in terms of critical process parameters, it is much easier for regulators to say with confidence that manufacturers truly understand their process," says Starkman.

Additionally, a risk-based approach encourages a more proactive view of emerging technologies, enabling drug manufacturers to take a hard look at the needs of a particular process and design technologies that meet those specific needs.

"Adoption of a true risk-based approach means manufacturers can ask themselves what equipment they really need to establish process control and then design technologies around that need — as opposed to designing a process around technologies that happen to be available," notes Baseman.

Another added bonus that could potentially come of a more risk-based approach is the introduction of new industry guidance in the area of aseptic processing.

"The guidances we have are geared toward larger scale aseptic production. There needs to be some work put into changing guidances or adding new guidances and approaches. It's important to consider that maybe the tried and true, traditional approaches aren't fitting as well with the manufacturing needs of new therapies," says Baseman.

If you were to view guidances as a compilation of best practices in the industry, it would follow that if the industry's approach to best-practice in aseptic processing was to shift, new guidance highlighting these changes should follow.

THE NEED FOR CHANGING MINDSETS

In addition to next-generation technologies, next-generation aseptic processing requires next-generation thinking. It can be said that the pharmaceutical industry is dominated by a generation of people who don't necessarily have a lot of experience managing industry-wide change. "There is a very different level of technical understanding necessary for managing change," notes Procyshyn.

"If you step backward, one of the challenges with our industry is that it's a lot slower and more glacial than people might think — but even if you look at glaciers these days, they change too. It may be a slow wave that goes through industry, but every sign is there that major changes are well underway," continues Procyshyn.

In addition, most experts in aseptic processing gained the bulk of their experience in large-scale processing, and are now being challenged to apply that knowledge to aseptic processing on a much smaller scale, notes Baseman.

"Manufacturers are going to hit this fork in the road where they either make the process fit what they know from large-scale manufacturing, or they take a fresh look. They can take the easier way, or they can take a way that will have more long-term benefits. Taking an honest, risk-based thinking approach will create a process that can give the industry high levels of assurance that is unquestioned by regulators and will allow new levels of production efficiencies," concludes Baseman.

Monitoring Plant Utilities for Operational Excellence

Pharma plants depend on plant utilities, and reliable data from wireless instrumentation can make it simpler and less costly to monitor these installations

By Michalle Adkins, Director, Life Sciences Consulting; and Wally Baker, Global Pressure Product Manager, Emerson Automation Solutions

PHARMACEUTICAL MANUFACTURING consists of a variety of processes with different equipment configurations and extensive instrumentation. But there is one common denominator from plant to plant: those processes are all supported by plant utilities to provide necessary material, control and support to the manufacturing processes. Most of the time, these utilities are taken for granted until there is a problem, but effective management can improve reliable performance and reduce costs.

For purposes of this article, we'll concentrate on three key areas:

- Steam is a source of gentle and controllable heat for some reactors, heat exchanges and other processes. Clean steam is used for sterilizing equipment.
- HVAC systems take on great importance in pharmaceutical manufacturing environments. Air handling equipment and filters are used to minimize airborne contaminants, control the temperature and humidity of the room, as well as control the differential pressure between rooms. There are important features for classified production and storage areas.
- Water is necessary in many forms, from basic potable tap water to highly treated water for injection (WFI) used as an ingredient.

These utilities must perform consistently and reliably to avoid the possibility of contamination, deviations and even quarantined inventory or lost batches. Outright failure can stop a manufacturing campaign. Even a minor disruption of flow or a temperature moving out of specification can sabotage a batch or result in approved additional processing. Such losses can be extremely expensive, however, many of these losses and problems are avoidable with effective monitoring and control. Utilities can also be expensive to operate, yet again, effective monitoring and control can be used effectively to reduce costs.

Let's examine common monitoring instrumentation for these three utilities in greater detail, keeping in mind that in each case the instruments send data to the appropriate plant personnel via the plant automation and/or asset management systems. Responsible personnel can then take the right actions to minimize or prevent losses.

STEAM

Steam is primarily a source of heat in pharmaceutical applications. One of its problematic characteristics is its perishability — when it cools, it turns back to water. It can be distributed through complex systems, but unless the flow

is constant, at some points there will be condensate, even if the pipes are insulated. Condensate eventually settles to the lowest points in the pipes and must be removed before it creates slugs of liquid that can be pushed through the system to undesirable places.

Steam traps placed at strategic locations address this and other issues by capturing and releasing liquid condensate, but not live steam. Well-maintained steam trap units can do an effective job, but since most designs depend on moving parts, they can and do fail. Traps that fail open discharge water but also create a steam leak, whereas those failing closed allows slugs of liquid to accumulate and continue to pass through the piping system.

Monitoring steam trap functionality in a pharmaceutical manufacturing environment is particularly important because:

- They are critical to basic steam management. Keeping the flow moving to where it needs to go and measuring consumption depends on maintaining clear pipes.
- SIP performance depends on achieving and maintaining minimum flow rates and temperatures throughout the entire SIP cycle.
- Cold spots in equipment caused by inadequate flow and sagging temperatures can result in incomplete sterilization.

Most plants check steam trap performance by sending maintenance technicians on rounds to verify water is being expelled at normal rates and there is no plume of live steam. More sophisticated techniques use a portable acoustic device to listen for the characteristic sounds of a properly operating mechanism.

There is a better solution: automated, continuous monitoring and wireless technologies make permanently mounted acoustic monitors practical and affordable (Figure 1). These devices have internal signal processing able to recognize the sounds produced by a properly functioning unit, and by common failure modes. They can send an alarm to the automation system if there is a failure.

Acoustic monitors are simple to mount on a working steam trap, with no shutdown required. They are internally powered and communicate using a WirelessHART network, so no cabling is necessary. They can even be moved when needed to monitor a different location, but most users leave them in one place.

Armed with this information, both overall steam system performance and maintenance operations are optimized, since only steam traps needing adjustment receive attention.

HVAC

Few industries need as reliable and controllable HVAC as pharmaceutical manufacturing.

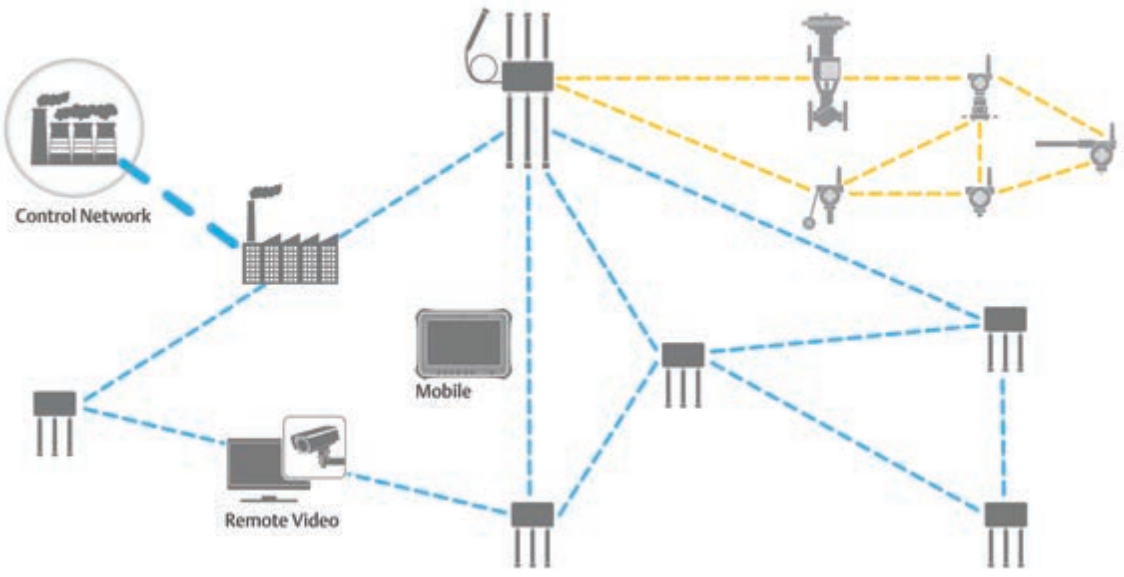
- Some product recipes call for specific ambient temperature and humidity conditions
- Effective air filtration is necessary to eliminate certain airborne contaminants
- Differential pressures between rooms are required to prevent cross-contamination and maintain room classifications for biologically active organisms, and
- Sensitive finished products may require specific storage conditions.

Courtesy of Emerson

Figure 1: Acoustic monitors can work with many different types of steam trap configurations.

HVAC systems typically depend on electric motor-driven rotating equipment, particularly compressors and blowers to chill and move air. If bearings fail on any of these pieces, some section of the process will go down. While people may be able to tolerate discomfort for a period of time, some products degrade in these circumstances. Other good manufacturing requirements may be violated if air movement through a filtration system or differential pressure between rooms cannot be maintained. These can result in quarantined or even discarded manufacturing batches.

Also as part of the HVAC system, air filtration is key to support an effective production environment. However, it can be difficult to determine when these filters need maintenance or cleaning. When the cleaning is done on a periodic schedule, premature or late filter changes can



Courtesy of Emerson

Figure 2: WirelessHART networks are self-organizing, but using network diagnostic tools allows users to monitor performance and optimize communication paths when necessary.

result due to seasonal and other changing environmental conditions. By adding a measurement from a DP pressure transmitter across the filter, flow data can be reported on a regular basis and thus appropriate and timely maintenance can be performed.

Like steam traps, rotating equipment is also monitored by technicians on rounds, and some may have portable devices to measure bearing noise, bearing temperature and vibration. Equipment mounted in out-of-the-way and inaccessible areas, as it often is, may not receive the attention it should.

Fortunately, permanently installed sensors communicating by a WirelessHART network (Figure 2) can monitor all the critical rotating equipment parameters. Changes in bearing condition and equipment vibration can warn of impending failures early enough to allow maintenance technicians to perform repairs before a full failure. With careful scheduling, disruptions to production can be avoided — preventing lost batches, ruined product or production delays waiting for equipment to start back up.

The sidebar on p.19 offers a closer look at a typical installation and how having this type of diagnostic capability can reduce costs.

WATER

Water is used in many forms in pharmaceutical manufacturing processes. Some applications need nothing more than potable water, but most need some additional treatment to remove various classes of contaminants. Filtration may be sufficient, while water for injection (WFI) requires additional processing, including reverse osmosis (RO) and/or distillation to achieve the sterility and purity needed for use as a manufacturing feedstock.

While water may be cheap, treating it to the extent necessary is not. Purification processes typically demand expensive consumables (filter cartridges, etc.) and are often energy intensive (distillation and RO). Monitoring water consumption in all its forms, along with the performance of purification equipment, is necessary to control costs and ensure everything is operating as necessary to maintain production.

Strategically placed high-precision flowmeters (Figure 3) can help compile more accurate use profiles for the range of treatment processes. This is typically the first step to controlling costs and optimizing production. Many types of flowmeters are available with the sizes and configurations needed for any manufacturing environment, including the most sterile wash-down applications. Some have native WirelessHART communication capability, and those that don't can be joined to a wireless network by adding an adapter.

Courtesy of Emerson

Figure 3: Understanding where water is being consumed is a critical first step toward improving system performance.

AIR HANDLER MONITORING AVOIDS A COSTLY PRODUCTION INTERRUPTION

One pharmaceutical producer had experienced multiple failures of air-handling equipment in several buildings on its manufacturing campus. This equipment was designed to provide clean-room quality air for a critical process, and any failure of a system during a campaign caused production interruptions, quarantined or discarded product, followed by re-cleaning the rooms to meet FDA standards. Total costs incurred for an air handler outage mid-campaign could easily reach $100,000. The company had tried to monitor equipment conditions using periodic operator inspection rounds, but failures still developed too quickly to be caught in time.

The company's reliability group worked with Emerson and its local business partner to design an air handling equipment health monitoring system, including bearing temperature and equipment vibration sensors for critical motors and fans. These devices were set up to communicate over a WirelessHART network. A basic asset management tool collected the data and analyzed it. This included a program to send alarms to the automation system when any critical parameter began to move out of a safe operating range.

The specialized manufacturing installations in the facility have two air handler units, one each for supply and return. They are belt-driven blowers, so monitors were installed on the two main bearings of the motors and blowers along with vibration monitors. The sensors communicate with Emerson's AMS 9420 wireless vibration transmitter that also monitors temperature via WirelessHART.

Early in the deployment program, the system detected a sustained spike in the bearing temperature of one unit during a production run. This information suggested a failure was imminent, which would have interrupted the run and caused product loss and associated cleanup. Since the operators were warned, they were able to reduce motor speed while still maintaining the minimum airflow requirement. After the batch was completed, repairs were performed.

While the diagnostic system cost $25,000 to install, the fact that it helped avoid a $100,000 cost allowed it to pay for itself, even before the entire project was complete.

PERVASIVE SENSING

The common element of all the examples discussed so far is the addition of sensors to gather information necessary to improve performance, increase reliability and reduce operating costs. Using traditional wired methods, costs can be high for adding a sensor or instrument and connecting it to an automation system via cables. This is particularly true when the sensor must be placed in a remote area, as is often the case with steam traps and HVAC equipment.

Wireless technologies, such as WirelessHART, have been proven in countless industrial applications to be reliable and easy to implement:

- Installation costs are much lower since cabling is not necessary
- Self-contained power sources can operate for years without replacement
- Many equipment monitoring and diagnostic devices require no process interruption for installation, and
- Wireless device-level networks are self-organizing (Figure 2) and require little manual setup.

WirelessHART networks can also be used with wireless devices on production equipment. In fact, facilities looking at deploying steam trap monitors may discover they already have wireless networks supporting other manufacturing areas. These new devices can be added to those existing networks, sometimes without any increase in infrastructure such as adding additional wireless gateways.

Information generated by new instruments added to existing automation systems, such as adding a flowmeter to a WFI distillation unit, can usually be integrated with the system without too much difficulty. Deploying a completely new system, such as adding steam trap monitoring where none has existed previously, may be more involved. Even so, there are many software platforms available for device diagnostic and asset management programs that can integrate easily with a WirelessHART network, gathering valuable information from a variety of equipment monitoring types.

Data from field instruments can provide the information needed to support decision making by plant operators, engineers and technicians. For pharmaceutical manufacturers, the ability to improve production while reducing operating costs provides a compelling reason to explore wireless instrumentation.

Driving Bioprocessing Efficiency

Continuous manufacturing, single-use systems and disposables are pushing industry boundaries

By Kathleen A. Estes, Ph.D., Director of Research Communications;
and Eric Langer, President and Managing Partner, BioPlan Associates

THE SINGLE most important biomanufacturing trend in recent years is manufacturing efficiency. Nearly 20 percent of the industry believes that it needs to increase efforts to produce more, do so more quickly, and with fewer resources. This conclusion, drawn from BioPlan Associates' *14th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production*[1], shows the bioprocessing industry continues to express concerns about its ability to optimize operations.

How the industry invests in improvements today will define the strategic direction bioprocessing takes for years to come. In our study, we identified the most important areas in which biomanufacturers expect their suppliers to be focusing their new product development efforts. The top five of 13 "upstream" bioprocessing areas of interest are shown in Exhibit 1. These include single-use devices and continuous bioprocessing innovations. Many of the remaining upstream bioprocessing areas also involved single-use devices as well.

Demands for "downstream" innovations mirror the upstream general areas, and include single-use purification (noted by nearly 36 percent), protein-A alternatives and multiple continuous bioprocessing options. In addition, other, general areas demanded for bioprocessing innovation include '"automation, instrumentation" (indicated by nearly 22 percent) and "analytical assays."

This granularity focused on interest in future innovation and provides a clear perspective of the factors driving needs for overall productivity and efficiency. These are the factors most likely to provide the forward momentum the industry needs to improve efficiency and meet its productivity goals.

The major factors that will continue to advance biopharmaceutical manufacturing efficiency include continuous bioprocessing and single-use systems implementation and integration. Implementing such manufacturing changes tend to require long-term strategic decisions. In a regulated environment, such changes are not done quickly, and introduction of new innovations is not straightforward in this industry due to regulatory issues and long product development time. Regardless, biomanufacturers are willing to pay for innovation to remain competitive, resulting in a continued demand for better ways to cut down time to market and streamlining the overall bioprocessing.

CONTINUOUS BIOPROCESSING

The migration toward continuous bioprocessing has been a natural progression following other major

manufacturing industries like chemical and steel. Traditionally, the industry has operated using batch processing modalities where operations are segregated spatially and temporally. Operating in this way for decades, the bioprocessing industry has relied on capital and operational expenditure to allow for growth and improvements while not significantly changing the process methodology.

In our report, 26.5 percent of respondents stated that the top new product development area of interest for biomanufacturers and CMOs is continuous bioprocessing-upstream, but 33.8 percent noted they need continuous downstream innovation. Continuous bioprocessing remains a key area suppliers are expected to focus their developmental efforts.

Continuous processing is also a logical next step for biopharmaceutical manufacturing. It reduces facility downtime, overall costs, equipment size, raw material need and the overall timeline. While continuous processing may not always make sense very early in a product's development, it can become more attractive once the long-term success of the product and demand for further manufacturing are known.

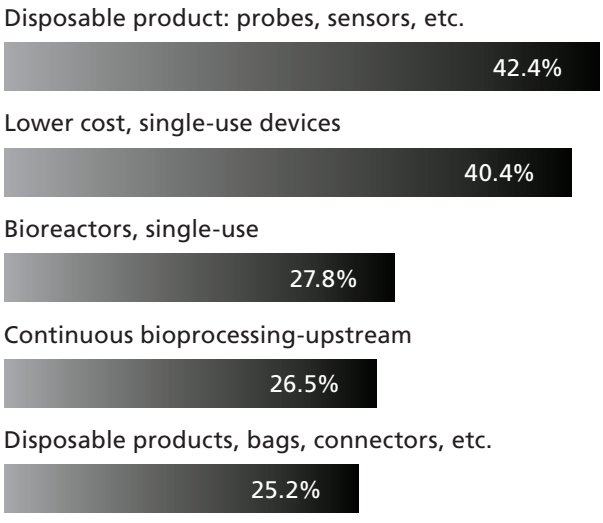
Implementation of perfusion technologies, which has been limited due to the overall complexity, has begun to pave the way for continuous processing in upstream manufacturing. The early adopters of continuous processing tend to be those who have experience with perfusion technology. These manufacturers have worked through some of the complexities. Recently, continuous processing is becoming more attractive due to the reduction in processing costs and the reduced scale needed. This is particularly attractive where smaller bioreactors and smaller downstream equipment are all that is needed.

One of the key challenges of continuous processing is the assurance that material removed from the bioreactor at different times is of consistent quality. Companies with experience in perfusion technology have demonstrated the steady-state capabilities of a perfusion process and the potential of a more homogenous product. This will be achieved through more real time process monitoring like biomass sensors, in-line metabolite analyzers and pCO2 sensors. Further gains in efficiencies will be seen from increased real-time analytical automation.

Looking forward, how the biomanufacturing industry handles downstream continuous processing is where the focus will lie. Perfusion processes have been well established for continuous upstream manufacturing, so the real leap for the industry will happen in downstream processing. While there are several hurdles to jump through, one example is continuous processing of the bioreactor harvest across the capture step. Reduction of harvest hold time will help reduce a major area of concern for product instability from chemical, physical or enzymatic degradation. It would also increase efficiencies as it simply reduces overall processing time.

Exhibit 1

Selected Upstream New Product Development Areas of Interest (Top areas suppliers should focus their development efforts on)



Adoption of continuous processing will occur, but the time frame and extent are difficult to predict. The interest is great, and many in the industry are evaluating how to implement and be successful with continuous processing. Advances in disposables, automation, process evaluation and an increasing need for small batch processing will all push the industry toward continuous processing that will eventually result in lower costs and increased efficiency. However, a major roadblock will be the perceived complexity of continuous operations. For example, nearly 43 percent of the industry still sees continuous bioprocessing (especially perfusion) to be defined as a "much bigger concern" regarding process complexity.

SINGLE-USE SYSTEMS AND DISPOSABLES

The use of disposable devices in the biopharmaceutical manufacturing sector has been increasing for over a decade, and is likely to continue in that trajectory. Single-use systems (SUS) provide a step in the evolution of biomanufacturing technologies.

For some bioprocesses, the push for reduced costs, speed to market and product changeover has resulted in significant implementation of disposable technology. For example, disposable bioreactors have allowed for a more rapid turnaround time with fed-batch processes and therefore have reduced the downtime within a manufacturing suite. They increase efficiency by reducing the risk of cross contamination and minimizing the need for extensive infrastructure around cleaning and autoclaving.

Even more basic operations like media and buffer prep are benefiting from innovations including new powder containment devices. These and other applications are simplifying bioprocessing, reducing staffing requirements and eliminating time-consuming operations like cleaning and validation.

The adoption of SUS and devices has grown immensely, with certain applications almost fully permeating earlier-stage manufacturing. Biomanufacturers using SUS are using disposable devices in multiple applications. According to the Annual Report, nearly nine out of 10 disposable users are implementing a variety of SUS applications from basic connectors and clamps, to sampling systems for scale-up and clinical productions, to commercial bioreactors. Although the adoption rate is lower for commercial production, most disposable users are relying on those applications and others for clinical bioprocessing. And these will increasingly be used in commercial manufacturing as device scales increase.

In our study, we asked biomanufacturers to predict their adoption of SUS devices. Two-thirds (66 percent) indicated that within five years, they expect more than half their GMP biomanufacturing will be "substantially" done using single-use devices. And in Europe, that percentage is nearing three-quarters.

Separately, we find that leading the charge to single-use applications are contract manufacturing organizations. CMOs will likely benefit most from the reduction of cross-contamination and the rapid change-over times that SUS can provide. Indeed, CMOs have adopted nearly all SUS areas at a higher rate with the exception of bioreactor usage. Altogether, respondents estimated almost 40 percent of their clinical production operations are single-use, with upstream being the highest. While estimates are lower for commercial production, respondents still estimated that almost one-fifth of their upstream and downstream production operations are single-use systems.

Despite the clear interest in single-use, innovation in disposables is likely to move slowly. Current manufacturers and vendors are inhibited in upgrading to new single-use product lines once they have established a manufacturing system. This is due to regulatory issues, as well as the expense, work and testing to make sure it works in specific applications, modification of regulatory filings, SOPs, substantial training and potentially requiring another round of validation testing. Highly innovative products are likely to come from small companies or new major corporate entrants.

Exhibit 2

Single-use / Disposable Device Adoption

Within five years at least 50% of my own facility's cGMP clinical/commercial unit operations will be substantially done using single-use (disposable) devices

Making better single-use devices involves developing newer, technically superior materials. In particular, what's needed are new and improved plastics that enable major design innovations, and offer better, stronger plastic films that are less reactive and that can be scaled-up from bench-scale. These innovations might involve homogenous polymers, or might even unitary molded, solid, structurally self-supporting plastic bioreactors. There is also very high interest in improvements in single-use bioprocessing sensors and probes. A few single-use sensors that are robust enough exist, but the sensors are restricted to a limited set of analytes.

Innovations in even the most common tubing and connectors are likely to be seen. These may include PFA and other homofluoropolymer tubing, fluoropolymer-lined tubing and new thermoplastics blended tubing. Many of these new tubing options, as well as improvements in connectors, will provide improved performance, last longer, result in less leaching from the plastics and perhaps be less costly.

SUMMARY

In moving the industry toward higher efficiencies and lower costs, integrating continuous bioprocessing and single-use technologies will promote reduction of scale, building in quality, and reducing cost of goods, in other words, increasing efficiency in the biopharmaceutical industry.

The implementation of disposable technologies, such as mixers for making and storing media, allows for a disposable means of continuous medium feed to a perfusion bioreactor. The stainless-steel bioreactors that have dominated the industry are beginning to be replaced by disposable bioreactor technology, which has seen a steady increase in adoption over the past few years. New facilities are being built based on disposable bioreactors, including in rapidly emerging regions such as China[2,3] and their output will be comparable, yet manufacturing on much smaller scales than traditional stainless bioreactors.

Process modernization, reduced costs, speed to market and product changeover have resulted in significant implementation of disposable technology. The use of disposable technology has changed the biopharmaceutical manufacturing landscape. Incorporating these technologies into the implementation of continuous bioprocessing will continue to advance the industry to be more efficient, ultimately driving innovation forward.

REFERENCES

[1] *14th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production, BioPlan Associates, Inc. April 2017, www.bioplanassociates.com*

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[3] *China's Advances in Global Biopharma and Bioprocessing: A 10-year projection in need for innovation and quality improvements; January 2017, White Paper Survey of 50 Chinese Biopharmaceutical Executives, BioPlan Associates, Inc. Rockville MD, www.bioplanassociates.com*

SURVEY METHODOLOGY

The 2017 14th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production yields a composite view and trend analysis from 227 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations (CMOs) in 25 countries. The methodology also included more than 131 direct suppliers of materials, services and equipment to this industry. For a copy of the 14th Annual Survey Summary, please email Donnie E. Gillespie, dgillespie@bioplanassociates.com.

Making the Move

A best practice approach to migrating to electronic batch records (EBRs) in pharmaceutical manufacturing requires MES technology

By Christian Fortunel, Vice President, LZ Lifescience

DUE TO a number of challenges associated with the use of paper-based systems to manage and record activities during pharmaceutical manufacturing, more and more companies are adopting MES (manufacturing execution systems) technology. With drawbacks of paper records including lack of information visibility, risk of error, downtime and loss of productivity, the drivers for change are clear. MES technology can help to eliminate many of these issues, ensuring that pharma manufacturers remain compliant and manufacture products "right first time."

REDUCING REGULATORY RISKS

With paper-based records sometimes leading to documentation errors and non-compliance issues, the fact that EBR systems can help to address these is often an important factor in the decision to implement such technology. In fact, a recent LZ Lifescience survey found that 90 percent of those in the life science sector state that they spend a significant amount of time on compliance issues for regulatory purposes. Therefore, systems that can reduce the risk of errors and non-compliance are extremely valuable.

Furthermore, when using paper-based systems, potential issues are not always identified and recorded as they happen, meaning there is a delay in resolving them. This can cause greater complications down the line such as higher rejection rates for batches. There is also a time lag between using materials and updating the system, meaning the inventory is not always accurate.

Electronic systems can help with a number of regulatory factors, for example, compiling a summary of product characteristics (SPC), which is required within the European Commission before any medicinal product is authorized for marketing. Good manufacturing practice (GMP) data can also be integrated into a single system, ensuring the highest quality manufacture and minimizing risks that cannot be eliminated through testing the final product.

TRANSPARENT INFORMATION SYSTEMS

The visibility of information is critical during pharmaceutical manufacturing. In traditional paper-based systems, data can only be located manually and, in order for it to be analyzed, must be transcribed into a system. Due to the lengthy process, this means the information is sometimes out of date by the time it has been extracted. EBRs eliminate these issues, therefore keeping information relevant, as well as reducing the risk of any human errors during input.

Another benefit of migrating to EBRs is the ability to view data in real-time. This feature allows for issues to be picked up as they are happening, alerting teams to react promptly and potentially avoid disruption or downtime altogether.

In addition, real-time data capture also assists with regulatory compliance. Many pharmaceutical manufacturers use enterprise resource planning (ERP) systems to manage the supply chain and automation systems to control their manufacturing process. MES technology can bridge the gap between these two systems, ensuring information flows smoothly around the facility, assisting in the production of quality products, manufactured "right first time."

LOW IMPLEMENTATION COSTS

In addition to the numerous operational benefits, MES solutions have the potential to generate a return on investment within just 12 to 18 months due to the low implementation costs provided by modular, flexible systems. By eliminating errors, allowing efficient and accurate data movement and improving regulatory compliance, these technologies have been shown to improve productivity by as much as 25 percent. This more than justifies the initial cost and operational changes that undoubtedly occur while the technology is implemented.

BEST PRACTICE APPROACH TO IMPLEMENTATION

Before starting the process of migrating from paper-based records to EBRs, pharmaceutical manufacturers must first establish solid project foundations. The deployment of an electronic system will affect all aspects of the business, not just the production line itself. As a result, the company must consider the challenges and benefits of introducing new technology and receive project buy-in from all levels of the business, but most importantly upper management, operations and quality.

However, establishing a business case is just the first step in the process. Once the need for the transition to MES and EBRs has been justified, it is important to review best practice for both planning and implementation, allowing the creation of a project plan.

Electronic systems have potential to impact planning, execution, control and documentation functions, as well as disrupting organizational structures, job roles and staff training. A key factor in ensuring success is therefore identifying a project champion who will drive the project forward. This person can ensure project plans are in place, take responsibility for briefing staff on new processes and delegate the various tasks that will need to be carried out.

Creating a project charter will allow you to establish accountability. Within this charter, clear goals should also be put in place to evaluate success. You must identify the key performance indicators (KPIs), which might include increasing productivity (increasing asset utilization) or improving regulatory compliance (decreasing the number of deviations).

As the project is likely to affect the whole organization, an effective way to ensure that everyone in the company is aligned is through a concept of operations (COO) document. This will outline daily operations plans, identify the benefits and explain the role of each organizational department for the duration of the implementation process and once the project goes live. The COO and project charter are critical in ensuring that the organization is prepared for the upcoming changes and the transition runs smoothly.

Once plans are in place, you can begin to initiate the implementation. This process first involves an analysis phase where existing business processes are converted into workflows, software functions and configurations. The software must then be qualified in accordance with established industry standards, such as the GAMP-5 validation model.

Following this, other key activities need to be performed to migrate from paper records to electronic reporting. This includes converting existing paper records into electronic forms and updating standard operating procedures (SOPs) to reflect the fact that paper systems are no longer valid. This is also where decisions must be made on which information should be included in SOPs and what is more appropriate for batch records. EBRs would include GMP and patient-related data, whereas SOPs would include information for operators and practical guides.

Once you are ready to go live, master and inventory data needs to be loaded into the production system. This involves transferring production records and the definition of material items from the quality system so that they can be properly approved.

The GMP data (such as Critical Process Parameters and Critical Quality Attributes) is of utmost importance here, bringing a number of benefits. First, it ensures that products are consistently produced to stringent quality standards, supporting the concept of "right first time" production. Additionally, inputting GMP data allows for the system to highlight any potential risks and issues that may occur during production.

It is quite normal to expect lower production output when the system first becomes operational as the company is still adapting to the new operating procedures. However, you can plan for this at the start of the project by perhaps increasing production before the changeover and ensuring customer expectations during this time are managed. You should constantly review and evaluate the system performance, particularly during the first six months. Review the actual performance against the KPIs and put a plan in place to resolve any potential issues. Once the system has been deployed, you should also consider and take advantage of new features, software upgrades and deploy new functionality. This will allow your system to remain relevant and efficient.

Although the process of migrating to MES solutions and EBRs has the potential to be challenging, with correct planning it need not be daunting. Essential drivers such as regulatory compliance, improved data accuracy and greater information visibility form an effective business case to make the transition. However, in order to ensure project success, each department within a pharmaceutical manufacturing organization must be engaged and on-board with the processes. Only then can you realize the high rate of "right first time" production that can be attributed to electronic data management and reporting.

Q&A: 3D Technology Emerges

With the FDA acknowledging 3D printing as an important emerging technology in the pharmaceutical industry, David Hess, Technical Solutions Consultant at Sparta Systems, explores the impact, benefits and risks of 3D drug printing

HOW WILL 3D PRINTING IMPACT KEY PLAYERS IN THE PHARMA SUPPLY CHAIN (SUPPLIERS, MANUFACTURERS, DISTRIBUTORS, ETC.)?

3D printing has a true potential to disrupt the generic pharmaceutical supply chain, giving local pharmacies and hospitals the ability to create their own medicines. API suppliers could ship directly to those endpoints, shipping to regions where their consumers will have their drugs rendered. Hospitals or large regional pharmacies could simplify their storage into larger containers for filler and common ingredients like acetaminophen, with smaller containers for less common APIs.

Contract manufacturers could diversify their customers' utilization of production lines, providing smaller batch runs a more cost-effective solution than the traditional molded offering. For a slimmed down pharmaceutical startup, those savings can be directed into their clinical trial efforts.

While it's doubtful that consumers will have in-home printers, it is feasible that their mainstream corner pharmacies will adopt the technology.

WHAT ARE THE BENEFITS OF 3D PRINTING DRUGS VS. USING TRADITIONAL MOLDS?

3D printing in general allows for several key benefits: customization in scale and density/infill, internal composition and rapid prototyping. Each of these transitions directly to pharmaceutical creation.

Being able to generate a dosing specific to a patient, with a certain subset of each compound in the drug, assembled for a precise time-release schedule means better treatment for a patient. Imagine a drug with a monitoring device at the core, able to transmit a patient's vitals immediately post-absorption.

Rapid prototyping allows new mixtures to be tested on an extremely small batch, without the need to place an order with a CMO or set up a full production run. Not having to buy time on a 24/7 CMO line translates into direct savings that can be spent elsewhere.

WHAT ARE THE RISKS OF 3D PRINTING DRUGS FOR PHARMA MANUFACTURERS SPECIFICALLY?

As with any 3D print, even under perfect conditions, the opportunities to deviate from spec are infinite. Calibration and preventive maintenance are already painstaking efforts for pharmaceutical manufacturers, with teams assembled to follow consistently scrutinized SOPs and work instructions for every piece of equipment on their production line; this is just as evident with a printing device, where things like bed leveling, material extrusion and retraction, surface adhesion and any number of other factors are accounted for.

Physical production complications aside, there are a number of other risk factors that may lose visibility in the transition to 3D printing.

- Was the printer sanitized properly after the last batch was printed? There would be serious adverse events if testosterone therapy medication was produced prior to prenatal pills, for example.
- Was the batch created with a single lot of API, or did the print run out halfway through, requiring a refill from a different supplier's stock?
- Did the printer operate at temperatures above the permissible limits of the ingredients?

Inconsistency in finished goods is an easy target for 483s, so do not expect larger, risk-averse, publicly traded corporations to pick up the technology while unproven.

PHARMACEUTICAL MANUFACTURERS WILL NEED TO STEP UP THEIR GAME WITH REGARD TO AUTOMATIC DETECTION OF DEVIATIONS.

— DAVID HESS

For smaller firms, balancing the budget may mean taking on a bit more risk.

HOW CAN PHARMA MANUFACTURERS ENSURE QUALITY WHEN LEVERAGING 3D PRINTING TECHNOLOGIES?

Pharmaceutical manufacturers will need to step up their game with regard to automatic detection of deviations; instead of random sampling, each pill can be measured for weight, size, and appearance during the printing process.

If drug production is more distributed, the traditional large manufacturer model goes out the window — each printing group would need specifications from their suppliers on how best to assemble the medication.

Regardless of the method used for manufacturing these medications, manufacturers should employ Good Manufacturing Practices, with full traceability in a 21 CFR Part 11 Compliant quality management system.

HOW WILL 3D PRINTING DRUGS IMPACT DRUG DELIVERY?

Aprecia's ZipDose is a huge leap in rapid release medication. Have you ever tried to get a toddler to keep a dissolvable medicine in their mouth without chewing or swallowing it? Being able to give them their dose in under 10 seconds means closer adherence to a physician's treatment plan.

We will likely see that technology extend to any number of pain management drugs, where instant relief is typically only available intravenously. Orally administered naloxone to counter heroin overdoses could find its way into the kits of EMS staff the world over.

WHAT WOULD YOU EXPECT TO SEE IN A FDA DRAFT GUIDANCE ON ADDITIVE MANUFACTURING FOR PHARMACEUTICALS?

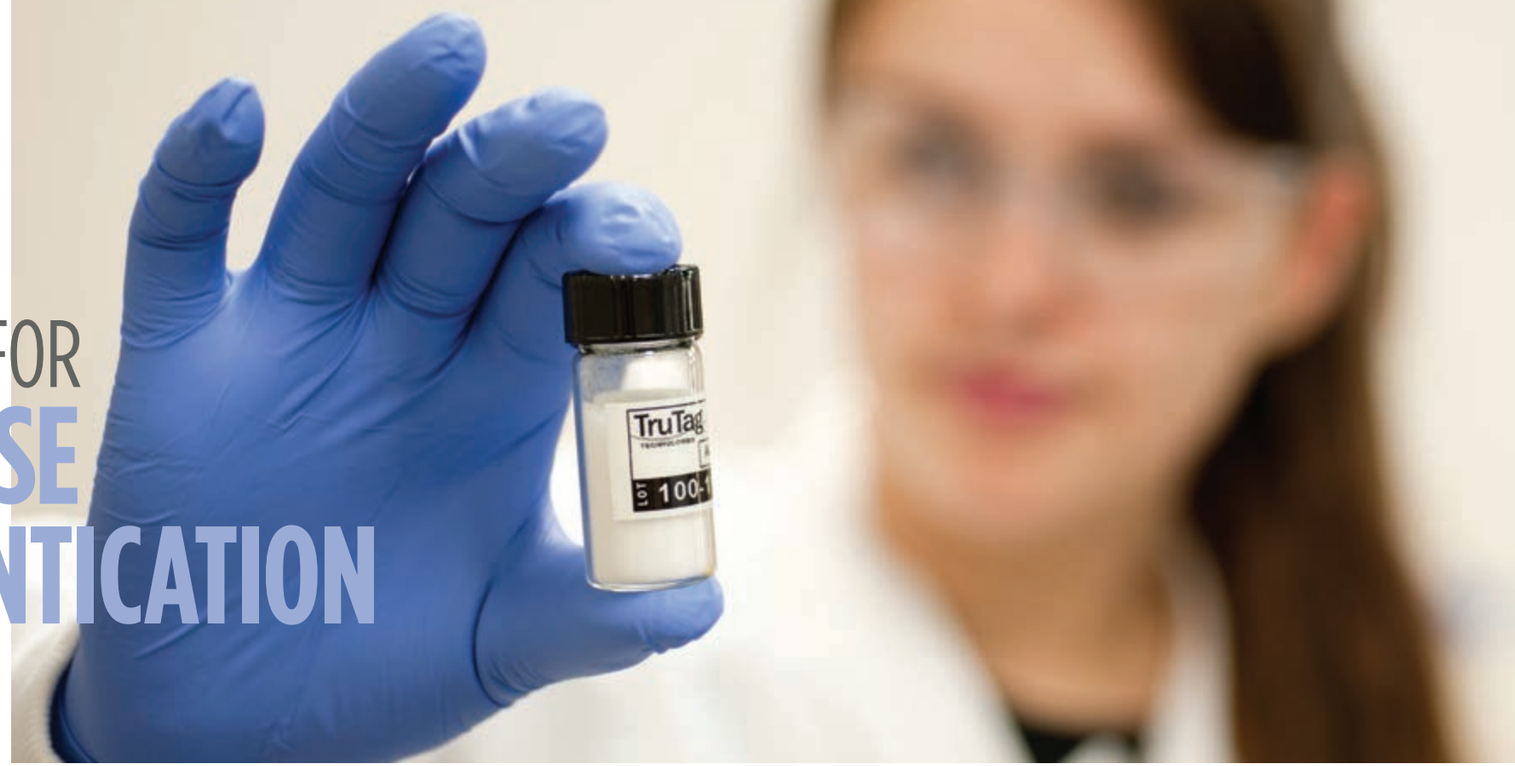
Given the variance in styles of additive manufacturing, expect a greater level of scrutiny regarding machine calibration/preventive maintenance.

The FDA may require manufacturers to fulfill specific pill tests:

- Variable time release schedules of the same size tablet
- Different density at the same size
- Same density at variable size
- Pausing a printing run, restarting the run and comparing those pills with normal batches

The FDA should specify which entities maintain the responsibility for adverse event reporting as manufacturing is shifted. Third-party additive manufacturing outside of major manufacturing is comparable to that of compounding facilities. In 2012 we saw a fungal meningitis outbreak stem from the New England Compounding Center's packaging of methylprednisolone. The incident killed 64 people, resulting in 2013's Drug Quality and Security Act, which added provisions for compounding pharmacies and supply chain security. Based on that act, a pharmacist is still required to oversee the production of those medications outside of a manufacturer's site. The push toward printed pills will need some federal oversight, lest we risk more lives unnecessarily.

THE CASE FOR ON-DOSE AUTHENTICATION



A microtag is an advanced, on-dose solution that can be safely mixed into a drug product, and when its presence is detected in the sample, it confirms authenticity.

Using inert microtags at the drug dosage level can provide both security and business intelligence

By Peter Wong, Chief Operating Officer, TruTag Technologies Inc.

PRODUCT SECURITY is a vital consideration for any pharmaceutical company due to the life-critical nature of drug products. There is much attention in the news media about the problem of fake medicine with alarming statistics about the estimated size of the counterfeit drug trade. However, the cost to pharmaceutical drugmakers of unauthorized and illegal drug diversion in both financial and human terms is potentially an even larger problem.

After the issuance of the U.S. Food and Drug Administration's PCID Guidance for "in-dose or on-dose" markers or tracers for use as authentication measures, the door has been opened for the industry to implement "on-board" physical or chemical identifiers that can help address the challenges of drug product counterfeiting and diversion. More specifically, brand owners can now use inert microtags or markers at the drug dosage level during the manufacturing process. These solutions can sometimes provide both security and business intelligence to allow drug companies to protect lives, enhance their bottom line, and maintain a "final audit" marker in the product, separate from packaging or labels.

HOW DOES PRODUCT DIVERSION OCCUR?

There are many ways that drug product is diverted illegally or without authorization. Product diversion is also commonly known as "pricing arbitrage," where operators will acquire legitimate product in a lower priced channel and resell it into a higher priced one, sometimes repackaged, sometimes not. The cost to brand owners of unauthorized diversion is massive, particularly since revenue lost to resellers drops right out of the bottom line. The manufacturer — in most cases, the innovator company that developed the drug — has already incurred the full cost of goods sold but does not bank the highest possible price for the product when the product has been arbitraged. There are two major types of pricing arbitrage diversion:

a) *Channel diversion*, where product is improperly taken from a lower price-point channel and sold into a higher-priced channel, with these diverters arbitraging the difference.
b) *Country diversion* occurs when a product is diverted from a lower price-point territory or country for resale in a higher price-point territory or country.

Both kinds of this pricing arbitrage diversion adversely impact the bottom line of pharma companies. But to go further, pricing arbitrage practices may even create other liabilities and patient risks if the diverted product is relabeled incorrectly, possibly misrepresenting instructions for use, or is subjected to improper handling and storage conditions.

This may occur when an intermediary sub-distributor simply acquires the product intended for sale (and often subject to strict contract terms that limit such sales) in the lower priced or discounted channel, then resells it for a higher price in a non-discounted channel. High-priced, patented drugs are often sold in countries with less developed health care systems at significantly lower prices. While the reasons for these pricing differences are complex and depend in part on global differences in intellectual property protections, healthcare reimbursement systems, political considerations and liability laws, huge opportunities exist to arbitrage this pricing gap. In Europe, repackaging and parallel importing is a legal practice, and allows for companies to take financial advantage of the pricing difference found between a market like Turkey versus the United Kingdom. However, this pricing arbitrage is not only a financial risk, it can compromise patient safety as well. "Even authentic drugs that have been improperly diverted due to price arbitrage can create health concerns if the diverted product is not properly stored or handled, or if the packaging is not in the correct language, which can lead to over-dosing," said Ron Guido, formerly the vice president of Global Brand Protection and Supply Chain Integrity for Johnson & Johnson.

Another form of product diversion is the unauthorized, out-of-scope and sometimes fraudulent return of product during the euphemistically named "reverse distribution" or product returns stage. This activity is a major source of what is known as "revenue leakage" and has a substantial financial impact on pharma companies. Most drug manufacturers have quite liberal returns practices, but they lack the tools necessary to confirm whether returned material is actually authorized and within scope of the returns policy.

Product received by a drugmaker's returns processing company is often in damaged or obliterated packaging, or even not in original packaging at all. This makes it extremely difficult for the returns processor to determine whether such product is out of scope and therefore not eligible for refunds. It is certainly possible to issue credit for product that is fake, stolen, diverted or improperly relabeled. Now a brand protection consultant to health care companies, Guido has seen these challenges arise across the industry.

"We saw situations where authentic pill bottles with genuine labeling were filled with fake material and then re-sealed and returned for credit," said Guido. Currently, returns monitoring practices often do not involve the checking of the contents of containers but instead simply authenticate by weight and a cursory check of outer markings.

Finally, "street" diversion is a dangerous form of drug diversion when prescription medication — usually controlled substances like powerful pain killers — get diverted to users and buyers without appropriate controls, instructions or prescriptions. The demand for this kind of diversion is due to the highly addictive nature of the drugs and has resulted in an epidemic of abuse and overdosing with often fatal consequences.

ADDRESSING PRODUCT DIVERSION

The current focus on drug product supply chain security in the United States can be found in the Drug Supply Chain Security Act, or DSCSA. The DSCSA is part of the Drug Quality Safety Act signed into law on Nov. 27, 2013, and is intended to produce end-to-end product traceability throughout the entire distribution supply chain. The intent behind the DSCSA is that by coordinating transaction records with pharmaceutical

distributors and retailers, authorized supply chain workers can theoretically follow a drug's chain of custody to help flag the source of fake or sub-standard drugs entering the chain. The DSCSA is an important step forward in strengthening the total drug supply chain. However, a major shortcoming of this legislation is that all of the traceability and security measures are focused at the packaging level.

"We have seen many examples of serialized bar codes being re-imaged from genuine packages and applied to fake packages," said Guido. "In some instances, 'fake' authenticating features such as rogue phone numbers, websites and holograms are added to packages to fool inspectors, traders and even patients."

And even if a package is authentic, without verifying the actual drug product directly, no one can determine absolutely whether the medicine inside is real or fake. And even if real, whether it has been improperly diverted, or if is it truly the right product in the right place at the right time?

COMPLEMENTING PACKAGING SECURITY EFFORTS

It is clear that to supplement all of the investment across the pharmaceutical industry in packaging security and traceability and fight the challenge of product diversion, on-dose authentication measures are needed for a complete product security program.

There are a number of technologies that can be applied at the dosage level to help demonstrate that a drug product is the real thing, including the following:

- Pearlescent coatings that are difficult to mimic so that counterfeiters cannot replicate the real product easily.
- Chemical or molecular markers where special ingredients are added to the drug formulation. Then, a quick chemical test that destroys the sample can confirm whether that special ingredient can be found.
- Chemical analysis, such as Raman or Near-Infra Red spectroscopy, to spectrally analyze the chemical make-up of the sample and compares the resulting chemical fingerprint against a library of fingerprints of the authentic formulation. A match would confirm that the sample's formulation mimics the target product.

MICROTAGS AND ON-DOSE FEATURES

An advanced, on-dose solution is the microtag. A microtag is a microscopic particle that can be safely mixed into a drug product, and when its presence is detected in the sample, it confirms authenticity. The most useful microtags are those that can carry information or provide a wide variety of differentiated identification that will allow it to distinguish between different codes so variations of business intelligence can reside on multiple drug products. This ability to have a multiplicity of identification numbers or fingerprints is what allows it to address the product diversion problem.

There are numerous packaging security features to assist a trained user in distinguishing between a real and a fake product, sometimes even without packaging.

Diversion is a more complex and challenging problem than counterfeiting. There are numerous packaging security features to assist a trained user in distinguishing between a real and a fake product, sometimes even without packaging. But for diversion, the sample product in question is the real thing, but may be in the wrong place at the wrong time. A pill sold in India for one dollar may be identical in look and substance to the pill sold in the United States for several hundred dollars, and it is that equivalence that makes diversion so appealing to both diverters and consumers. If a microtag could act like a bar code and provide a link to the product intelligence that confirms where that product was made, when it was made, when it expires and what territory it was sold into, a drugmaker could more easily determine if that product had been improperly diverted from the channel or location it was intended.

TruTag Technologies, for example, offers an advanced microtag consisting of silica micro particles that can be safely added to most oral solid dosage form drugs without modifying the manufacturing process already in place. Once included in the medicine itself, the taggant will last indefinitely through the product's lifecycle and can be scanned using one of TruTag's portable detectors.

In order to address the enormous challenge of product diversion, pharmaceutical companies should be incorporating on-dose authentication as part of a complete product and supply chain security program. Microtags can offer the security and business intelligence to fully complement packaging security and traceability systems.

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TRENDS IN Excipient Demand

Pharma manufacturers are seeking out innovative excipients that address bioequivalence development and solubility challenges, while enhancing formulation

By Nigel Walker, Managing Director, That's Nice LLC/Nice Insight

EXCIPIENTS PLAY a key role in helping pharmaceutical manufacturers serve patients better through improved compliance and efficacy of treatment. They also help reduce developmental costs and provide opportunities to differentiate products through new modes of drug delivery.

Experts identify several trends driving excipient demand: solubility and bioavailability challenges, as well as the desire to increase the lifecycle of a drug, improve manufacturing efficiency and address the growing bioequivalence market.

Development of new treatments for chronic diseases, increased access to medication through generic drug production, increased research and development spending, growing competition, and new technologies are driving these trends, says Bosh Chattopadhyay, business director, BASF Pharma Solutions. As a result, he says there is a desire to:

- Provide access to new treatments and improve the efficacy of new chemical entities (NCEs), which are typically less soluble;
- Address specific needs for pediatrics and geriatrics – taste masking, ease to swallow, alternative dosage forms (orally disintegrating tablets);
- Improve compliance – controlled release to reduce frequency of administration and extend duration;
- Provide different product options – alternative routes of delivery/dosage forms;
- Improve ease-of-use – no need to take with food / water, no need for refrigeration, lower risk of overdose due to consumption of alcoholic beverages; and
- Improve production technologies and realize more efficient and effective processing.

SOLUBILITY AND TARGETED DELIVERY

The solubility and permeability of many new chemical entities — which are very often highly potent — is a key issue for the development of new drug formulations. As a result, the industry is in urgent need of new approaches to drug development and tailored drug delivery. The 2017 Nice Insight Pharmaceutical Excipients Survey indicates that solubilizers — commonly used to improve the

solubilization of hydrophobic substances and to increase bioavailability — experienced a 49 percent increased use over the last year among survey respondents.

"In oral drug delivery, we see an increasing interest in excipients and formulation techniques to enhance drug solubility and improve the bioavailability," says Dr. Thomas Riermeier, vice president, Pharma Polymers & Services, Evonik Health Care. "The industry is adopting more innovative formulation technologies that appropriately target the improvement of the transcellular and paracellular uptake of both small molecules and biologics requiring new types of excipients, like permeation/transfection enhancers, enzyme inhibitors and polymers with advanced functionalities."

Riermeier says solid dispersions and solid solutions, combined with targeted drug delivery, are the future for oral drug delivery. "If you have a BCS class IV API with poor solubility and poor permeation, increasing the solubility alone may not solve all your problems, but delivering the now soluble drug to the right area of the GI tract may be able to boost bioavailability. Hence, methods for absorption window mapping gain importance in formulation development," he says.

As an example, Riermeier says that Evonik's functional polymer excipients, EUDRAGIT, can significantly increase bioavailability through delivering the active to the appropriate area of the GI tract where absorption is the highest or to the site of action where the active is needed.

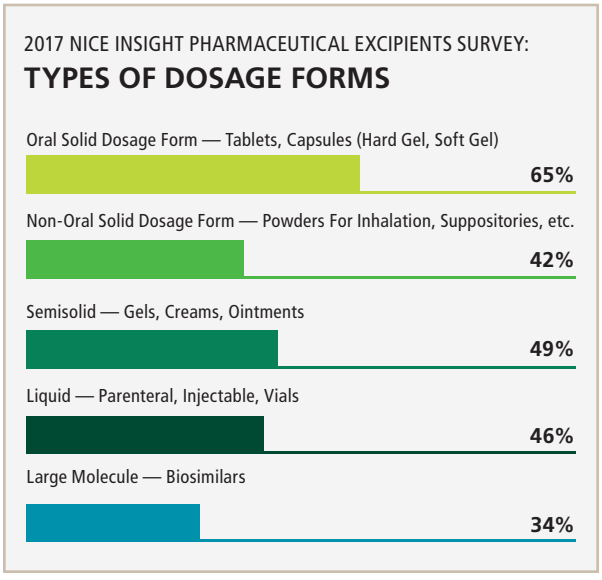
Chattopadhyay says that leveraging the characteristics of excipients to modify the release profile of a drug can increase the lifecycle of that drug.

"In parenteral drug delivery, there is a greater focus on developing more advanced complex formulations such as liposomes and polymer-based microparticles, allowing for specific drug targeting or extended release, where a single injection can provide the dose for a week, a month or even longer," says Riermeier.

BIOSIMILARS REQUIRE NEW EXCIPIENTS

Biosimilars are driving demand for excipients used to manufacture biologicals. In fact, the 2017 Nice Insight Pharmaceutical Excipients Survey also indicates that large-molecule (biosimilars) manufacturers represent a growing group of excipient purchasers. "Thus, excipients that can mitigate biological production risks and improve process yield are in high demand," says Chattopadhyay.

The number of biological actives coming off patent will increase in the near future. Developing biosimilars is significantly more challenging than conventional small molecules as different physico-chemical properties and specific sensitivities to regular manufacturing parameters have to be handled, explains Riermeier. "Biotechnology-based products require greater attention to stability in the dosage form as well as unique approaches to overcome biological barriers to target site delivery," he says. "New types of excipients and innovative formulation and manufacturing technologies offer new opportunities to formulate these drugs with high bioavailability."



MULTI-FUNCTIONAL EXCIPIENTS MAKE BETTER PILLS

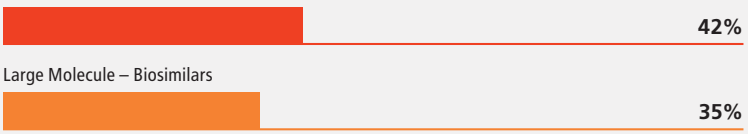
As the number of difficult-to-develop compounds continues to rise, the industry is taking bolder steps in evaluating non-conventional technologies for effective delivery to mitigate risks while enhancing the efficacy of drugs and bringing these compounds to the market much faster.

"Today, more than ever, pharmaceutical formulators are seeking ways to improve the manufacturing process and product quality through the use of multi-functional excipients," says Chattopadhyay. "Multi-functional excipients play an important role in innovating delivery technologies and helping in-line extensions of marketed drugs."

Multi-functional excipients can help pharma manufacturing by improved flowability, enhanced compressibility, improved bioavailability, particle size distribution and reduced dust generation, etc. Aware of their benefits, the use of excipient combinations has grown 56 percent among respondents to the 2017 Nice Insight Pharmaceutical Excipients Survey.

Additionally, Riermeier says that multi-functional excipients represent significantly less development costs

2017 NICE INSIGHT PHARMACEUTICAL EXCIPIENTS SURVEY:
% OF RESPONDENTS WHOSE BUSINESS IS ENGAGED IN THE DEVELOPMENT OF BIOLOGICS



and regulatory hurdles than creating completely new excipients. "Multi-functional excipients can accelerate or even enable the development of new products that otherwise would not be possible," he says.

For example Evonik's newly launched EUDRAGIT FS 100 is a solid version of existing EUDRAGIT FS 30 D. This new multi-functional version allows pharmaceutical companies to use the polymer in many new applications, such as hot melt extrusion, solvent spray-drying and solvent coating, which Riermeier says was impossible to achieve in prior decades where only the aqueous version was available. "This kind of multi-functionality allows overall new development possibilities within the pharma industry," he says.

THE COST OF USING EXCIPIENTS

Whether it's improving solubility, enhancing biosimilar delivery or using multi-functional excipients, pharma manufacturers always want to find ways to reduce costs while improving manufacturing efficiency. In fact, the 2017 Nice Insight Pharmaceutical Excipients Survey shows that affordability is among the top-five purchasing criteria when choosing an excipient supplier.

Excipients can be a key tool to help address the desire for low-cost medicines as they can significantly improve production efficiency. For example, BASF's Kollicoat IR has a polymer structure with low viscosity and high film flexibility that allows the coating to be applied much quicker, resulting in a homogenous flawless surface, explains Chattopadhyay.

"Excipients are usually not the primary cost driver for drug products, but they can play a vital role with respect to the overall therapeutic costs and efficacy," says Riermeier. "A versatile excipient combined with the know-how of well experienced drug formulators can reduce the development costs of new drug products significantly and increase the chance to hit the right therapeutic window."

Risk goes hand-in-hand with cost. As the pharmaceutical industry struggles with high failure rates and enormous development costs, companies want to keep the risk as low as possible. One way to do this is to use existing excipients. "The majority of pharmaceutical companies prefer using existing excipients with extensively documented use in previously marketed products rather than new excipients that may require cost-prohibitive toxicology studies," says Riermeier. "This is why co-processed excipients and new technology platforms using existing excipients are gaining market share."

SIMPLIFYING FLOW AND LEVEL Instrument Verification

Automatic verification can minimize the need for expensive instrument calibrations

By Ravi Shankar, Endress+Hauser

RECENTLY, QUALITY Risk Management (QRM) has become a mandatory regulatory requirement for drug manufacturers. The U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) publish guidelines and requirements which customers and vendors are expected to follow. Guidelines such as "Process Validation: General Principles and Practices" by the FDA and Annex 15 issued by the EMA offer input to help drug manufacturers design processes correctly.

Based on the new process validation model published by the FDA (Figure 1), validation is never finished, but is instead a process of continuous improvement. Maintenance and calibration activities of instruments are part of stage three in the model.

QRM is an overall and continuous process to minimize product quality risk. Instrument calibration/verification interval definitions are part of QRM risk analysis, and guidelines for these procedures are described by the FDA and EMA accordingly. Selecting the correct instrument for the application is absolutely crucial in the design phase of the project, and the criticality of the measuring point defines the required reliability and measuring accuracy of the instrument.

ISO 9001:2008 section 7.6 requires instruments to be calibrated or verified at regular intervals. The following basic requirements have to be fulfilled:

- Calibration/verification must be traceable to a national standard
- Calibration/verification must be performed at regular intervals, and
- Calibration/verification must be documented

CALIBRATION AND VERIFICATION

The first step in verification is to determine if the instrument is still operating within specifications before it is taken out of service for calibration. A calibration of an instrument — for example, a flowmeter — involves determining and documenting the difference between the measured and the correct value.

Traceability is accomplished by a formal comparison to a standard which is directly or indirectly related to national standards. Detected deviations between the measured value and the reference value can be corrected after the calibration by adjusting the calibration factor. A calibration protocol is issued to document the findings, and recorded for possible audits.

A substantial number of FDA warning letters are issued because remedial action after a calibration check has been considered insufficient.

Documentation about instruments and their maintenance activities has to be filed for inspector visits. Even if a flowmeter theoretically could be operated for

25 years without calibration due to its excellent safety and reliability parameters, it would most likely trigger some critical questions during an audit if no paperwork was available to prove it remained within calibration.

Calibrations are expensive, but provide very clear results for the user. Even though many instruments have proven exceptionally long-term stability which exceeds the entire lifetime of the equipment, they still have to be checked regularly to avoid legal implications.

Today, modern instruments have built-in technology to simplify compliance and verification. Several instrument vendors offer this capability, but all approach the solution in different ways.

AUTOMATIC VERIFICATION

Automatic verification is an accepted procedure. For example, Heartbeat Technology from Endress+Hauser has been tested and independently certified by the European agency TÜV. Heartbeat verification fulfills all requirements specified in ISO 9001:2008 section 7.6 and can be used interchangeably with traditional wet calibrations for traceable instrument checks.

Heartbeat Technology continuously monitors the entire signal chain for deviations within a very tight band. The failure threshold is defined by the specified accuracy of the instrument. Therefore, Heartbeat Diagnostics will trigger an alarm as soon as the sensor or instrument is no longer operating within the original specification. With automatic verification, a sensor does not have to be removed from the process until the diagnostics sound an alarm.

The entire signal chain of the instrument is analyzed for possible errors and their subsequent impact on the system and its measuring

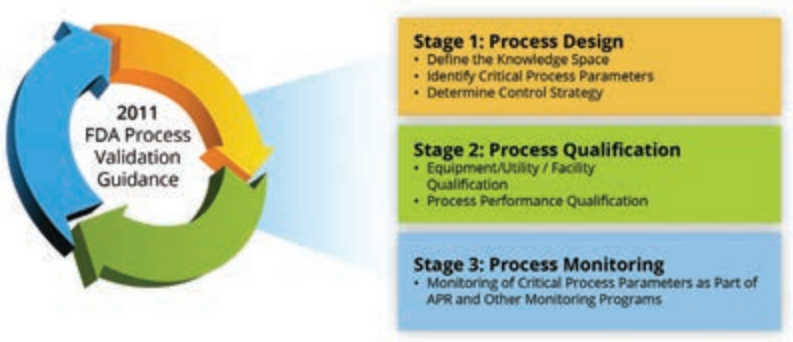


Figure 1: The FDA Process Validation Model.

accuracy. Typically, a failure modes, effects, and diagnostic analysis (FMEDA) is used during the device design phase to identify critical components in the signal chain.

FMEDA is a systematic analysis technique to obtain failure rates, failure modes and diagnostic capability. The FMEDA technique considers:

- The functionality of each component
- The failure modes of each component
- The effect of each component failure mode on the product functionality
- The ability of any automatic diagnostics to detect the failure
- The design strength (de-rating, safety factors)
- The operational profile (environmental stress factors)

As a result, a proper safety measure has to be assigned to every critical path or component. Measures include digital signal processing and continuous loop checks with the help of internal reference components. In order for an internal component to be used as a diagnostic reference, it has to fulfill special requirements such as factory traceability and exceptional long-term stability.

FLOWMETER VERIFICATION

Modern flowmeters, which operate based on a Coriolis, electromagnetic, ultrasonic, vortex or thermal measuring principle, do not have any moving parts that are subject to wear. They have been tried and tested in thousands of applications and are well known for guaranteeing highly stable measurement results over a long period of time.

The reason for this long-term stability stems from the technologies' resistance to wear provided by the lack of moving parts in the sensor. Therefore, for these measuring principles, it is assumed that they will exhibit long-term stability if they are properly selected, sized and installed. Good engineering practice eliminates the possibility of systematic errors.

Verification does not require fluid going through the meter (Figure 2); instead, it verifies a number of internal components (secondary variables), which are closely correlated to the flow measurement.

During verification, the current conditions of the secondary parameters are compared with their reference values, thereby determining the device status. Verification produces a pass or a fail statement, depending on whether the assessment is positive or negative. A traceable and redundant reference, contained in the verification system of the device, is used to ensure the reliability of the results. In the case of a Coriolis flowmeter, this is an oscillator, which provides a second, independent reference frequency.

Coriolis, vortex and ultrasonic flowmeters apply time-based principles, measuring the frequency of the sensor oscillation with the help of quartz clocks as digital frequency generators.

Magmeters rely on precision voltage references to measure the voltage induced in the magnetic field of the sensor.

Flowmeters are often used for many years in biopharmaceutical applications. References with long-term stability ensure that deviations due to aging or external influences are extremely improbable. However, if this should occur, it is immediately detected by the integrated continuous monitoring system. This ensures highly reliable operation and, by detecting errors in a timely manner, prevents the device from working outside of the factory specifications. This increases the safety of plant operation and ensures consistent product quality.

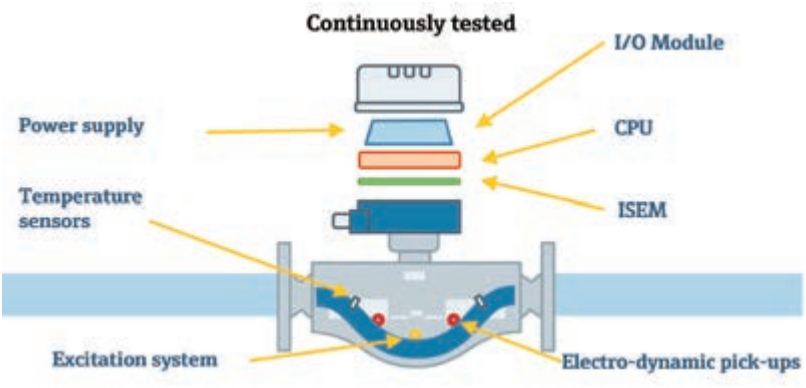


Figure 2: Modern instruments, such as this Coriolis flowmeter, can automatically verify correct operation. Any deviations will send an alarm.

LEVEL INSTRUMENT VERIFICATION

Level instruments do not need calibration as flowmeters do. Level instruments can be verified periodically without process interruption, verifying the accuracy compared to when it was installed.

For this reason, verification is vital to ensure proper operation and to provide added confidence to operators. A modern level instrument equipped with verification capabilities and its ability to conduct continuous automatic internal checks and diagnostics allows for added safety and reliability. Some of these internal checks include:

- Reference pulse
- Quartz synchronization
- Clock verification
- Cycle time measurement
- Supply voltage check
- Temperature monitoring
- Check sum in RAM
- Cable breakage

Level instruments are also able to diagnose process problems. For example, a radar level instrument can monitor for buildup in the area around the horn — the area of the coupling signal — and detect material buildup on the antenna by evaluating the quality during installation as a clean horn. A threshold can be set for build up to notify the operator before the unit would lose its echo. The notification can be from the front display and an analog or open collector output.

PAPERWORK FOR AUDITS

In addition to the continuous monitoring functionality running in the background, a traceable verification report about the health status of the sensor and instrument can be generated on demand. This report is produced, without the need of external devices, directly within the instrument. The operator does not have to write any results down on paper, which makes the entire process faster and reduces costs. The quality of the verification results improve, as there will be fewer mistakes due to human error.

Devices with internal verification can store multiple results in the transmitter. In addition to the verification result (pass/fail), the transmitter logs the actual measured values for all tested parameters. This data can be used for tracking trends in the lifecycle of the measuring point. This allows for timely conclusions regarding the measuring point's state of health and it assists in preventing unexpected failures. Verification data may be transferred to asset management software for archiving and trend analysis.

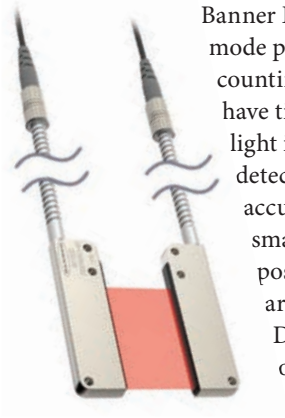
By comparing the data from multiple consecutive verifications, trends can be detected and systematically tracked during the lifecycle of the measuring point. This allows for timely conclusions regarding the measuring point's state of health or process-specific influences on the measurement result.

Continual internal diagnostics and internal verification capabilities reduce maintenance expenditures because calibrations on flow instruments are done only when needed, and diagnostics built into the level devices along with the ability to verify periodically identify problems with instruments. It leads to a better overall equipment effectiveness as it results in less process downtime for maintenance and fewer shutdowns from instrument failures.

Automation, Sensors and Measuring Devices

In pharma and biopharma industries, process efficiency relies on innovations such as flexible control systems, autoclavable electrodes, sensor boxes, data storage capabilities, smart diagnostics and real-time monitoring

BY KATIE WEILER, MANAGING EDITOR



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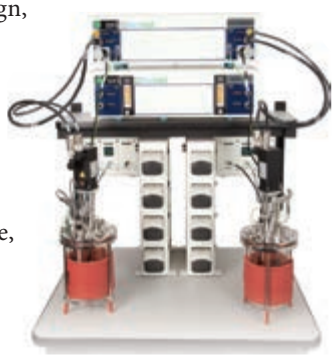

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Crazy About Quality and Compliance?

All elements and levels of the organization must be engaged to create effective manufacturing processes

BY MICHALLE ADKINS, DIRECTOR, LIFE SCIENCES CONSULTING, EMERSON AUTOMATION SOLUTIONS

ARE YOU passionate about quality and compliance? If not, you should be. The most effective companies know how to meet the industry's stringent regulatory requirements while manufacturing safely, efficiently and profitably.

Have you ever stopped to ponder how many things can go wrong during the planning, manufacturing, testing, reviewing, releasing and storage of a batch? Thinking back to my production management experience at a pharmaceutical manufacturer, I can recall my own amazement at the number of things that could and did go wrong, even when the production process was supposedly fully automated.

I was equally amazed that while running a rather manual process we somehow managed to prepare, manufacture, document, test and release batches without a deviation or problem. Unfortunately, at that time, this error-free state was a rare and amazing feat worthy of a celebration.

Fortunately, we now live in a world where at least some of this turmoil can be averted with appropriate planning and the use of modern automation and technologies. There are several sources to consider when looking at how to "poka-yoke," or error-proof, manufacturing processes. Error-proofing can aid in achieving compliance, and figuring out how to get there is the key. The mantra is, as Stephen Covey says, "Begin with the end in mind," and it's important for everything we do in this industry.

Sifting through quality and compliance challenges brings to mind critical attributes we see working with many companies: Successful manufacturers supply quality products by putting compliance-ready processes in place from research through commercial manufacturing, within the supply chain process, as well as on the shop floor and in the labs.

Do you think this may be why we hear so much about data integrity, data analytics, continued process verification, PAT, electronic batch records, electronic log books and predictive analytics? These are not just buzzwords, but are several of the right-first-time or compliance enablers used to produce beneficial products that ultimately improve the global quality of life — yours and mine.

Taking a multi-dimensional view of successful organizations, there are many places to build in compliance enablers. Starting in the pipeline process from R&D to commercial manufacturing, here are some of these enablers: build process understanding, design capable processes, and deliver appropriate controls. Design of experiments and PAT are also important pieces of this process. In addition, tools enabling process control, product data collection and recipe management across the product lifecycle are pertinent as well.

With appropriate modeling tools developed and transferred across the lifecycle into the commercial manufacturing environment, process fault detection and predictive diagnostics can be used to identify, alert or avert production problems.

SUCCESSFUL ORGANIZATIONS VIEW TECHNOLOGY AS A TOOL TO PROVIDE PEOPLE **WITH THE RIGHT DATA AT THE RIGHT TIME.**

Looking at another dimension, manufacturing business processes include shop-floor components all the way up to the ERP system, and everything in between. There are many useful, compliance-enabling tools in this dimension.

Reliable flow, temperature and pressure instruments provide insight into the process. Analyzers verify product composition and quality. Automation systems and actuators act on these measurements to control the process.

Diagnostics, predictive sensing, process analytics, electronic batch records, electronic log books, process verification tools and predictive reliability tools enable right-first-time manufacturing. Looking across the supply chain network, many of these tools need to be shared with contract manufacturers and suppliers.

Successful organizations have a right-first-time culture, and view technology as a tool to provide talented people with the right information at the right time so they can make the best possible decisions.

Manufacturers must be passionate about quality and compliance, and committed to effective manufacturing. Companies with these attributes can put compliance-ready processes in place from research through commercial manufacturing and within the whole supply chain. Right-first-time is a key part of compliance. Technology enables it in manufacturing, and organizational culture plays an important role in producing the best possible products.

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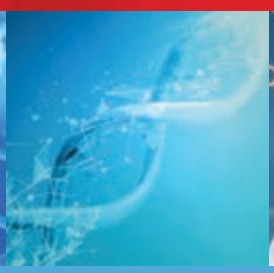


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- Innovation and regulatory, tackling the importance of expedited pathways, advanced therapies and a discussion of the current regulatory findings

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