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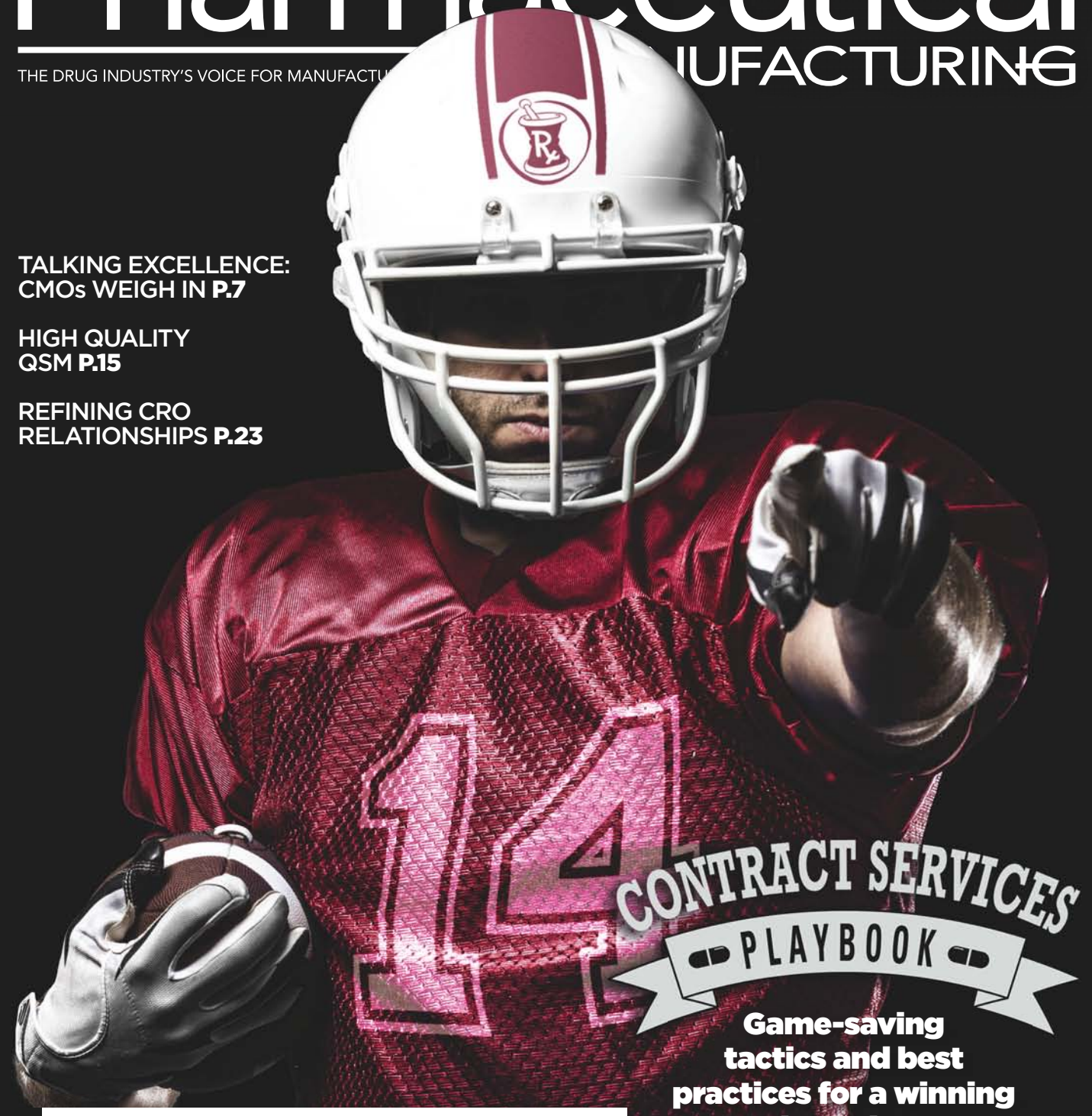

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CONTRACT PHARMA TAKES THE FIELD

Contract services companies are playing great cGMP ball

Welcome to *Pharmaceutical Manufacturing*'s 2014 Contract Services Playbook. It's an exciting time to be in the contract manufacturing organizations (CMO) business as more and more branded pharmaceutical producers seek strategic and competitive advantage by outsourcing production and other key services including research, development, as well as excipients, filling and packaging services and more. CMOs are making some big plays out there and scoring especially well with regulators, making extra points by actually helping the FDA's refs understand better how cGMP is being practically applied in the field. Recently I was exposed to some FDA data that revealed a real trough in inspection activity from 2005 - 2007 — a gap that one of my trusted contributors surmised was the unintended effect of budget cuts. The ripple effect, he said, of this scarcity of resources was that the agency and inspectors were stretched to a point that impinged on the agency's ability to understand, articulate and execute on its cGMP compliance regime.

FDA's CDER director Janet Woodcock perceived a disconnect: According to industry media reports in the wake of her ISPE appearance, "To my knowledge, there's no detailed common understanding within the United States about what GMP compliance exactly means," admitting perhaps controversially, that "In fact, the effectiveness of our inspection programs is unknown — even to me." She commented that there are not many written standards, and when they are written, they're high-level. "As a result, they don't tell you whether [the industry's] operations are going to make the grade or not." In other words, even at the highest levels to both regulator and regulatee, cGMP compliance is open to some interpretation. Fortunately for the industry, Contract Pharma is becoming really good at it, and in the process, helping regulators regulate from a better base of knowledge and understanding.

Since their regulatory debut, both the industry and its regulators have worked to introduce and refine the application of cGMP principles in pursuit of quality. In the long march toward compliance, pharmaceutical companies accepted the challenge and got busy adapting and implementing cGMPs into their operations, albeit with varying degrees of success. For many companies, compliance was problematic because implementing cGMPs across aging facilities with outdated, obsolete processes and operational procedures proved to be both economically and technically challenging to even the most prominent, financially healthy organizations.

But a funny thing happened on the way to the patent cliff, the market for contract services heated up, and with it competition for the BIG dollars coming out of Big Pharma as it pursued new strategies to cope with its own changing markets. That competition, naturally, has bred organizations that are, well, competitive. Oh, Big Pharma still has plenty of juice operationally, but in striving for its business, Contract Pharma has clearly shown how well it can manage risk and quality across the enterprise and implement cGMP to achieve operational excellence — and make some money doing it.

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By Steven E. Kuehn, Editor-in-Chief

THE ROAD AHEAD FOR CONTRACT SERVICE EXCELLENCE

Leading contract service organizations discuss operations and strategies driving success

SAY WHAT you will about contract manufacturing and services companies, but the operations they've got out on the road these days are driving more and more of the industry's strategic successes — and that's pretty exciting. While The Maybachs, Rolls-Royces and Cadillacs of Big Pharma were cruising rough roads, finding new strategic routes past cGMP construction zones and patent-cliff detours, The Aston-Martins, Porsches and Maseratis — Contract Pharma's Grand Tourers — started downshifting, not only to better compete for the growing business opportunities that their executive-class clients were offering, but also to accelerate their own strategic ambitions as independent pharmaceutical manufacturing concerns.

Whether CMO, CDMO, CRO or some combination of all three, Contract Pharma is taking advantage of lighter, better handling operational platforms, high performance quality regimes and new sport-tuned process and information technologies to accelerate their capabilities and keep pace with the demand for their services.

Last summer, Catalent opened its new biomanufacturing facility in Madison, Wis. The new plant features state-of-the-art disposable technology and an efficient process layout that supports sterility and throughput.

ON INDUSTRY TRENDS

Patheon's Harry Gill, senior vice president, quality and continuous improvement, finds that for the customer market, "We are observing a shrinking fixed asset base among large Pharma, as there has been 4% CAGR decline since 2007." He notes that more mid-sized and specialty pharmaceutical companies are maintaining core competencies in research and commercialization while outsourcing the rest. "Additionally," says Gill, "we are noticing that more emerging biotech companies are using virtual outsourcing models and generic companies are outsourcing more of their complex products."

In 2012, says the August 2013 Frost & Sullivan report "Global Pharmaceutical Contract Manufacturing Market," the global pharmaceutical contract manufacturing market generated $13.43 billion in revenue and a CAGR of 6.6% through 2017. Solid dose formulations comprise the largest segment, say Frost analysts, constituting 49.8% of the total CMO market, but point to injectable dose formulations as a primary outsourcing growth driver through the forecasted period with a strong 13% CAGR. Frost & Sullivan's study points to several key drivers of this growth, including increasing demand for safe effective solid-dose generics

In an effort to utilize technology to improve communication processes with its customers, Patheon established a customer collaboration strategy and platform that provides the needed framework for information exchange and enables the company to share information electronically with its customers.

and sterile products and increased focus on complex disease therapies answered by lyophilized and sterile cytotoxics for oncological disease management. Behind it all: "Because of Big Pharma's increased outsourcing, the pharmaceutical contract manufacturing market is expected to show consistent growth."

Ajinomoto Althea, which says it specializes in cGMP-compliant manufacturing and aseptic filling of sterile injectable therapies, is also producing protein delivery technologies for recombinant protein and parenteral products. According to Ajinomoto Althea's Jack Wright, vice president, sales and marketing, "One of the biggest market trends that will impact … our business specifically in the years to come, is the increase in outsourcing by Pharma and Biotech companies. The improvements in the CMO market environment stem primarily from new drug approvals, greater funding of biotechnology companies and demand for new services." Biologics hold great potential, he says. "In an effort to cut costs, many biopharmaceutical companies are choosing to outsource the manufacture of their drugs instead of investing in [the] … facilities suitable for manufacturing the drugs themselves."

Biologics (as do opportunities from complex solid dose formulations) do hold great potential for CMO business, and to better meet such demand, companies are merging and acquiring new capabilities to meet it. Case in point is the November 2013 announcement from Royale DSM that DSM Pharmaceuticals, its finished dosage business, was being combined with Patheon to form a yet-to-be-named (dubbed NewCo in the press release) company that will create an "industry leader" custom development and manufacturing organization (CDMO) for the pharma sector. According to DSM, the creation of NewCo will take DSM from being one of the smaller units of the larger parent to that of a dedicated CDMO with Patheon, and in the process promulgate $2 billion in sales from the work of 8,300 employees worldwide with capabilities for the manufacture of small molecule API and intermediates, biopharmaceuticals via mammalian cell cultures and microbial fermentation. Comprehensive dose form capabilities ranging from oral solid dose to sterile injectables are also on the menu as well.

A merger, no doubt, that's a strategic response to market trends. DSM's Hank Nowak Sr., director, business development & account management notes that analyses of pharmaceutical product pipelines clearly show evidence of an increasing trend towards two major growth areas:

Irvine Pharmaceutical Services Inc. and its subsidiary Avrio Biopharma, which prides itself on its fast turnaround times, sees an increase in requests for nano-particle formulations and suspensions for both marketed products and NCEs.

large molecules (proteins, peptides, nucleic acids, etc., and oncology indications. "Most large molecules require sterile production, whether liquid or lyophilized, says Nowak, noting that, "technologies to handle, compound, formulate and fill these types of products will certainly see adoption and growth over the next five years."

Clearly market forces and opportunities are being responded to in different ways by Pharma's contract services community. Take fill and finish operations, for example. Peter Soelkner, managing director of Vetter Pharma International, oversees the operations of six production facilities and some 3,300 employees. "Vetter's business strategy has been entirely focused on the aseptic fill and finish of parenteral customer's drug products." What market trends are important to Vetter and most likely to impact their business? "The continuing erosion of the blockbuster model and the overall growth of the syringe market are the … trends that we foresee affecting business in the immediate future." Related to this, says Soelkner, is the "monoplant" model which Vetter believes is no longer viable, "and will result in a growing need for production sites that allow for efficient and flexible manufacturing of complex and sensitive compounds …"

Far from the monoplant model is Irvine Pharmaceutical Services Inc. and its subsidiary Avrio Biopharma. The 26-year CMO veteran prides itself on being able to take on projects with unique challenges and needs and fast turnaround times. "We are seeing an increase in requests for nano-particle formulations and suspensions for both marketed products and NCEs," offers Irvine's Kale Ruby, senior vice president, operations. "We believe that the broad experience of our formulation and manufacturing groups will aid our clients in the challenges associated with new formulation technologies."

ON INNOVATION

In a piece published by Results healthcare, "Pharmaceutical Manufacturing trends and investment opportunities in 2013," authored by Dr. Sarah Houlton, prominent Pharma journalist and Kevin Bottomley, Results healthcare's managing director, Contract Pharma's agility and technical acumen is an acknowledged fact: "Many CMOs have developed significant chemical synthesis capabilities and are now able to take on complex chemistries. They can also design new and improved routes to make API

DSM has integrated its own innovative and proprietary technologies including XD process technology and its RHOBUST direct capture downstream technology that optimizes bioprocess manufacturing processes, driving down cost and processing times at its new Brisbane facility.

molecules more cheaply and efficiently. If a better, more cost effective synthetic route can be devised, particularly if the IP is protected in some way, this can enable CMOs to gain advantages in the manufacture and supply of individual APIs to secondary manufacturers."

Whether through research, survey or anecdotal evidence, there is plenty of data supporting Holton and Bottomley's assertion that CMOs are the engines revving development and manufacturing innovation, something backed up by the CMOs queried for this look across the CMO fleet. "Customers come to DSM Pharmaceuticals for support of complex drug product development," says DSM's Nowak. "As a traditional contract manufacturing organization DSM must continually innovate its processes and technologies to stay ahead of the ever-changing and complex requests made by our customers. Pharma companies will continue to increase their demands for flexible, reputable and high-quality CMO partners. Many Pharma companies will co-invest to build out particular technologies, processes and capacity. Some CMOs will begin to assume more risk during the product-development phases, and in turn, will expect to receive milestone payments."

Elliott Berger, Catalent's Vice President, Global Marketing & Strategy explains that with a high proportion of drugs in development suffering from poor solubility and/or permeability, customers are increasingly looking for partners to help improve the bioavailability of their development products or to optimize the treatment to patients. "Formulations vary significantly, so it is helpful that Catalent is able to offer a variety of technologies that improve the effectiveness of pharmaceutical products for certain patient groups; for example, those who have difficulty swallowing, to alter the release profile of an API into the bloodstream, perhaps making the dose more convenient or minimizing side-effects — that is, to delay or pulse release, or to combine multiple APIs in one convenient dose form — to prevent abuse or redirection, and ultimately to make better treatments that are clearly differentiated from a patient and payer perspective."

Vetter's Soelkner finds that the ability to innovate in response to a customer's technical roadblocks is really the stock-in-trade of successful CMOs. "As a strategic partner for (bio-) pharmaceutical companies in today's complex environment, we are continually being challenged to develop new services and products in order to support them in the best possible way." He explains that state-of-the-art technology, while critical to the process, is not the only requirement that it takes to be successful. "This is particularly true when considering the ever-growing share of more and more complex molecules and sensitive drug substances. Experience-based solutions that conclude in innovative and product-specific approaches in development and commercial manufacturing are equally important and are playing an ever-increasing role in realizing successful outcomes."

Ajinomoto Althea's Wright notes that innovation in Pharma is characteristically different than other industries. "While many other industries are made up of individual innovations that can be differentiated, the Pharma industry as a whole represents innovation. The mere nature of the industry is comprised of continuous advances that strive to push the frontiers of medicine and bring life-saving medicines to those in need. In an industry as complex as pharmaceuticals and life sciences, there are many challenges to overcome, and a single solution to a challenge helps push the entire industry forward."

As a whole, the industry is now less able to sustain the research and development budgets of years gone by, says Catalent's Berger. "If innovation were ever proportional to R&D activity, then it would naturally have declined unless new models of research and development were found.

Innovation is becoming more challenging for pharma because of the more difficult molecules coming through their pipelines — often for rare disease states and specialty treatments. "We believe innovation is ramping up of late, taking advantage

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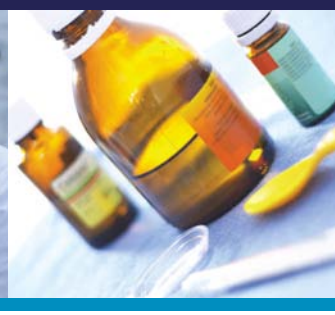

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of better economic and funding environments," says Berger. "We partner with customers in helping to drive this innovation with advanced drug delivery technologies that help take these molecules from 'desired drug delivery profiles' into 'successful treatments,' facilitating a less difficult road from lab to patient."

For biopharmaceuticals it's well established that the process is the product, but it might be fair to say that for CMOs — regardless of small or large molecule production — process is their true product, and strategically the means in which these companies excel and differentiate themselves by creating and sustaining the value (and hence profitable sales) for their services. "In regards to DSM's high-value offerings," says Nowak, "we were the first Safebridge Certified cytotoxics sterile production site globally. We also have the largest lyophilization capacity in the North American CMO industry category."

One notable challenge within Pharma, notes Wright, is the difficulty of getting certain complex proteins to express accurately and with high purity. Low yields, protein degradation, aggregation, and timely purification processes are common frustrations with protein expression in microbial systems. "Through its patented and novel expression technology, Corynex, Ajinomoto Althea can provide the industry a solution to many of these problems, says Wright. "Using the bacterium strand *Corynebacterium glutamicum*, Corynex is able to secrete fully active and folded proteins, with high initial purity, directly into the cell medium. This eliminates many of the costly and time-consuming purification steps required with traditional expression systems."

Last October, DSM Pharmaceutical Products officially announced opening of its new cGMP facility for biopharmaceutical contract manufacturing in Brisbane, Australia. The Brisbane facility serves DSM's blueprint for its future. Not only does the facility field current industry standard technologies, DSM has integrated its own innovative and proprietary technologies including XD process technology and its RHOBUST direct capture downstream technology that optimizes bioprocess manufacturing processes, driving down cost and processing times. DSM's proprietary techniques and technologies, says the company, can cut out several processing steps. According to DSM, its XD cell culture technology achieves 5 to 25 times higher product output than standard processes, producing very high cell densities while retaining high cell viability and consistent quality.

Catalent continues to make significant investment into drug delivery technologies, capabilities, as well, maintaining the presence necessary to help Pharma's innovators bring better products to market. "In fact," says Berger, "around $1 billion has been invested globally over the last five years. Catalent's strategy has, for some time, been to build deep expertise in those segments in which we operate, and we have invested on a major scale in quality people and processes to ensure reliable global supply." Speaking of reliable supply, last summer Catalent opened its new biomanufacturing facility in Madison, Wis., that features state-of-the-art disposable technology and an efficient process layout that supports sterility and throughput. "We don't compromise on quality. We maintain a single Quality Management System and our inspection outcomes are three times better than the industry average, and we are approved to ship to over 80 countries," says Berger.

Catalent counts among its value leaders a number of innovative offerings including advanced SMARTag ADC technology in partnership with Redwood BioSciences, an advanced oral dose form development and supply including OptiMelt hot melt extrusion technology in Europe, expert development to final dose scale up and manufacturing in the U.S., as well as OptiDose tableting technologies for sophisticated drug delivery profiles including combination therapies, complex timed delivery and pulsatile release. Catalent says it also offers oral delivery of macromolecules with its new industry-leading technologies OptiGel Bio and Zydis Bio.

Irvine Pharmaceutical Services says supporting its value to customers is the company's ability to accelerate

Vetter finds that the ability to innovate in response to a customer's technical roadblocks is really the stock-in-trade of successful CMOs. As a strategic partner to companies in today's complex environment, CMOs are continually being challenged to develop new services and products in order to support customers in the best possible way.

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its processes to meet customer's needs. "We believe our manufacturing turnaround time, typically less than 25 days, is among the best in the CMO space," says Ruby. "We can accomplish this task because we have invested in experienced operators and talented scientists."

INFORMATION SHARING AND COLLABORATION

A key area in which Catalent is making rapid advancement in data and information sharing is with its global Clinical Trial Supply business focusing on digital solutions for advanced Clinical Supply Management, inventory and supply transparency and customer data access. Irvine is currently in the process of moving its IT infrastructure to a secure and compliant cloud-based system. "With well established systems and contingency plans," says Ruby, this update in infrastructure allows Irvine to have even stronger data security and system reliability. We are also implementing secure, Web-based client access to real time data and project status updates."

With broad geographic operations, Patheon's systems landscape is complex, which can make collaboration and information sharing tough. "As a global CMO," explains Charlie Lickfold, Vice President and head of IT, "We have specific challenges that we use information technology to help resolve. In an effort to utilize technology to improve communication processes with our customers, Patheon established and utilizes a customer collaboration strategy and platform. This platform provides the needed framework for information exchange, which enables us to exchange and share information electronically with our customers." This electronic collaboration solution, says Patheon, allows the company to expedite supply chain processes and simplify the means of information exchange by providing a single integration point for all of Patheon's sites to its customers.

LAST WORD

"Innovation comes from many sources," explains Catalent's Berger, "and through effective collaboration between those engaged in the improvement of medicines, improved clinical outcomes can be found." Berger says that is why his company established the Catalent Applied Drug Delivery Institute with the aim of "harnessing the knowledge of the world's leading experts; partnering with pharmaceutical companies; facilitating mutually beneficial collaborations; and sponsoring, educating and counseling to advance the adoption of emerging technologies."

By John Briggs, ASQ, CQA, Quality Assurance Manager, ASI

CHANGE MANAGEMENT FROM A SINGLE-USE PERSPECTIVE

Effective quality management systems demand robust change control

DURING THE last six years, single-use systems and devices have emerged as key agents in the biopharmaceutical landscape.[1] Single-use solutions have revolutionized the Pharmaceutical and Biopharmaceutical industry due to their effectiveness in reducing the risks of contamination and allowing faster changeovers. These advantages, coupled with the significantly reduced time and costs required to establish a new manufacturing facility, have made single-use a very popular choice.

Single-use products have gone well beyond an early-stage technology, and it is likely that the popularity of these devices will continue to rise over the next few years.[1] Therefore, it is becoming increasingly important to view single-use system suppliers, not only in the context of "can they make the disposable," but also from the perspective of "does the single-use system supplier maintain strong quality oversight to support their product from a control process and ensure regulatory compliance." The recent *10th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production* found that 65.7% of end-users of single-use devices agreed use of disposable/single use devices are factors in creating "significant" or "some" improvement to biomanufacturing performance[2].

Drug manufacturers — especially biopharmaceutical contract manufacturing organizations — must ensure their operations maintain a robust quality systems infrastructure to ensure production efficiency and superior operational excellence thereby driving the continuous improvement cycle. The resulting manufacturing distinction will provide customers with the confidence to withstand regulator scrutiny while providing with certainty that quality products will be available to meet the therapeutic markets demand for its therapies. The manufacture of high-quality single-use systems and process solutions requires the same from its suppliers to minimize risk and ensure safety, traceability and compliance at every stage of production. To minimize risk, single-use system

The FDA's guidance for single-use system suppliers clearly reinforces the importance of implementing efficient change control procedures as a critical element in an overall quality system.

suppliers similarly must control and document each production step from raw materials and assembly to final test, packaging and sterilization.

As a result, change control has become an important factor for the biopharmaceutical industry. Indeed, the FDA's guidance for single-use system suppliers clearly reinforces the importance of implementing efficient change control procedures as a critical element in an overall quality system, and suggests the scope of a successful change control program must cover a broad set of possibilities, including changes to the supply chain and product specifications or design, as well as upgrades to facilities, utilities, equipment, computer systems, manufacturing instructions, SOPs, test methods and any changes in policy.[3]

WHAT IS CHANGE?

Change can be defined as a movement out of a current state, through a transition state, to a future state. In biopharmaceutical manufacturing, change can be internally or externally motivated, as well as minor or dramatic departures from what is known, anticipated or unexpected, including alterations to facilities, products, processes, equipment or computerized systems.

Change may be required due to:

- Design and development review, verification, or validation (IQ, OQ, PQ)
- Requests from engineering
- Requests by customers or suppliers
- The need for corrective or preventive action
- Safety and regulatory requirements, and
- Improvements to the function and performance of a product

Effective change control systems take time to establish and must be continuously updated. A mature change control system becomes intuitive and remains relevant. Intuitive in that it fosters a structured approach toward managing and documenting change in an environment that engenders continuous improvement, and relevant in that it stays centered on the objective and nature of pending change, and focused on the exact scope of imminent change.[3]

Key components of a change control system include[3]:

- End-to-end communication with all stakeholders from raw materials vendors to product end-users
- Documentation of the details of change, change approvals and implementation, thereby tracking changes effectively for visibility and traceability
- A consistent, structured and sequential approach toward managing change
- An automated system that provides redundant flags/alerts, the ability to search by various criteria, and requires authorization via user credentials in order to make changes
- Routing of change requests to individuals for approvals
- Easy retrieval of information
- Provision of an audit trail
- Demonstration of compliance to FDA regulations
- Speed to allow due deadlines to be met, and
- Education on change control methodology for all employees, to allow timely execution of inventory disposition and existing job orders

Incorporating these key components allows for a dynamic change control system that can help end-users implement continuous improvement and manage impending change with their own products and systems.[3]

Drug manufacturers must ensure their operations maintain a robust quality systems infrastructure to assure production efficiency and superior operational excellence standards.

MITIGATING INCONVENIENCE

In particular, a change control system must effectively accommodate supply chain interruptions, as the ability of a single-use system supplier to provide accurate raw materials data is crucial to the quality of high-value products. Raw materials changes are notoriously inconvenient for the end-user, often unavoidable and include changes to component specifications, suppliers and resins.

It's imperative any change control system accommodate the inevitable and minimize inconvenience to end-users by streamlining provisions for the tracking, reviewing and receiving customer approval of raw

materials changes. The system must be flexible so as to allow appropriate, rational documentation of change justifications. Furthermore, the system must extend change control to raw materials vendors, so that the change control procedure can be initiated before the processing of any components impacted by the changes.[3]

CONSISTENT YET FLEXIBLE

ASI fields a structured, consistent, yet flexible change control system. As a fluid-management technology supplier, ASI manufactures single-use systems and bioprocess equipment for the Pharmaceutical, Diagnostic and Biotechnology industries. ASI offers single-use bags with sizes ranging from 50 mL to 5,000 L and inventories more than 900 components as well as more than 80 tubing types and sizes for customized systems.

In its operations, ASI maintains exceptional quality management supporting its products by carefully controlling the manufacturing process. All control processes within the company are centrally coordinated by a customized Enterprise Resource Planning (ERP) software system. This system allows the traceability, document control, quality control and price control essential to implement the strongest quality oversight. It is a fully automated system that provides flags, alerts, the ability to search, and requires chronologically appropriate, timely authorization.

In particular, an appropriate ERP System must coordinate effective change management in the key areas of inventory, compliance, processes, document control and suppliers.

Inventory: Assurance and security of supply. Effective procurement tools ensure existing inventory is managed, and accounts for change that can occur should there be a depletion of inventory or change of raw material or supplier. The best single-use system product features and solutions may become completely useless if a supply of relevant products has not been secured for many years.

An effective Inventory Change Management Program should consider proper inventory control by establishing reordering points, forecasting, safety stock (reserves) programs, material control and inventory reconciliation.

Compliance: The capacity to evaluate change from a regulatory and compliance aspect is critical. In addition, users must be provided with supporting information during change notification so they may determine risk and how a change affects product design.

An effective Compliance Change Management Program must be able to review a change against the established product to ensure the change is equal to or better than the current product and continues to meet customer and regulatory requirements.

An effective Change Management Program must consider regulatory, compliance and vendor requirements.

Processes: Capacity to perform a validation review to ensure changes do not impact processing parameters, or that the integrity of the single-use system is not compromised if processing parameters are impacted.

An effective Process Change Management Program must assess the mechanical attributes of the single-use system and include methods for testing of processes that ensure integrity and performance of products. Key components of a process change management program include but are not limited to a validation of the manufacturing process, assessment of the need for equipment changes and assessment of the bonding properties of various sealing methods.

Document Control: The process should identify the various documents required for change management and have the capacity to review and revise as needed based on an assessment. (Drawings, specifications, operating procedures and test methods.)

An effective Document Change Management Program provides transparency to the changes so there are no surprises when change is implemented. Document change management must ensure that customer specifications are still applicable following a change.

Suppliers: Change agreements, supply agreements and quality agreements ensure the base structure of change management is formed. An effective Change Management Program requires excellent communication between the customer and manufacturer. Agreements should outline the need for proper and timely communication, and assure that no change is implemented prior to notification. Agreements will ensure the manufacturers are aware that any change in the manufacturing, processing, or even the manufacturing location are important enough to be communicated to the customer.

Integrity: Regardless of the ERP systems robustness, the people who interact with the system ultimately assure transparent, reliable communication.

IMPLEMENTED BY QMS

Change control is implemented by the Quality Management System (QMS) according to a well-defined internal ASI procedure that involves responsibility and accountability. Change notifications are logged and maintained under the

Change control is implemented by the Quality Management System (QMS) according to a well-defined internal ASI procedure that involves responsibility and accountability.

QMS. ASI's Engineering Change Order process identifies the items affected by change and the steps required to control how the changes are executed. Examples of such changes include tooling and equipment changes, bill of material changes, product drawing changes, compliance changes, manufacturing routing changes, raw materials changes and process changes. A Raw Material Review Board comprised of key decision makers from the Quality Assurance, Engineering, Purchasing and Inventory Control departments within the organization meet regularly to ensure that the change control system is working effectively and efficiently. All ASI personnel understand the need for and challenges associated with change control. The company's ERP and QMS are integrated throughout every aspect of its organization and accessible throughout the facility.

Importantly, ASI understands that one of the most critical aspects of change control is end-user change notification. The ability to inform any end-user of change within the product lines they specify requires a very mature Quality System; in ASI's case, the company maintains 5,000 product codes that support end-user change management communications.

For more than 25 years, ASI's QMS development has reached a level that ensures complete quality assurance throughout each phase of a product's lifecycle. The process allows the company to minimize risk, guarantee product quality, deliver safety, traceability, and compliance and provide the highest standard in quality production, assembly, final packaging and sterilization.

ASI's change control is the most critical element in the company's quality management system. This is essential, as proper quality systems that maintain control provide key benefits for all stakeholders by improving supplier quality and helping both single-use system suppliers and end-users achieve their business objectives.

References

[1] *Langer E. Single use technologies changing the biomanufacturing landscape. RAPS Advanced eCTD Submissions Workshop 2012*

[2] *Langer E. Bioplan Associates. Tenth Annual Report and Survey of Biopharmaceutical Manufacturing Capacity/Production, April 2013.*

[3] *Change Control in the FDA-regulated Industry.http://www.metricstream.com/insights/chg_ctrl_FDA.htm*

By Jeff Cawley, vice president, Northwest Analytics

CONTROLLING PREFILLED INJECTABLE DOSAGES

Manufacturing analytics help reduce risk and costs

MIGRATING FROM vials to prefilled syringes is a trend gaining momentum in the pharmaceutical industry, especially for biologics. Because this is the final administered dose, fill control requirements are rigorous and pharmaceutical producers are relying heavily on manufacturing analytics (MA) for control. Reducing risk, cost control and more accurate drug delivery are driving the migration from vials to prefilled injectables; other drivers include:

Overfill reduction
- Eliminates the need to overfill vials to ensure adequate dose delivery
- Eliminates fraud due to retrieval of left-over medication
- Reduces costs, especially for expensive biologics
- Increases dose yield per batch

Risk reduction
- For the manufacturer – individually packaged doses reduce chance of contamination and degradation
- For the medical practitioner – reduces chance of administering wrong dose
- For the patient – more accurate dose for self-administered pharmaceuticals

While inspection is necessary, real process control depends on MA, specifically statistical process control (SPC) methods. SPC is essential to actually delivering on the promise of greater compliance and better control of delivered doses while minimizing syringe production failure and production disruption.

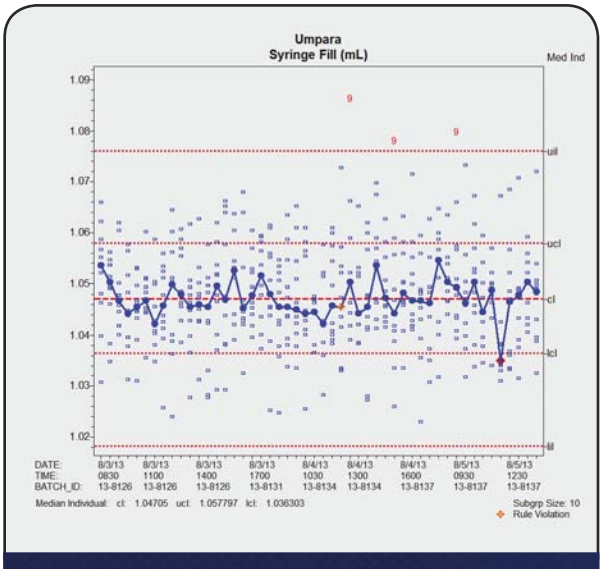
HIGH PERFORMANCE SPC

Life sciences companies try to increase throughput while maintaining process stability, product quality and compliance. One common solution for prefilled injectables is to deploy equipment that simultaneously fills multiple syringes with each cycle.

Multi-head syringe filling equipment fits the definition of a "family" process where individual sub-processes are constituent parts of a global process. Conventional SPC methods do not deal effectively with family processes and the median-individual (M/I) chart was developed to efficiently monitor and manage family processes such as syringe filling systems. Family processes share many or all the following characteristics:

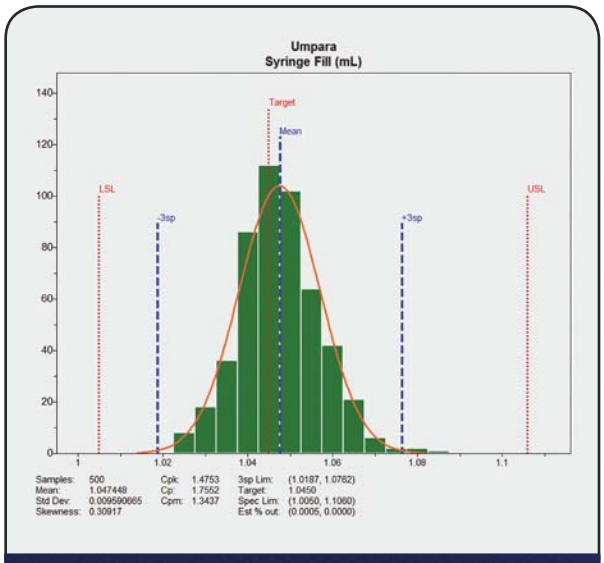
M/I CHARTING TO MONITOR SYRINGE FILL

Several leading pharmaceutical firms have adopted the M/I methods to monitor and control their filling operations for vials, syringes and capsules. Tight fill process control is especially critical for syringes since that fill is the final administered dose.



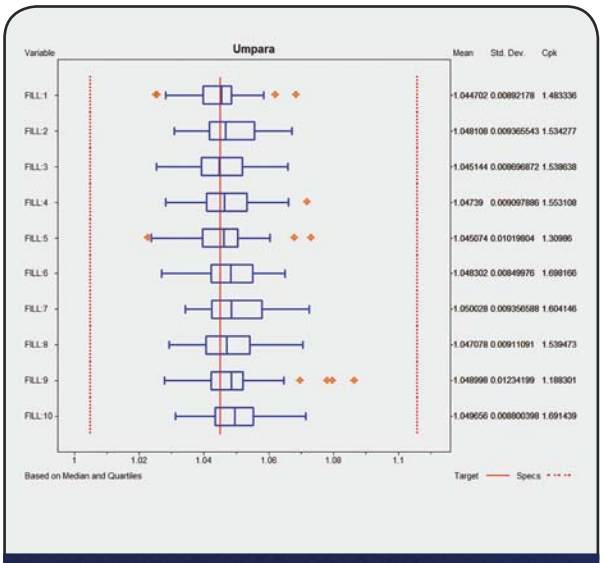
M/I chart monitors 1 mL syringe filler

FIGURE 1.



Process capability analysis of syringe filler

FIGURE 2.



Box plot of syringe filler head performance

FIGURE 3.

Family processes such as syringe filling machinery are widely used because they substantially increase the throughput and operational convenience of a manufacturing line. However, there are real problems monitoring and controlling family processes with conventional charting methods.

Family processes are affected by two types of factors: those that influence all family members and those that influence only the individual member. Since control charts such as X-Bar show only global sources of variation, they cannot pinpoint local assignable causes for individual family members.

For example, consider the results when a single-fill channel is blocked in a 10-orifice filler. An X-Bar control chart uses a random sampling from all cavities and therefore cannot identify the specific cavity with the obstructed channel. The channel may remain blocked, yet the chart will show the overall process to be in statistical control. Conversely, charting each orifice — each family member — would be impractical and time-consuming.

In the process charted in Figure 1, a 10-head system is filling syringes with a nominal 1 mL dose. The solid blue line represents the global fill process, and the blue characters represent the performance of individual heads. The individual values in control are plotted anonymously. Out-of-control values are plotted in red and the individual heads identified.

In this case the individual plot shows an overfill problem on filler orifice 9 on August 4, which directs engineering to correct the problem. The median line representing the global process exhibits two signals, a rule violation on August 4 and an out of control signal on the 5th. The process was restabilized rapidly. Fortunately, the out-of-control fill head did not produce out-of-specification product.

ADDITIONAL SUPPORTING ANALYTICS

As can be seen in the process capability report (Figure 2), the filling process is nominally capable with a Cpk of 1.4753 and no out-of-conformance product was produced. In critical processes such as producing prefilled injectables, it is best practice to increase the process capability as much as possible to virtually eliminate

M/I ANALYTICS WHITE PAPER

NWA has led the development and implementation of the M/I methodology. The white paper Median/Individual Measurements Control Charting and Analysis for Family Processes (http://tinyurl.com/k5la43d) details the method and its application. Multi-head filling systems such as syringe filling are one of the most common application areas. Using M/I analytics fits the intent of PAT and gives individual pharmaceutical firms the chance for competitive advantage while developing higher compliance.

Characteristic	Example
The "family" consists of multiple similar or identical member processes originating from a common source or manufacturing stream.	Syringe filling machines typically use multiple fill heads.
The member processes are completed more or less simultaneously.	All syringes are filled in a single step.
Each member process may have its own mechanical component(s) or subsystem.	Each syringe filler head has its own peristaltic pump and fill orifice.
Each member process has its own sources of variation.	Syringe filler head performance can vary independently.
The family process as a whole is subject to its own global causes of variation.	Syringe fill line pressure or material viscosity may fluctuate.

the likelihood of producing out-of-compliance syringes. This involves either shifting the mean value or reducing process standard deviation. Drug administration safety is a compelling reason for high capability manufacturing.

Other analytics techniques such as exploratory data analysis provide additional insights into the process performance. Box plots, for example, provide an alternate means to view process variation compared to histograms.

With box plots, engineering can quickly and easily review behavior of both the overall process and the individual heads. In Figure 3, the box plot shows the behavior of each fill orifice graphically along with selected statistics. The outliers from fill head 9 are clearly evident.

MA - THE MEANS TO HIGH CAPABILITY

Prefilled injectables represent the state-of-the art technology to administer pharmaceuticals and biologics. Since the syringes represent the final administered dose, the fill is critical and the process needs to be tightly controlled.

Manufacturing Analytics is the state of the art methodology to monitor and improve pharmaceutical production. Advanced SPC methods such as M/I charting enable pharmaceutical manufacturers to maximize compliance and process efficiency while reducing risk and cost.

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By Tara Gladwell, Vice President of Operations, Rho

BUILDING AN EFFECTIVE EFFECTIVE RELATIONSHIP WITH YOUR CRO

Successful partnerships begin with shared goals

DRUG DEVELOPMENT is an entrepreneurial endeavor, fostered by a passion for scientific discovery of new treatments to help patients. The focus is to commit the right resources to reach the end goal of providing life-saving drugs to patients quickly and cost effectively.

A successful partnership with a CRO begins with a shared goal and passion for delivering good medicine. Though the dictionary definition links entrepreneurism with assuming risk, successful partnerships are often based on working with CROs that thrive on creating a business and culture that reduces risks.

A CRO partner with a track record of stability, low-employee turnover and long-standing relationships with customers can establish a solid foundation for a new business relationship.

Whether seeking a CRO relationship for full-service development or a specific service expertise, some basic guidelines can help ensure a successful relationship:

• **Cultural Fit:** Select a CRO partner that views itself as an extension of your team and demonstrates a clear understanding of your specific program and its challenges. Strategic partnerships anticipate the need to quickly address challenges along the way. Involvement from senior management and the development of clear and effective governance at the executive, functional and clinical research levels can be the cornerstone of a successful relationship to ensure that time is spent effectively to achieve objectives and control costs.

• **Flexibility:** Working with a CRO that is experienced in developing long-term partnerships with customers and the flexibility to meet the needs of each customer can minimize the time required to achieve success. An ideal CRO partner is one that is nimble enough to quickly adjust to last-minute changes in the program to overcome

potential work flow challenges. The results are faster cycle times and improved quality. How can you tell if the CRO is actually flexible? Ask for case studies and references.

• **Cost Control Approaches:** Defining goals, methods and what metrics to measure prioritizes key objectives and establishes a path to success. Whether the business relationship is driven by cost constraints, a desire to accelerate speed to market or both, the objectives should be explicitly addressed in governance and the contractual terms of the relationship.

• **Quality Control:** CROs with a reputation for providing high-quality results and meeting deadlines can reduce time and energy spent on project oversight. Work with a CRO that prides itself on scientific integrity and precision, and a culture of customer attention and reliability proven over time.

• **Stability:** The flurry of industry consolidation in the CRO industry has many observers speculating on the role small and mid-sized CROs will play in the future. These CROs — focused on long-term objectives and avoiding the turmoil of public stock offerings, mergers and acquisitions — can provide an advantage of stability.

In an industry where the goal is speed and efficiency to get drugs to market as rapidly as possible, consistent growth and stability is a winning formula to shape a CRO that customers can trust.

ABOUT THE AUTHOR

Tara Gladwell is vice president of operations for Rho, a full-service CRO based in Chapel Hill, N.C. She received her undergraduate degree in Biology from Guilford College and her M.B.A. from Duke University's Fuqua School of Business. She joined Rho in 2001 as a project manager.

FIVE TIPS FOR DEVELOPING ORPHAN PRODUCTS

Rho, a contract research organization (CRO), offers five tips to selecting the right development partner to accelerate approval for orphan products.

1 **Work with CROs that have strong scientific, regulatory, and statistical expertise.** A strategic approach with a focus on key milestones is critical to gain approval as quickly as possible. Look for CROs whose strengths include the ability to conduct challenging clinical trials, knowledge of the regulatory process, and scientific and statistical expertise to develop a plan for success at the outset to reach approval in an expedited, speedy manner. Your CRO should have successfully obtained marketing approval for other orphan products previously.

2 **Know the "ins and outs" of the FDA's approval mechanisms to help speed orphan drug approval.** Many orphan diseases represent serious or life-threatening conditions. Consequently, working with a development partner that understands each of the accelerated development pathways (i.e., Accelerated Approval, Priority Review, Breakthrough Therapy, and Fast Track) and the potential benefits or lack thereof is critical.

3 **Apply for U.S. and European Orphan Drug Designation simultaneously.** There is a combined form that can be used to obtain orphan drug status simultaneously in the U.S. and EU. It is an option that is not being used broadly, but can result in significant reduction of time and effort.

4 **Look for a CRO partner with experience working in small patient populations.** Working with small patient populations requires building communities and developing close connections with research foundations, advocacy groups, patients and health care providers for a purpose-driven approach to product development. It will also be important to gain buy-in from key opinion leaders.

5 **Validate your population.** Before investing time and energy in an orphan drug application, make sure you are eligible. Regulators are on the lookout for developers who try to "slice the salami," meaning that your orphan population is really just a subset of a larger population from which there is no substantive difference.

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By Raied Saleh, Diyan Parichkov, Anil Kane and Vinayak Sant, Pharmaceutical Development Services, Patheon Inc.

PREVENTING FILMING, STICKING OF COHESIVE COMPOUNDS

Inline cooling to reduce temperatures at tablet compression offers relief from this sticky issue

TABLETS ARE one of the most popular and convenient solid oral dosage forms used today (IMS Midas Database, 2005). The tablet manufacturing process typically involves mixing active pharmaceutical ingredient (API) powder with a variety of powdered excipients (fillers, diluents, lubricants, binders, glidants, etc.). These powder mixtures are subsequently processed, compressed and mass produced using automated tableting equipment.

TWO MOST COMMON PROBLEMS

Many APIs that are used today are cohesive and have low bulk densities. These properties can pose significant physical challenges when developing a robust manufacturing process. Two of the most common problems encountered in a tableting process when using this type of API include sticking and film formation.

Sticking occurs when particles adhere to the punch face during the compression process. Filming is a slower form of sticking which can occur over time on the punch surface during the tableting process. Film formation and ultimately sticking during compression can lead to problems with tablet thickness, embossment (legibility) and coating. Frequently, film formation and sticking may not be observed until scale up of a tableting process, at which point it may be undesirable or difficult to alter drug formulation parameters.

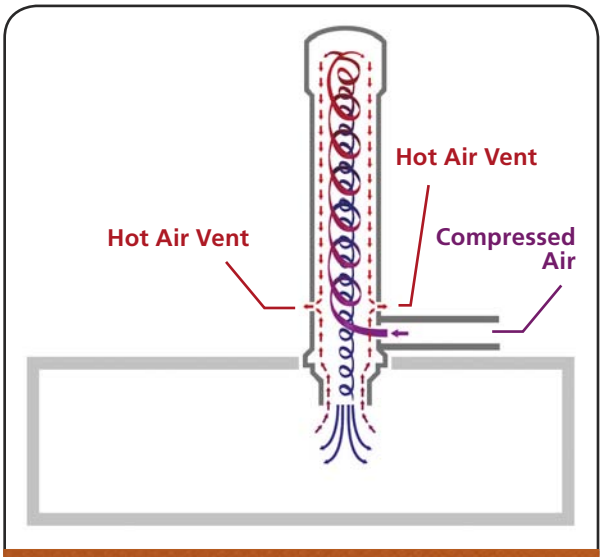
Korsch XM 12 (Single layer/Bi layer) 18 station Tablet Press

FIGURE 1.

NOT COST EFFECTIVE EITHER

Tableting processes that are susceptible to film formation and sticking are problematic, inefficient and not cost-effective. In many cases, the compression process must be terminated early or processing times increased (due to the requirement of frequent cleaning and reinstalling to restart the compression process) which may lead to physical properties of the tablet such as tablet thickness and embossing quality to be compromised. Lower tablet yields and long equipment downtimes can substantially increase manufacturing costs and reduce product profit margins.

The goal of the current study was to develop methods to reduce the likelihood of film formation and sticking during compression using a highly cohesive, hydrophobic API in a tableting process. The use of Vortex coolers that reduced and controlled the temperature of tableting equipment during compression substantially reduced film formation and sticking, eliminated equipment downtime and improved tablet yields by 50% without impacting tablet properties/quality.



Vortex cooler internal air flow

FIGURE 2.

TABLETING MODS WON'T PREVENT IT

Film formation and sticking can occur when excess moisture or under-lubrication occurs during compression of a tableting mixture. Modification of a tableting process can sometimes reduce or eliminate film formation or sticking during compression without making any drug formulation changes. To test this possibility, modifications including changes to pre-compression force, compression force and tableting turret dwell time/speed were implemented during tableting of a hydrophobic API using a small scale rotary press (Korsch XM 12 Single layer / Bilayer 18 station Tablet Press). Tableting was conducted at turret punch temperatures ranging from 25 degrees Celsius to 34 degrees Celsius.

Varying pre-compression (0.0KN- 2.0KN), compression forces (7.0KN-13KN), turret dwell time (0.10msec-0.30msec) and speed (800-1,200 tab/min) failed to eliminate or reduce film formation and sticking. An inspection of tablets produced from three separate batches revealed decreased tablet thickness and illegible embossments that resulted from film formation and sticking. In fact, each of the three batches had to be prematurely terminated (after 50% of the run) because of product filming and sticking on tableting tooling. In each case, tableting equipment had to be disassembled, cleaned, reassembled and compression restarted. About 1,500 tablets per punch were successfully compressed in each run prior to batch stoppages.

VORTEX COOLERS: LABORATORY SCALE

It is well established that hydrophobic interactions tend to strengthen as the temperature of a process increases. Interestingly, the tableting experiments described above were conducted using turret/punch tip temperatures ranging from 25 C to 34 C. This suggested that reducing the temperature at which compression is performed may help to reduce or eliminate film formation and sticking during tableting of hydrophobic drug mixtures.

The effect of lower temperatures on tablet compression was first assessed by lowering turret/punch tip temperature of a Korsch XM 12 Single layer/Bilayer 18 station Tablet Press (Figure 1) to 18 C to 20 C by using Vortex coolers (manufacturer details required) (Figures 3 and 4). Turret/punch tip temperatures were reduced to 18 C and maintained between 18 C to 20 C (monitored via an IR thermometer) during the four-hour tableting run.

Cooling of the turret/punch tips during tableting resulted in a 50% increase in tablet yield and a 100% batch completion rate. Moreover, tablet thickness was maintained at 4.56mm - 4.57mm and there were no embossing problems (embossments were fully legible according to Level II AQL testing requirements) or coating issues with tablets manufactured using the vortex-cooled, small-scale tableting machine. Finally, tableting at the lower temperatures eliminated film formation and sticking and allowed batch completion without any downtime.

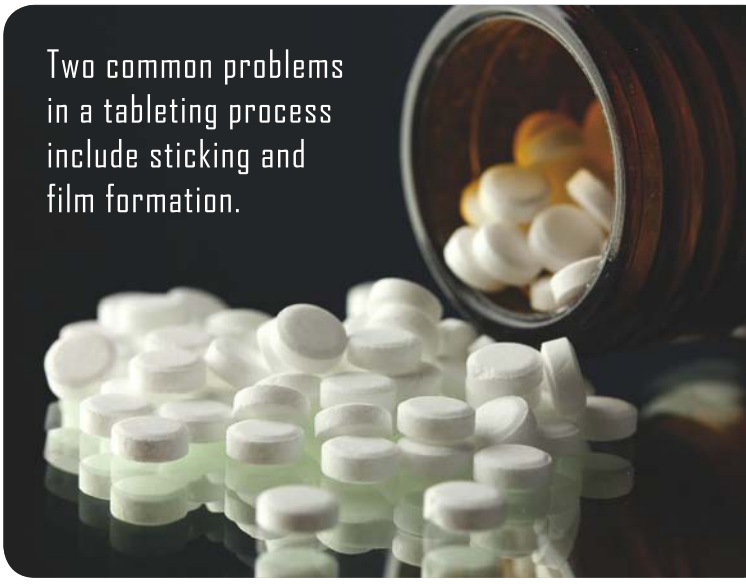
Vortex cooler

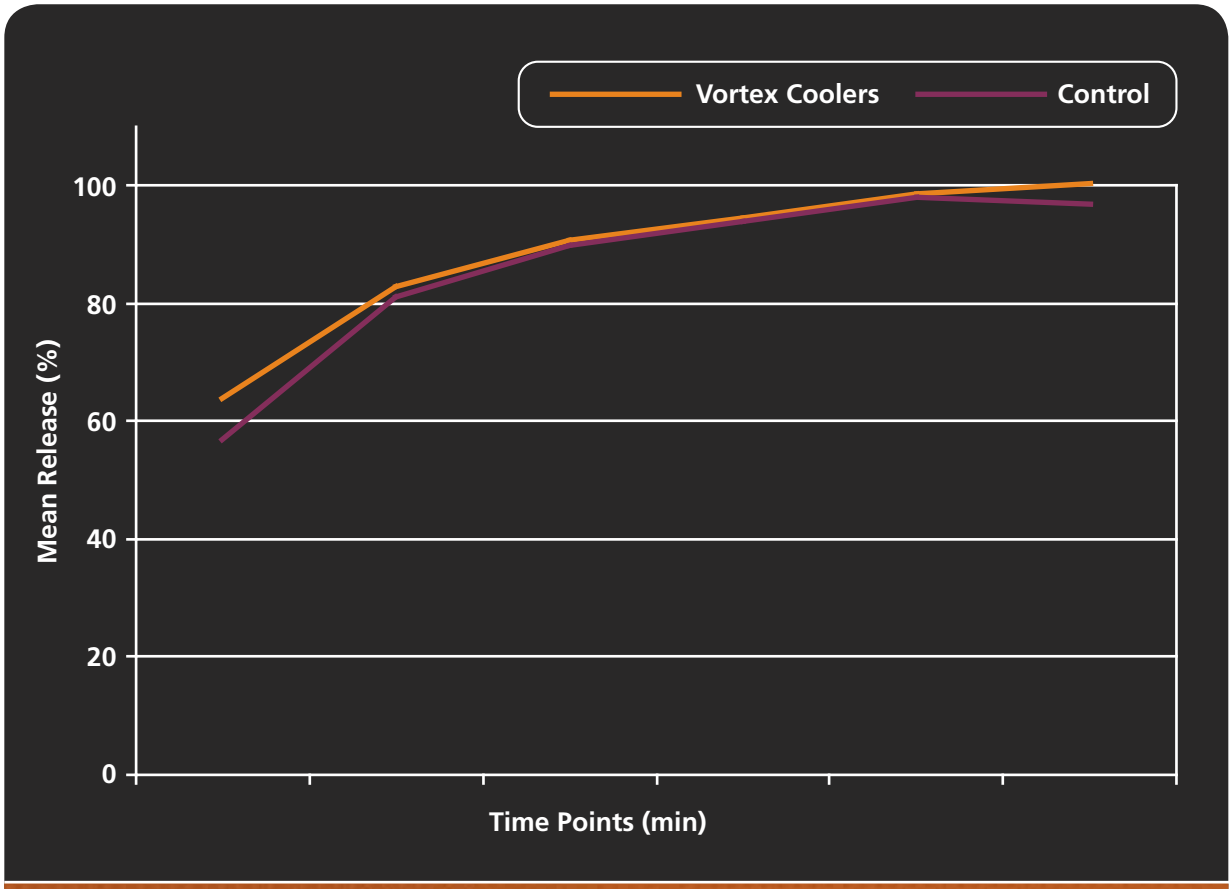
FIGURE 3.

COMMERCIAL SCALE UP

The successful application of Vortex coolers to a small-scale tableting process prompted additional experiments involving the device and a larger commercial scale tableting machine. Because of the larger size of commercial presses as compared with small scale machines, it was necessary to add an additional vortex cooler to the Stokes D34 (34 station) Tablet Press to cool turret/punch tips to 18 C to 20 C during tableting runs.

Results from these experiments were consistent with those obtained during compression using the vortex-cooled small scale tableting press. Vortex cooling of the commercial press resulted in substantial increases in tablet throughput and batch completion without any equipment downtime. Likewise, tablet thickness and embossments were significantly improved as compared with tablets manufactured using non-vortex cooled tableting presses.





Impact of Vortex Cooling During Compression on Tablet Dissolution

FIGURE 4.

VORTEX COOLING IMPACTS TABLET DISSOLUTION

While vortex cooling improved the compression process, it was possible that compression cooling may have altered dissolution properties of the finished tablet. This was assessed by comparing the dissolution rates of tablets manufactured without vortex cooling with those produced using vortex-cooled small scale or commercial tableting presses in standard tablet dissolution tests. Dissolution rates were determined by the amount of API released from the tablet over time in aqueous solutions.

The results from these tests (Figure 4) showed that there were no significant differences in the dissolution properties (percent release) of tablets manufactured using either method.

> Vortex coolers have the potential to be used to improve other manufacturing processes.

Increasingly, many new molecule entities destined for solid dosage formulation are poorly soluble or hydrophobic and susceptible to filming and sticking during the tableting process. The results from this study show that filming and sticking of a hydrophobic API during tableting can be overcome by the use of vortex coolers. The coolers offer a low cost and easily scalable option to improve tablet compression without the need for formulation changes prior to tableting.

Vortex coolers have the potential to be used to improve other manufacturing processes including automated encapsulation, roller compaction and hot melt extrusion in which film formation and sticking may be problems. Additional studies will be necessary to determine a role for vortex cooling in these processes.

References

1. IMS Midas Database, 2005. IMS Health, CT, USA.

2. Zheng, J. (2009). Formulation and analytical development for low-dose oral drug products. Hoboken, N.J.: John Wiley & Sons

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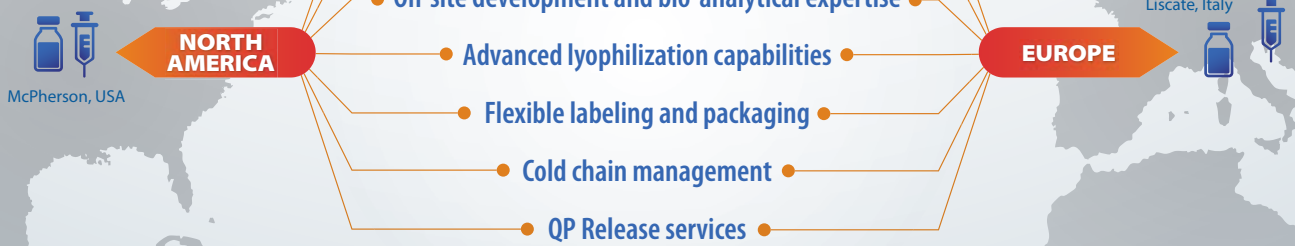

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By Susan Kheen, Contributing Editor

NOT ALWAYS FROM THE TOP DOWN

Manufacturing operators key to quality culture

JANET WOODCOCK was quite clear in her 2013 plenary speech at the national ISPE meeting in Washington, D.C. The Food and Drug Administration (FDA), she said, is interested in creating a quality culture inside organizations "from the shop floor to the boardroom." This is not a new message, but the urgency for doing it is being translated into action, with the addition of hundreds of millions of additional budget dollars to the FDA budget in 2014 from the GDUFA (Generic Drug Users Fee Amendment) statutes, at a time when most government agencies are seeing budget cuts[1].

The vision of a quality culture across an entire organization is even more critical to FDA for both the pharmaceutical industry and their contract manufacturing organizations (CMOs) to execute than ever before, given that global manufacturing supply chains are used to manufacture 70% of the generic prescriptions used by the U.S. public every day. The FDA is going to "measure, incentivize and reward" the companies that implement a quality culture. And what the FDA says, industry executes.

WHAT ABOUT THE LINE WORKER?

So the question becomes: What is meant by across an entire organization when discussing quality culture? After all, don't we usually hear that to be successful, a company's strategic vision must be driven from the top, and communicated articulately, with passion and vigor, by a company's CEO down through the organization? There are hundreds of examples of great companies whose CEOs are synonymous with a company's excellent execution of a CEO's vision. Think about the late Steve Jobs of Apple, or James Dimon, CEO of JP Morgan Chase, both dynamic speakers with clear and passionate vision. But what about the line workers — the operators and technicians who make the products? Do you think they've heard the speech? In the pharmaceutical and medical device manufacturing industry (which have huge levels of manual interventions), it is obviously more critical that those who are charged with "making safe and effective medicines and devices for the public," understand what a quality culture truly means for them, in their jobs, every day.

As we have moved two centuries beyond the Industrial Age and decades past the age where U.S. manufacturing dominated the global economy, it might be expected that there be less attention paid to the role of the hands-on manufacturing, shop-floor employee. How often do we hear about a strategic vision being executed from the workforce of an organization? Yet, how can a true quality culture, developed to manufacture safe medicine, exist without the buy-in and understanding of the hands that are producing those products — the workforce operators and technicians?

In this era of a globalized manufacturing industry, it's imperative that strategic vision be focused from the bottom up. There are guidelines already in place, of course, through Standard Operating Procedures (SOPs) and current Good Manufacturing Practices (cGMPs). But these are not enough, as evidenced by an unacceptably high level of product recalls, which impacts the continuity of supply of key drugs and devices to the public. SOPs are looked at early on when an operator learns a process, but blind repetition of said process does not lead to continuous improvement; instead it can breed boredom and the likelihood of mistakes over time. Poor handling and a laxity of attention to following the SOPs are not deliberate — it may simply be a lack of knowledge and the lack of a quality culture that encourages learning more about the "Whys of cGMP" that underpin the "How of SOPs" in making safe and effective medicines.

There is value in educating technicians and manufacturing employees to better understand the Whys of cGMP. FDA comments aside, it is simply good business to address a continuous quality improvement

mindset, and to institute consistent quality-based learning — learning that goes well beyond senior operators demonstrating SOPs to the junior operators in a plant. Instead, linking your operations to the good science and good data on which those processes are based, and showing all employees why processes are performed the way the SOPs are written, creates an environment that invites your manufacturing staff to interact, question and potentially spot quality risks before they become a problem.

COMMERCIAL ADVANTAGES FOR CMOs

CMOs in particular will find a real advantage in the marketplace if an operator education program is visible, measurable and consistent. Showing existing and potential new pharmaceutical partners that such training is in place can be a true differentiator when tendering for business. While their pharmaceutical clients will audit and verify the quality and safety of products being produced on their behalf, few will mandate training programs for their CMO's operators even though they often have in-house customized training for many in-house, manufacturing-specific scenarios. So CMOs need to be able to step up to the plate themselves and show their own commitment to quality training programs for their operators and technicians and demonstrate the added-value of their overall commercial offering rather than simply its price when trying to expand their customer base.

To truly showcase a company's dedication to quality culture, the manufacturing floor operator training must go beyond just an understanding of SOPs, to more comprehensive understanding of the "Whys of cGMP." Gerry Creaner understands this very well. As CEO of a company that uses short, precise videos to convey the quality message to a global audience in pharmaceutical and medical device manufacturing, GetReskilled's CEO says, "Where FDA is focused, industry will align." He goes on to say that "early adopters of this comprehensive view of quality culture development are clearly going to benefit from the FDA's stated intention to measure, incentivize and reward those companies that implement a quality culture. The pharmaceutical industry has been mandated for some time now with the intent to build continuous quality improvement into their manufacturing, now that their quality culture is going

With pharmaceutical sites and their CMO partners dispersed across geographies, consistency in operator training can be a challenge. Training delivered in local languages can be a plus.

FIGURE 1.

WHAT TO LOOK FOR IN A QUALITY LEARNING PACKAGE

The learning industry has migrated from a classroom environment to an online environment, with content delivered in smaller, bite-sized pieces over a longer period of time. This is perfect for the manufacturing workforce, and operators and technicians will value the ability to learn at their own pace using on-line learning.

1. Look for learning programs that focus on the Whys, not simply the Whats.
2. Look for video learning that can be delivered in small, 5-10 minute snippets. This allows for a more realistic schedule of daily interaction than longer courses.
3. Make sure the learning package chosen can grow with your company; multiple local language capability is key.
4. Ask for easy customization. If you have a particular need, ask about the time and cost to customize. If the online learning focuses on the pharmaceutical and medical device industry, this should not be a problem.
5. Ensure that the Support function is available across time zones, 24/7.
6. Look for the ability to track students' participation.
7. Simple reporting functions are key for CMOs who will want to want to showcase training results for use in marketing.
8. Look for training packages that allow operators to learn at their own pace, but allow managers to track and see their progress.

Look for learning that encourages the application of knowledge and a curriculum that encourages written responses that display acquired knowledge, rather than standardized multiple choice testing. The idea is to encourage learning about the quality process, and engagement/writing/instructor interaction is far better at achieving learning than requirements to fulfill a certain grade on a multiple choice test.

to be measured, it's going to happen from the ground floor up. And as sure as night follows day, rankings of companies and their manufacturing locations (however they enter the public domain) will drive this initiative."

Online video training (see sidebar) allows operators to watch daily or weekly short 5-10 minute videos that describe the thinking behind cGMPs. One of the training modules explains, for example, why it is important to move slowly and deliberately inside a cleanroom — because the airflow inside the room is designed for calm, methodical handling, not for quick motion and movement, or excited hand-waving while an operator shares the latest weekend football scores. The take-away: Disruption of the airflow too dramatically can be detrimental to the safety and efficacy of the products, by increasing the potential risk of contamination. Another module emphasizes that the medicines — the products being handled by the operators daily, are being ingested or injected by operators' loved ones — parents, wives, husbands, sons and daughters. This module teaches that the job they do each day is always patient-centric, everything from gowning up, or putting on a hairnet properly. "It seems obvious, but developing a patient-centric philosophy and showing who will use the products being manufactured, go a long way toward driving the quality message," says Creaner.

It seems intuitive to understand how training operators about why certain manufacturing practices make safer medicine, will lead to higher quality products, but that is not the full story about how manufacturing quality training can help organizations spot potential quality risks before they become issues.

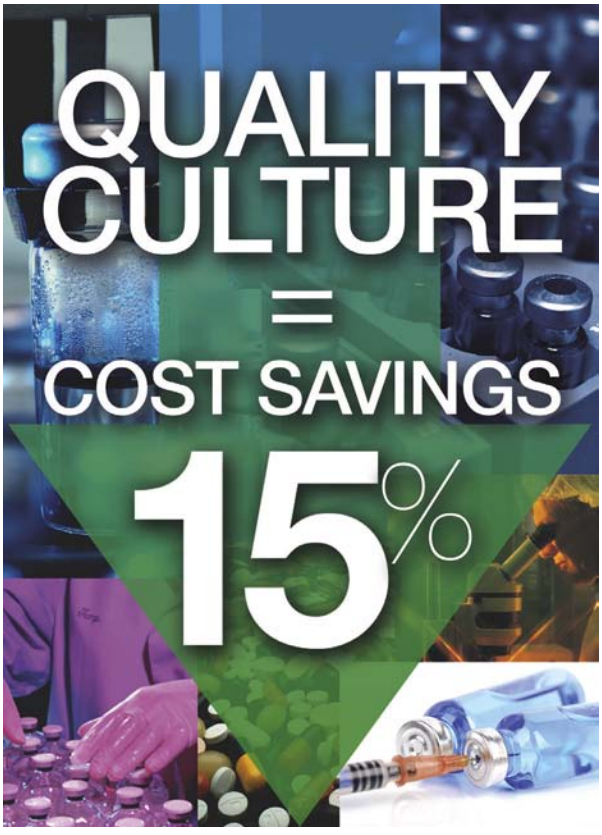
QUALITY HAND-RAISING

Differences in customs and traditions can come into play when implementing a quality culture. In the Asian-Pacific region, manufacturing workforces represent a mindset which may emphasize deference to superiors, the importance of status within an organization, and an abhorrence of 'losing face,' and may result in operators and technicians being less likely to speak up about risks to the quality of the product or suggesting better ways of doing things than simply following the way it has always been done. Western cultures may not see it as a negative to speak up to a superior, but new operators would naturally defer to the tacit knowledge of the experienced ones or to the loudest voice in the room. However, experience has shown that if operators understand why a particular task is being performed in a particular way, then the likelihood increases that they will raise a hand when a task is being performed incorrectly or a potential problem of future risk is spotted.

It's a good idea to educate operators about the science and good data needed when making suggestions and decisions about the process, so as to meet the intent of the GMPs. A great example of this concerns injectables:

Example: Teaching manufacturing operators and technicians the simple science behind SOPs comes alive when you talk about injectable products. Students are taught that injections bypass all the body's defense mechanisms because the drug goes directly into the bloodstream. Creams, ointments and tablets on the other hand, benefit from the many of the body's own defenses, with natural filters such as the skin, stomach, liver, etc., before entering the bloodstream. Learning the science behind Injectable Manufacturing SOPs makes routine procedures come alive.

Understanding the "real science," as Creaner puts it, lessens the cultural taboos against bringing problems to the attention of superiors, because the operator understands he is questioning the science and the data as to why things have always been done in a particular way, and not that he/she is questioning the individual or his supervisor. So, education and training modules teach students how regulations, SOPs and cGMPs are based on simple, good science, which is the same approach that the regulators take when approving new drugs and auditing their manufacturing process. Understanding how a drug's chemistry works in the process, and how the equipment is used to protect that process — the temperatures, mixing, agitation, reaction times — are simplified and explained. Understanding the real science leads to a clearer understanding of the Whys of GMP and fosters a quality culture.



In a paper presented at last year's ISPE annual meeting, savings from increasing product quality was quantified at 15%. An effective training program investment can help realize the quality gains to achieve those savings.

FIGURE 2.

CONSISTENCY OF TRAINING ACROSS SITES

If your organization decides to embark on an operator training program, then consider this: Quality training consistency across geographic borders and between a company's multiple sites is important. With 90% of the medicines people ingest produced generically and 70% of those medicines also produced overseas[2], make sure the training you provide is consistent across your global organization, and it is available in multiple languages. Again, this sounds obvious, but your competitive advantage is lost if the cGMP education is only available in English. A CMO who can show a Web-based training program for its operators across its global organization with access to multiple languages will have a competitive advantage in the marketplace.

RISK-BASED AUDITS

Increased levels of scrutiny will be felt inside organizations. FDA's Woodcock made no secret of the fact that she is dedicating higher levels of funding to the effort of audits and is increasing staff. However, FDA is also quite clearly on a path to conduct more risk-based audits, as it has been mandated to do under FDA Safety and Innovation Act (FDASIA). There have been multiple meetings with industry to define the quality metrics necessary for consistent measurement of a risk based approach to measuring an organization's quality culture. While there is an ongoing debate on how to define a consistent measurement of company risk profiles, there seems little doubt that more frequent audits will be the result for those who have the poorest quality rankings. If a quality culture can be clearly demonstrated, at all levels of an organization — from the operators who manufacture the drugs and devices at the shop floor and throughout all levels of an organization, one of the FDA rewards will be less frequent audits, because a manufacturing organization would have a lower risk profile than its peers.

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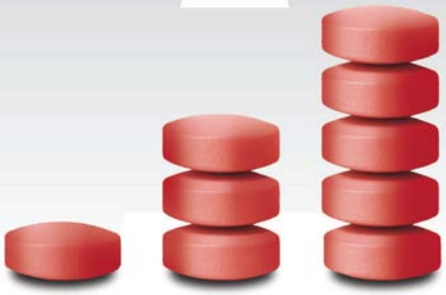

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Year Founded: 2001
Number of Employees: 85 (approximately)

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> Focus on your manufacturing floor, because FDA is focusing there, in a big way.

Fewer audits mean measurable cost savings to an organization; just the cost difference between bi-annual audits and annual or multi-annual FDA audits alone is substantial. In addition, higher quality can mean commanding a better price in the market for a CMO's products. For a CMO, going back to re-negotiate a contract with a client pharmaceutical company there is no question that their bargaining position will be stronger if the CMO organization has taken a proactive role in continuous quality improvement: developing, measuring and communicating their quality culture with its pool of potential clients. At the ISPE annual meeting last year one of the papers quantified a 15% cost saving from increasing product quality. So, while it may take investment up front, there are excellent commercial, market and operational reasons to consider investment in quality improvement and culture across all levels of your manufacturing organization.

Operator training is certainly not the only answer to enhancing an existing quality culture. But it is one that clearly deserves attention, based on recent FDA-speak, that they are re-focusing on manufacturing and cGMPs. Commercially, there are clear reasons to become an early adopter and invest in operator learning. In short, focus on your manufacturing floor, because FDA is focusing there, in a big way. If you head up a CMO or are the VP Manufacturing for a company using CMOs, begin a discussion today about how to institute, measure and demonstrate a learning program that encourages shop floor operators to go beyond the SOPs, to truly understand the Whys of cGMP.

References

[1] Food Safety News Obama Administration Seeks FDA Funding Increase for FSMA Implementation by Helena Bottemiller, April 11, 2013

[2] Janet Woodcock plenary speech, ISPE Annual Meeting, Washington, D.C., November 2013.

By Steven E. Kuehn, Editor in Chief

ABILITY TO EXECUTE

PTI hires management vet Tony Mitchell to lead operations and growth

PHARMA TECH Industries (PTI) is identified as the largest pharmaceutical contract manufacturer and packager of powder products in the world. The closely held private company has been serving the supply chain needs of global pharmaceutical and personal care companies for more than 40 years. Recently, PTI hired management veteran Anthony Mitchell to lead operations, naming him President and Chief Operating Officer (COO) and set him to the task of leading the company's strategic growth and expansion into new product areas and emerging markets.

According to PTI, in addition to helping set the company's growth plans, Mitchell "will be charged with fostering skill set growth amidst the company's workforce," a job that, says the company, "is especially challenging" given PTI's varied production environments. Certainly challenging, and a task requiring leadership if Mitchell is to keep his new team a winner. "It's an honor to be joined with the winning team," says Mitchell. "To me, leadership is that intangible art of accomplishing the impossible and being able to replicate it over and over and over again. We've accomplished a significant amount of that at Pharma Tech."

TONY MITCHELL
Pharma Tech Industries

With more than 25 years experience, the last 13 spent with Morrison Management Specialists, it's clear Mitchell understands the DNA of highly complex manufacturing environments. To Mitchell's mind, success in such environments really gets done by people: "There's a quote out there that says, 'Leaders don't create followers, they create more leaders' and I think that is a value critical to sustained growth and continued prosperity with our clients. We have to produce more leaders at Pharma Tech." Mitchell explains that it's imperative then to hire the right folks to complement the team. "When you're recruiting people the difficulty is to not settle on someone that just can do," Mitchell says. "You have to be strategically selective; you can't just hire or promote the first person that meets the position's requirements, you have the right person that matches your culture and your team."

PTI recently broadened its onsite testing capabilities at its Royston, Ga., facility by finishing a new analytical laboratory for both Rx and OTC drugs. It's also making a multi-million dollar investment to expand its Union, Mo., plant adding some 60,000 square feet to produce more ingestible powders. Like Mitchell's hire, PTI's facility enhancements are intended to serve growth and deliver more capacity, process throughput and quality at a competitive price to its customers. "Even though I've been in the industry a short time," notes Mitchell, "what I've quickly gathered is that at the top of the list of needs for our clients are quality, excellent service and cost. And if we can deliver those three at a high level, then that builds the trust that everyone needs in a partner."

Mitchell explains that whether it's the CMO business or some other business, they all strive for what we as consumers demand in any medicine we take, and that's quality. "So in my experience," says Mitchell, "if you can consistently deliver quality on a long-term basis, at a high level, then your clients are going to beat their way to your door because that's hard to deliver, all day, everyday on a long-term basis."

Mitchell points out that PTI has attained its prominent market position developing and delivering effective solutions that help its customers meet their business goals. "Once you do that within one space your clients start to ask you what can you do in other spaces that are tangential to them," says Mitchell. "We have very strong relationships. We have clients that right now are coming to us saying, 'This is what we want PTI to do, how can we do it? How can we accomplish it?'" Mitchell says that because PTI has such an amazing group of

people, the company is able to deliver on those R&D and development inquiries and then execute on what customers are hoping to accomplish.

But in Mitchell's view, being responsive is only part of the equation and that to succeed a CMO needs to anticipate opportunities, especially if it involves integrating more efficient or emerging technologies into its process capabilities. Sometimes a CMO needs to get out in front of technologies and that means taking a bit of a speculative leap — his philosophy: "If you want to speculate on a technology, go buy the machine. Start to work with it, figure it out and then demonstrate that capability so that when a customer is looking to you for something innovative, you can back that up with facts and operational experience."

As a veteran operations executive, Mitchell understands that a company's manufacturing acumen is supported by continuous improvement and that often involves ongoing investment in production and information technologies in order to deliver on customer expectations. "Right now we're investing in technology that will make life easier for us internally, especially managing the quality environment. Being able to invest in technology so that we can satisfy all the quality demands and stay ahead of the curve is critical. We're quite proud of the technology landscape that we have, but we're not settling there. We're investing in it as we speak, and we're looking to continue to take technology to the next level."

As mentioned, PTI is a closely held private company and Mitchell agrees that gives the firm a bit more agility. "The beauty of being a midsize company is that you have more latitude to experiment and able to try different solutions, ones that are not as cost prohibitive as they would be for a multi-billion dollar organization with significant legacy systems."

Certainly the ability of CMOs to stay ahead of the curve technically is important to be successful both as a business and for its customers. But to deliver on its customers' vision, says Mitchell, "comes back to that trust."

Mitchell says that the true imperative, the secret sauce to CMO success, is the ability to execute. "In this business it's becoming apparent that talk is cheap, but people are more interested in 'are you going to be able to execute, and are you going to be able to satisfy quality demands,' and that's important when you're going through the transfer process. "The beauty of it is, I'm leading a winning team, one that's been able to deliver on that reputation." PM

By Steven E. Kuehn, Editor in Chief

THE PROCESS IS THE PRODUCT

Seasoned veteran Dr. Harry Lam shares insights from his 30-year career in CMOs

KALOBIOS PHARMACEUTICALS Inc. announced in January it had appointed Harry Lam, Ph.D., as head of manufacturing. His appointment is an important one, no doubt signaling KalosBios' intention to secure strong leadership to successfully guide the development and commercialization of its portfolio of patient-targeted, first-in-class monoclonal antibodies designed to treat cancer and sever respiratory disease.

Strong leadership is guided by experience and KalosBios' president and CEO David Pritchard points to it directly: "His experience in directing science and technology on a global basis for drug substance manufacturing will be especially pertinent … as we continue to advance the development of our patient-targeted antibody therapeutics toward commercialization."

HARRY LAM
Ph.D.

His new appointment aside, over the course of his 30-year career, Dr. Lam has maintained a focus on operational leadership across some of the industry's most prominent and innovative companies. Most recently, Lam was vice president and head of manufacturing for Shire Regenerative Medicine, preceded by 17 years at Genentech where ultimately he served as global head of contract manufacturing. During his time at Genentech, Lam led and managed the technology and operations groups in the commissioning, qualification, tech transfer, process validation and licensure of Genentech's bacterial facility in Singapore.

Lam's resume highlights a career spanning the institution of cGMPs and the growing role and prominence of CMOs in supporting the strategic business aspirations and competitiveness of Pharma on the global stage. The state of contract manufacturing is incredibly dynamic of late, and branded pharma as well as generics are increasingly turning to contract manufacturing organizations for higher, more sophisticated levels of support across multifaceted global supply chains. "They have to have the right capacity at the right time, and that's not a simple thing because sometimes you want to field a lot of capacity to take advantage of scale and emerging markets," says Lam. "But as everyone knows, things can change quite dramatically so you don't want to be over built, but you also want to be able to capitalize on business trends and deliver drug product reliably."

In recent years organizations have pursued operational flexibility, seeking to have the ability to quickly introduce capacity to support a given customer's strategy in developing and emerging markets through the support of CMOs. "Each drug owner has a different percentage of what it produces in-house versus what is provided by external manufacturing partners," says Lam, using a term he finds more apt in characterizing contract manufacturing relationships. In general, the strategy is about looking for a sweet spot in terms of what percentage of manufacturing assets is in-house, and what's provided by external partners."

IMPACT OF CGMP

Ever since they were introduced more than 14 years ago, the impact of the FDA's GMPs for the 21st Century are still being felt, and Lam has had a seat at the implementation table from their inception. "I think, in general, there are those in the industry with the view that the bar is being raised all the time by the authorities," notes Lam, "but actually through all the years, I really believe that the health authorities are truly looking out for the benefit of the patients, the safety of the patient. So [the FDA] came up with a way to lead the industry on how to produce high quality product for the patient." Lam explains regulators

are trying to find the right balance a safe supply and a reliable supply to meet consumer demand. "It's about reliable supply of high quality product to the patient," says Lam, "so through the years, I think if you look at the industry and cGMPs it's certainly continuing to evolve, but it seems to be increasing the quality products."

Lam explains that in his experience all Pharma companies, including contract manufacturers, have different degrees of success approaching and meeting the high expectations of health authorities. "Some companies are much closer to meeting them, others not so much," says Lam, "something reflected by their regulatory inspection of performance. It's like water, either you're below the surface or you're above it. I think some manufacturers may be closer to the water's surface and occasionally dip below it — and that's when you're in trouble."

It seems to Lam that when one looks at major contract manufacturing organizations and at levels of inspection, as well as levels of 483 observances, warning letters, and consent decrees, etc., if you're able to manage well, and if you have operational excellence in the forefront of your organization, then you're able to respond well and push your head above water. "I would say manufacturers, either internal or external, that in our business, that you really have to pay attention to your operations — it's a slippery slope. If you don't, it can get you below water pretty quickly."

Lam explains that it's about regulators' confidence in a manufacturer. Once the regulator loses confidence, everything that was previously acceptable now becomes unacceptable and then become citations and warning letters.

"The second thing regulators do, especially with manufacturers that have a network of facilities," notes Lam, "and so are many of these are multinationals, with big formal networks. [Regulators] really expect the standard to be maintained for every site; one can not just say, 'Well this is just one manufacturing site' — if one site has problems, then the entire network has problems. That's a lesson learned for me."

Quality and risk management are at the forefront of this conversation, says Lam, and Pharma companies cannot just offload manufacturing to CMOs and expect to shed the risk and liabilities along with the contract. Recent guidance from the FDA regarding the roles across quality systems and risk management with CMOs and the substance or drug owners is being defined a little bit better and, ultimately, that looks like a good thing.

DIFFERENCES BIG AND SMALL

All CMO pharma manufacturers will face challenges, with regulators, with quality processes, with operations on the road to compliance and commercial success, says Lam; in the cGMP world order he accepts that contract biopharmaceutical manufacturers may be particularly challenged. "In the small molecule world, the focus is a lot more about — because we can characterize the final product so well — that you can put in a lot of testing and quality control to assure QA and make sure that it's safe, high quality and meeting all the expectations of identity and all the detail things that one can do to characterize it," explains Lam.

"But it's well known that for biologics, the process is the product. For small molecule [compounds] there's a lot more focus on the end product, because the product is well characterized to begin with," says Lam. "However, from a compliance perspective, regulators are actually putting more and more emphasis on process because it's a biologic, it's so difficult to really fully characterize the product." Lam says the entire process is important from a regulator perspective, and that it is important self-impose requirements to make sure the entire process is well characterized because with biologics one cannot fully characterize the final product.

Managing toward operational excellence is more or less mandatory and Lam agrees. "I cannot tell you enough how important it is, not just to the regulator. I think it's a good thing to do, as a manufacturer, to be able to continue to look at what are the potential risks in your process that may not allow you to make the products that you need to make."

Lam explains that there are doubts about QbD because it's so complicated and it requires so much work that some regulators are realizing that full-blown QbD may be the provenance of only a few really big manufacturers because they are the ones who can afford it.

"But let's not throw away the baby in the bath water," says Lam. "It's a fact that it's difficult to do, perhaps we need to just agree that sure it's a great concept and always strive to look at and understand process and keep working on implementing it to meet its intent." Lam notes that the industry and regulators are evolving in that direction.

"I think that regulators are really concerned about shortages and again it's about what I said right from the beginning. It's about balance; it's about needing to have high quality products and make sure that patient safety and quality, as well as availability are delivered," Lam concludes. "The regulators really want to work with the industry to make sure that we have this quality culture; that throughout the entire lifecycle of the process, from development to getting approval to post approval, there is continuous monitoring and improvement. I totally understand where the FDA is coming from, and I agree that it is the right thing to do and the right way to do it." PM

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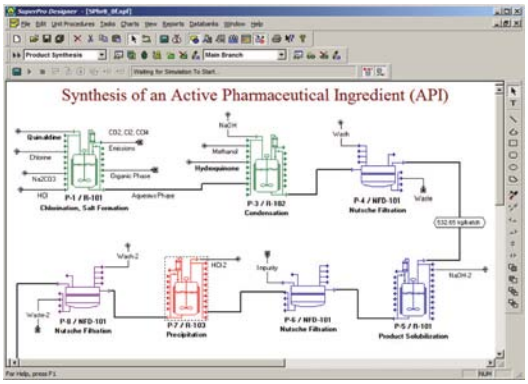
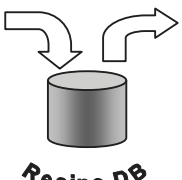
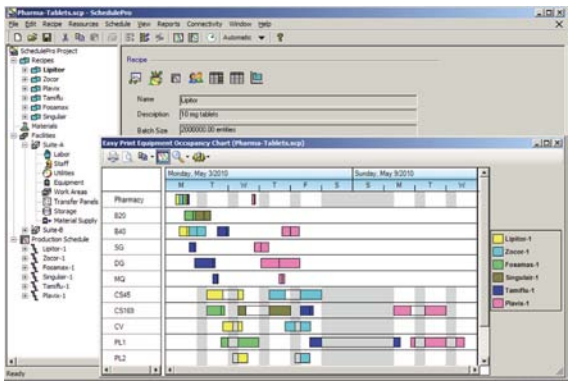


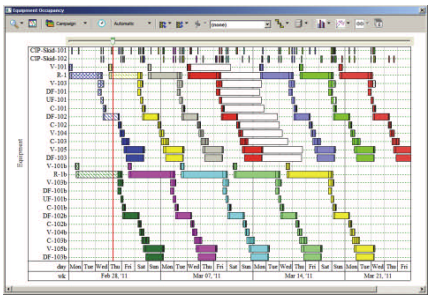
Use SuperPro Designer to model, evaluate, and optimize batch and continuous processes



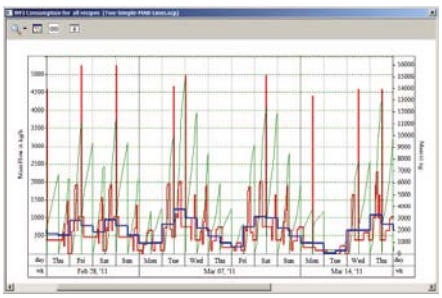
SchedulePro®



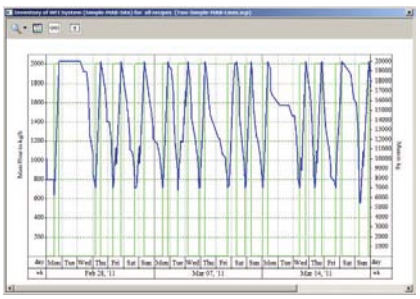
Migrate to SchedulePro to model, schedule, and debottleneck multi-product facilities



Easy production tracking, conflict resolution and rescheduling



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



Managing inventories for input, intermediate, and output materials

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

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

Visit our website to download detailed product literature and functional evaluation versions of our tools

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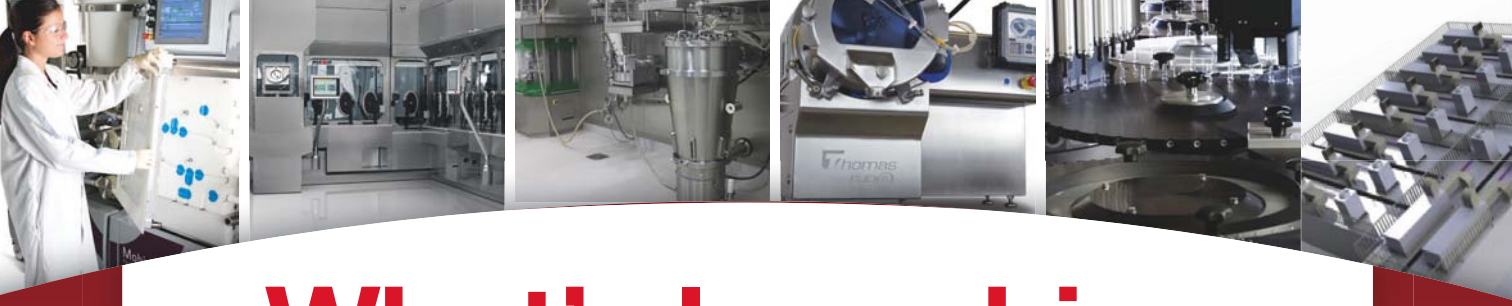

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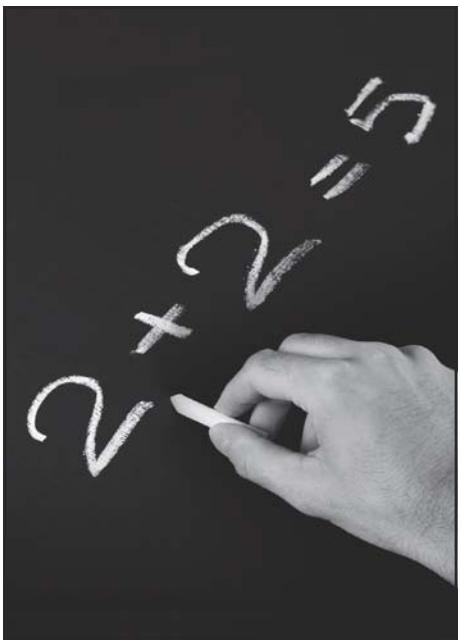

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