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Cover Feature

Packaging Delivers

2015 PACKAGING TRENDS

For Pharma, what's on the outside counts as much as what's on the inside

BY STEVEN E. KUEHN, EDITOR IN CHIEF

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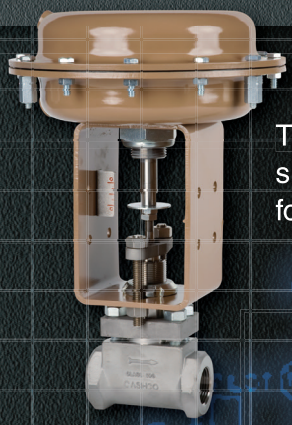

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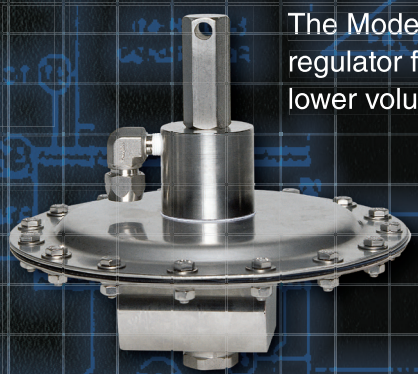

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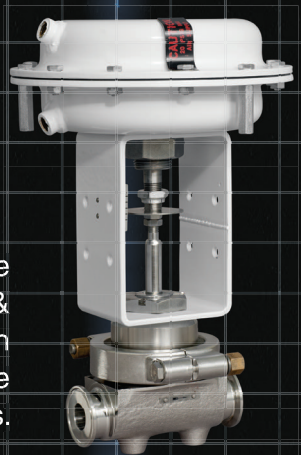

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I'm Printing Your Prescription Now, Ma'am

Building better medicines one layer at a time

NOT SURE, but I think Aprecia Pharmaceuticals' August 3, 2015, press release announcing FDA approval of its anti-seizure SPRITAM levetiracetam almost broke the Internet. Why? Unless you were trekking in the Himalayas the entire month of August, you likely know why. SPRITAM uses Aprecia's proprietary ZipDose platform, a technology based on three-dimensional printing (a/k/a additive manufacturing) to print its formulation into a porous matrix that quickly dissolves with a sip of liquid. While the additive manufacturing (AM) technique has previously been approved to manufacture medical devices, says Aprecia, it's the first time the FDA's approved 3D printing to manufacture an orally ingested solid dose formulation. Who out there is not excited about this development?

Don Wetherhold, Aprecia's CEO, explained that "By combining 3D printing technology with a highly prescribed epilepsy treatment," SPRITAM is designed to fill a need for patients who struggle with their current medication experience." According to Aprecia, SPRITAM is first in a line of central nervous system products it plans to introduce as part of a strategic initiative to transform "the way patients experience taking medication."

The font of all human knowledge, Wikipedia, revealed that in 1981 Hideo Kodama of Nagoya Municipal Industrial Research Institute invented the first two AM fabricating methods. Thirty-plus years later we're seeing what may prove to be the first truly commercial, 3D-printed consumer product.

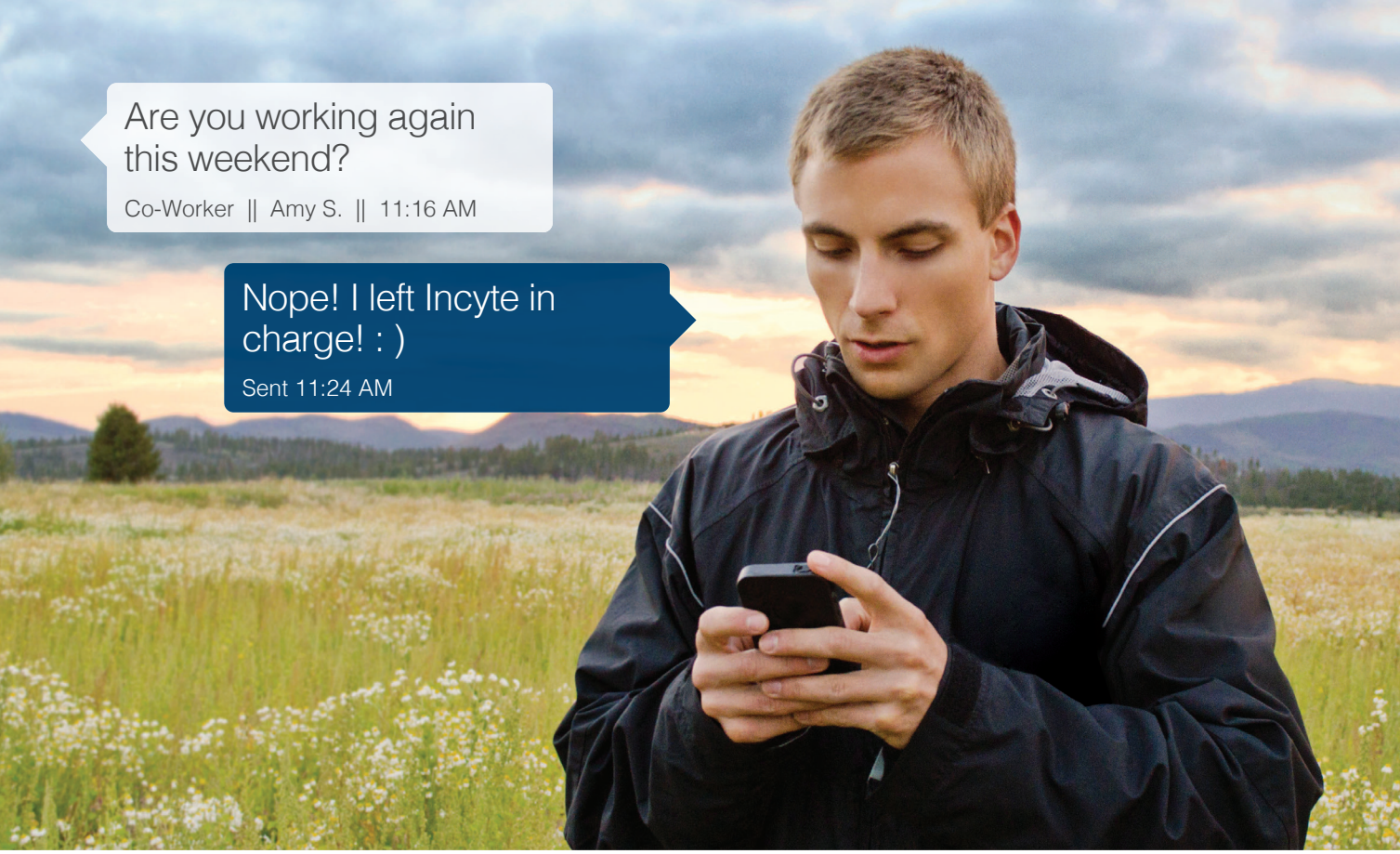
Regardless, the news of Aprecia's breakthrough spread across the Net like wildfire, with story after story touting the milestone and reviewing the potential and ability of this technology to supersede the invention of sliced bread while eliminating drug factories and pharmacies because everyone will soon be printing their own drugs at home! OK, that's a bit of an exaggeration, but the bottom line is the technology has a high degree of potential to support patient-specific formulation and tailored release characteristics. First off, Aprecia's ZipDose methodology enables the delivery of a high drug load, up to 1,000 mg in a single dose, with just a sip of liquid.

Engineering OSD release characteristics via 3D printing techniques have been attracting researchers interest and investor dollars in equal measure because the technique offers such a compelling a solution for manipulating release performance. For example, Professor Ricky Wildman of the EPSRC Center for Innovative Manufacturing, University of Nottingham, is recognized as one of the emerging authorities on the physics and engineering associated with biomedical-related 3D printing. Presenting at Medtec UK last March, Wildman noted 3D printing has a real role to play in personalized medicine. Noting that current forms of treatment require a systemic flooding of the system (ingesting of a tablet), printed drug delivery systems present the opportunity to tailor formulation, developing a release strategy at the design stage and enlisting geometry and material functionality to achieve specific release characteristics. Wildman asked the audience to imagine being assessed and then having the treatment manufactured specifically to treat their disease.

ZIPDOSE METHODOLOGY ENABLES THE DELIVERY OF A HIGH DRUG LOAD **WITH JUST A SIP OF LIQUID.**

Of course, getting there is not without its challenges. Wildman maintains diagnostic capability needs to be matched to manufacturing. He notes that to design such specific platforms, drug makers will need a thorough understanding of its formulation's material and structural characteristics including degradation and dissolution mechanics. Fortunately, advanced PAT technology has that covered. Freeman Technology's FT4 Powder Rheometer delivers data that support process and product understanding and the optimization of powder processes. The system, says Freeman is currently being used to assess exactly how AM powders pack and flow to ensure process efficiency and consistent product quality.

Wildman says the current understanding of how drug developers can fine tune the "functionalization" of given molecules is relatively limited — one can't "dial up" the needed molecule or material for an intended, specific purpose. Sure, we're a ways away from when "bespoke" AM-printed drugs are commonplace, but thanks to Aprecia, and PAT vendors like Freeman, we're all that much closer to this reality.



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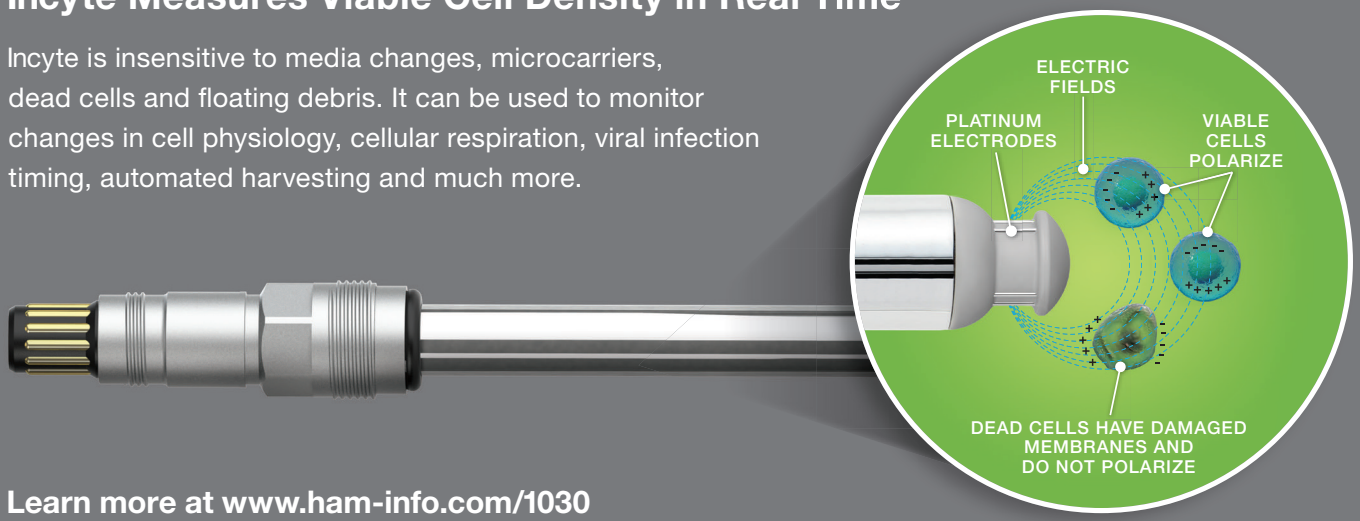

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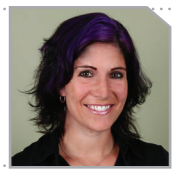

New Dogs, Old Tricks?

E-learning is advancing, but should we kick it old school when it comes to preparing manufacturing workers?

BY KAREN LANGHAUSER, DIGITAL CONTENT MANAGER

IT'S THAT time of year again: kids begrudgingly board school buses, as parents around the country silently rejoice. During back-to-school season, talk often turns to learning. Educational theories vary sharply in our country and there is much debate surrounding educational goals and, more specifically, how to prepare newer generations of people to achieve these goals.

Learning doesn't end after graduation, obviously, and there is constant discussion in the pharma industry and manufacturing in general about the "people factor," and the industry's ability to close the manufacturing skills gap and put the right people in the right positions.

"Millennials" (those born in the early '80s and '90s) are bringing a new set of obstacles to the industry because they tend to push back on "traditional" approaches to learning in the workplace. While this can be challenging — and in some cases, plain annoying — great ideas have been born out of the need to innovate learning.

E-learning offers a great solution to an industry that is ever-changing and also requires highly customized training. Vendors have come up with truly out-of-the-box methods to train employees. For example, Pharmaceutical Training International, a supplier of event-based training courses for the pharma and biotech sectors, recently launched a range of game-based e-learning courses that allow employees to learn and compete through interactive quizzes and 3D virtual environments. Users benefit from a more engaging and entertaining method of acquiring new skills through role-play in real-world scenarios.

But should we abandon the tried and true methods of learning? There is no arguing the historical significance of manufacturing in the U.S., and the country saw much success from a very traditional learning structure. Jerry Jasinowski, former President of the National Association of Manufacturers, recently published a blog advocating a more traditional approach to training new workers for the modern manufacturing workplace.

Jasinowski points out that the apprenticeship concept — pairing new employees with trained veterans — is still a valid and reliable method of grooming qualified workers.

In fact, the apprenticeship model is alive and well in UK pharma, and apprenticeships are largely built into the training infrastructure. GSK offers paid hands-on apprenticeship programs in the UK in specific areas such as supply chain, IT, lab, manufacturing and packaging; Novartis and Takeda offer similar programs at their UK branches.

Critics are quick to point out that given time and financial constraints, as well as lack of government support, a full-scale European-style apprenticeship model in U.S. pharma isn't the answer. But the idea that many have proposed is perhaps more along the lines of bringing back aspects of apprenticeship.

Indeed a "blended approach" to learning — a mix of digital and traditional hands-on teaching — appears to be highly regarded in the pharma industry. Millennials in the workplace push companies to take a fresh look at training and development approaches, and those revised approaches, combined with time-tested methods, can lead to better performance from an organization as whole.

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China's Crouching Pharma Tiger

CFDA ready to enforce GMP; industry investing to comply

BY STEVEN E. KUEHN, EDITOR IN CHIEF, AND KATIE WEILER, MANAGING EDITOR

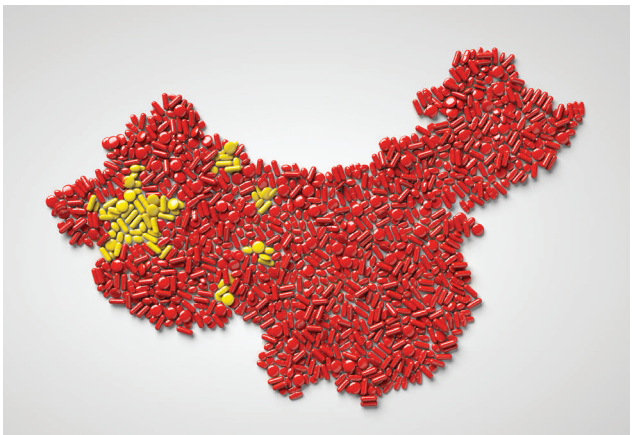
CHINA CONTINUES to flex its global, economic muscles and demonstrate its willingness to compete on the world stage, and that includes Generic pharmaceutical and API manufacture. In response to a rising number of quality excursions, some highly publicized, China's API and pharmaceutical processors continue to face increasing scrutiny by the world's Pharma regulators. However, to meet its own internal and growing demand for Western-style drugs and pharmaceutical therapies, as well as pursue global API and Generic markets, China's regulatory agency, the CFDA, has bolstered its efforts to enforce GMP-based drug quality standards. Recently returned from China, Scott Bass, head of Sidley Austin's global life sciences practice, says he is seeing the Chinese government increase its focus on GMP-based quality.

"The increased focus on GMP is part of a move to play a larger role on the worldwide finished dosage market — and of course, in part, a response to Heparin and other quality concerns that occurred years ago," says Bass. "China began its entry into the market by cornering much of the API business, and by focusing heavily on domestic-oriented generic drug production. While the focus on generic drug production has not changed, and while China is now, along with India, a major source of global API, the industry has evolved both in terms of innovative research and investment and in terms of facility upgrades."

According to Bass, new GMPs issued several years ago by CFDA appear now to be ready to be enforced, in part, he says, because the government believes that companies have evolved to the point where enforcement will actually be meaningful. China has now permitted 17 additional U.S. FDA inspectors to obtain visas, notes Bass, explaining that move will support greater scrutiny over exported pharmaceutical, medical device and food products. Pithily, Bass notes, "China is also well aware of the U.S. enforcement against quality concerns in India," as another motivator prompting the Chinese government's push for pharmaceutical manufacturing quality.

CHINA'S GETTING THE MESSAGE

To be a global player one has to play by the rules and China, apparently, wants to play and by the industry's established rules. "They are getting the message that quality drives international participation," says Bass,



FUNNY PHARM

"GMP is simply just good mopping practice."
— Seshu Gudlavalleti

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

explaining that the Chinese government is also investing in research and development incubators and other discrete innovator strategies. "China is also ostensibly avoiding some of the problems that plague the manufacturers in India," says Bass, "who are subject to multiple Import Alerts in the United States and some investigations."

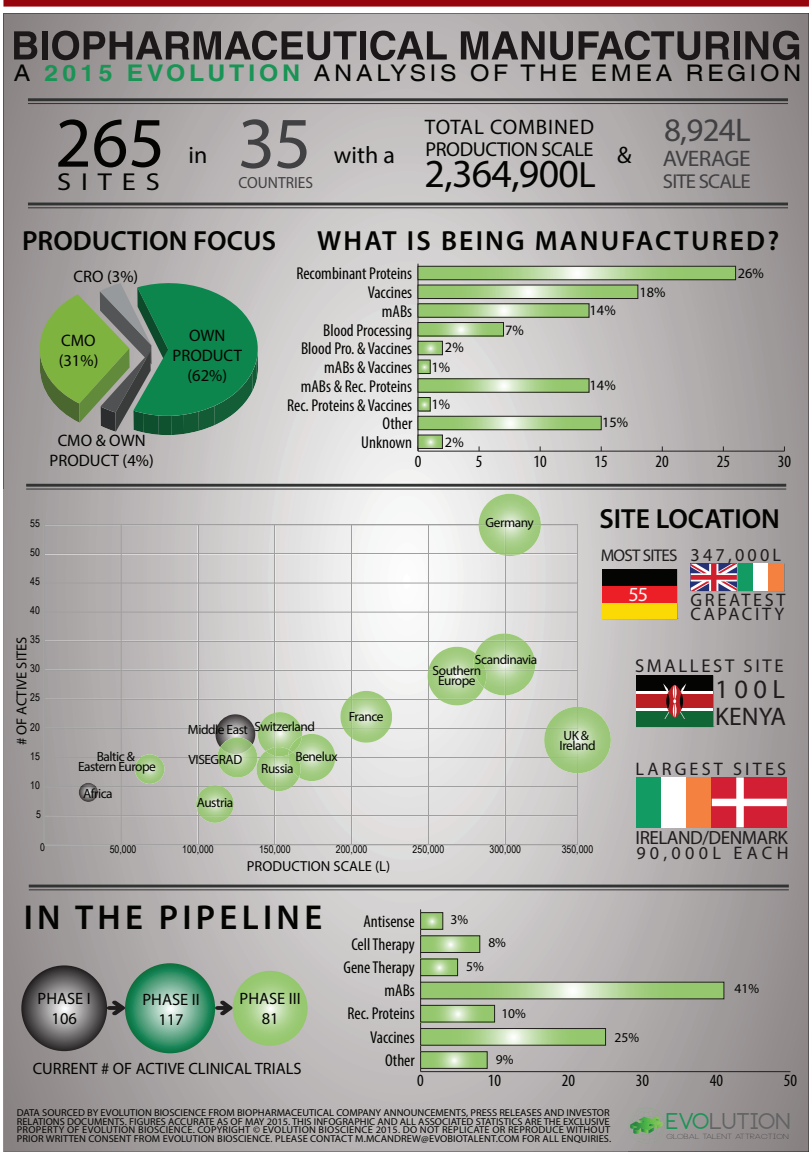
For most observing China's pharmaceutical industry, what appears is usually a study in contrasts, with the forces of free-market capitalism bumping up against centrally planned socialistic economic doctrine, as well as other social and political dichotomies that tend not to support operational excellence and an institutionalized and pervasive quality culture. "Like much of the business, politics and life in China, there are always two stories at the same time," says Bass. "It will be a long time before the underdeveloped, rural poor areas of China meet the same standards that the highly industrialized, export-oriented provinces/cities demonstrate. So quality remains the main theme."

BIOPHARMA MANUFACTURING IN THE EMEA REGION

FROM THE 100-liter facility in Kenya, to 90,000-liter facilities in Ireland and Denmark, Europe, Biopharmaceutical Manufacturing in the Middle East and Africa (EMEA) region may be more robust than one might think. To lend transparency and illuminate the regions' activity in this sector, analysts at EVOLUTION Global Talent Attraction put together an accessible, informative infographic that assessed 265 facilities across the 35 different countries that make up the EMEA region.

A scan of EVOLUTION's nearby infographic reveals that European Union companies are producing biopharmaceuticals and biologics at commercial scale with some operating at tremendous capacity. With a combined production scale of some 2.3 million liters, EMEA producers have developed a dynamic presence in the market, something that is also driving demand for highly qualified, experienced and effective professionals to fill critical development and manufacturing roles.

See the full case study online at: http://bit.ly/1LMJJbQ



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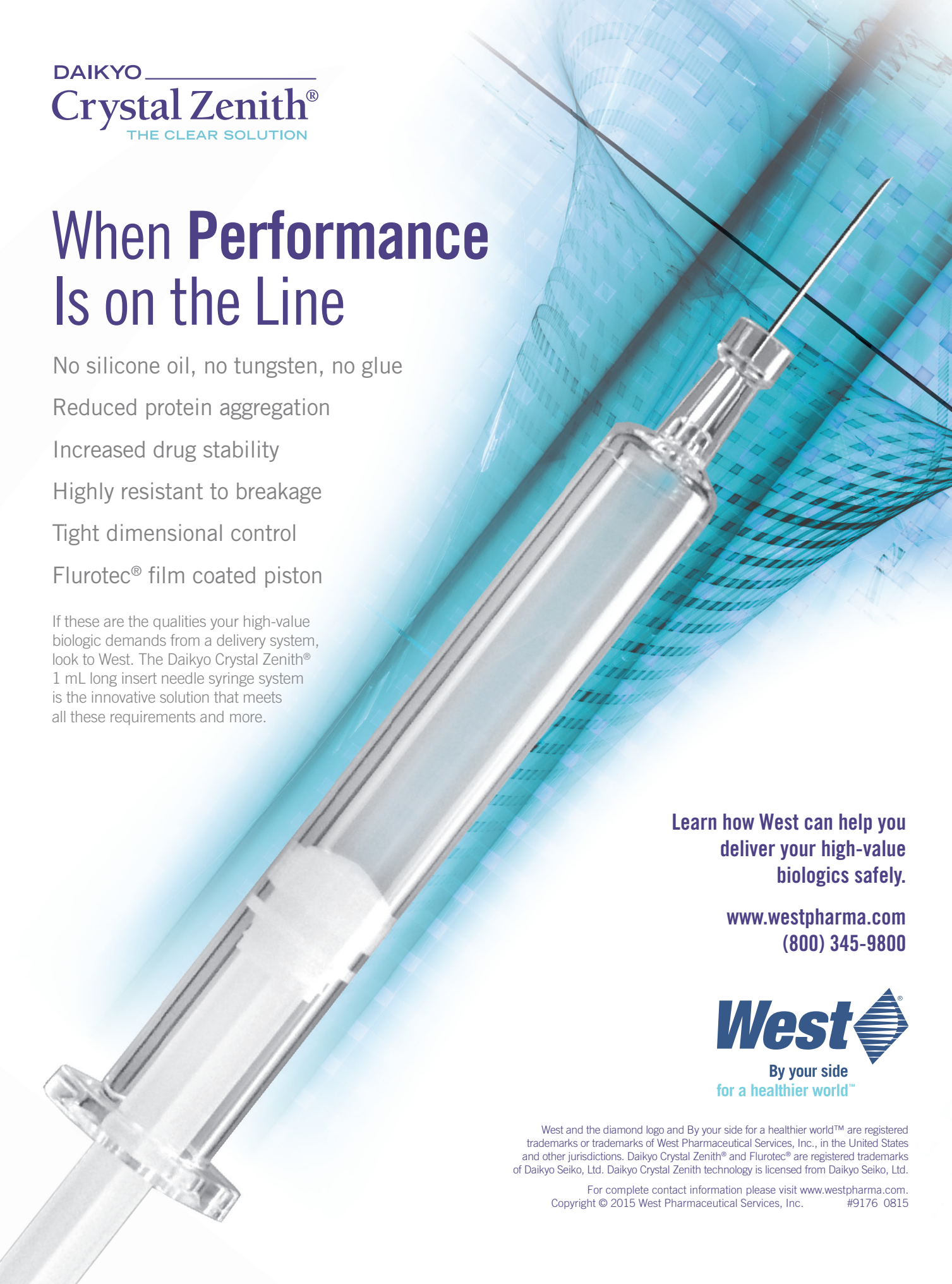

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Advanced Filtration Optimizes High-Viscosity BFS

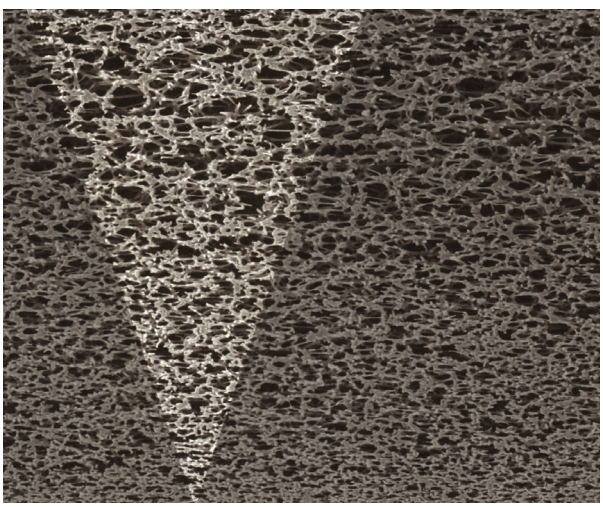
To resolve bottlenecks, Spanish CMO Unolab switches to Pall's polyethersulfone membrane filters to great effect

BY ANSELM GAYNOR, PALL LIFE SCIENCES

UNOLAB MANUFACTURING S.L., a Spanish CMO dedicated to the manufacture of sterile monodose parenteral products, offers its customers access to advanced blow-fill-seal (BFS) technology to accomplish sterile filling of these products into their final dosage containers. Specializing in liquid ophthalmics, Unolab processes a variety of formulations including highly viscous, high-density, large molecule formulations with viscosities as high as 80 centipoise.

Liquid handling in BFS systems is now sufficiently well developed to enable the filling of a broad range of formulations, including those which may be more difficult to process and prepare for filling. One particularly challenging process step for viscous formulations is sterile filtration.

Parenteral products which are heat-labile are filter sterilized to maintain efficacy and to render them safe for injection in humans. Filters designed to achieve sterility are usually rated at 0.2µm and will have been validated to produce a sterile effluent under the end-user's operation conditions, having already been qualified by the filter vendor as retentive for Brevundimonas diminuta at a challenge level of 107 cfu /cm2 membrane area in challenge tests correlated to ASTM Standard Test Method F838-05 (ASTM F838-05).



Cross-section of highly asymmetric filter membrane used to facilitate high flow/high throughput filter performance.

At the fill stage of a given pharmaceutical manufacturing process, low-viscosity aqueous fluids are commonplace and considered easy to filter. These fluids do not tend to incur a rapid deterioration in filter throughput or flow rate performance at a given differential pressure. As a result, they present a low likelihood of filter blockage and consequently any undesirable filter change-outs and associated costs.

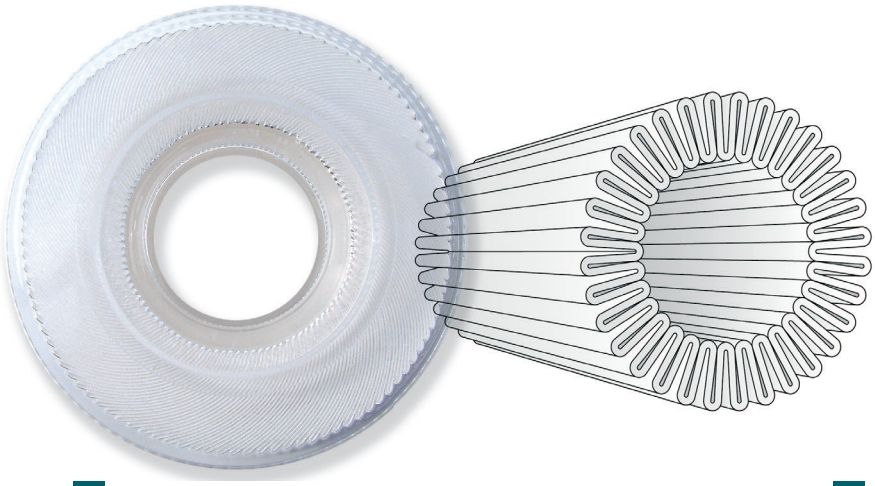
There are also plenty of liquid formulations that require viscous properties or contain suspended particles to ensure the right environment for stability and the correct delivery of the active pharmaceutical ingredient. The composition of such fluids may feature a higher particulate load, or be of a viscosity which may not be easily accommodated by a sub-micron rated membrane filter. Examples of hard-to-filter final formulations containing active ingredients of a more particulate nature would be those incorporating liposomes or nanoparticles. Those of a more viscous nature may use active ingredients such as hyaluronic acid or carboxymethyl cellulose (CMC).

IT WAS TIME TO SPECIFY A HIGHER-PERFORMING FILTER DESIGNED FOR VISCOUS PARTICULATE-LADEN FORMULATIONS.

In pursuit of continuous process improvement and operational excellence, as well as to avoid excessive downtime and costs related to filter change-outs when filtering highly viscous products, Unolab's process engineers identified an opportunity to update and improve filtration processes and remove a bottleneck that, among other things, diminished product yields. Unolab's operations director, José Ignacio Villarino Otero, characterized the issue this way: "We find that large molecule, high density formulations — essentially viscous products — can be challenging to sterile filter. These products typically present problems for us."

CHOKE HOLD

What was putting a choke-hold on sterile filtration throughput? It was the filters themselves; the use of a 30-year-old technology employing a polyvinylidene



A B

(A) Laid-over pleat geometry, narrow internal core used in 10-inch Supor EX grade ECV filters (1.04 m^2) and (B) Traditional fan pleat geometry typically used in 10-inch filter elements with EFA of 0.5m^2- 0.7 m^2.

difluoride (PVDF) membrane. Though the filter technology Unolab traditionally specified functioned correctly in the company's validated, compliant process, when used for the filtration of high viscosity, large-molecule formulations, Unolab found the use of these filters led to a significant compromise in performance and cost efficiency. This was thought to be due to the PVDF filter's symmetrical pore structure and comparatively lower clean water flow rate than that of other newer sterilizing-grade filters.

While Unolab's filtration operations are relatively straightforward, they have the potential to become labor and material intensive when viscous products are filled: They found that where one 30-inch PVDF filter would typically be required to prepare one batch of low viscosity product, for a highly viscous fluid using the same filter, seven filter change-outs were required to dispense 210 liters of product in final dosage format. Each change-out cycle required steam-in-place sterilization prior to resumption of filtration — a total of 16 hours downtime per cycle — this generated 96 hours of lost manufacturing time per batch! Further, Unolab had to filter almost 350 liters of product to achieve the 210 liter per batch yield, due to inter-batch product loss.

Recognizing recent advances made in filtration technology, it became apparent to Unolab's process engineers that it was time to specify a higher-performing filter with a design that could offer improved flow rates and with a particulate capacity better suited to viscous particulate-laden formulations. The ultimate goal was a practical and economical filtration system for hard-to-filter fluids.

Filterability testing (assessment of filtration performance in terms of flow rate and throughput) with a bench-top filter test device indicated that Pall's 30-inch Supor EX grade ECV filter using the industry standard 3x10 inch filter element construction would offer dramatic advantages over their incumbent (PVDF) filter of the same size.

The performance advantages of Pall's filter technology can be attributed to a highly asymmetric filter membrane, a structure which provides improved fluid permeability and more effective particle capture. The filter's performance is further augmented when deployed in 10-inch filter sub-units that support an effective filter area of slightly more than 1 m^2.

Ultimately, Unolab found it was able to use the Pall filter to process all the fluid required to fill a 210-liter batch of viscous product without a change-out, resulting in ease of use and cost advantages over the technology with which they had encountered considerable challenges.

According to Unolab's Otero, "Supor EX grade ECV filters have enabled us to optimize our manufacturing for a range of different product types. With these filters we can process up to five times more fluid. This means we can dispense more final dosage units per filter and optimize the manufacture of our bulk material. The result is not just reduced filtration consumable costs, but minimization of product losses and a lowering of time related costs: Supor EX grade ECV filters allow us to dose our ophthalmic products with BFS systems with fewer limitations."

Ultimately careful filter evaluation and successful implementation delivered significant process improvements to Unolab's highly critical process. In addition to benefiting from a reduction in consumables usage, minimized product losses and improved yields, Unolab is now able to enjoy savings in time-related costs including fewer start-ups, fewer sterilization cycles, reduced frequency of integrity testing and less information capture per lot.

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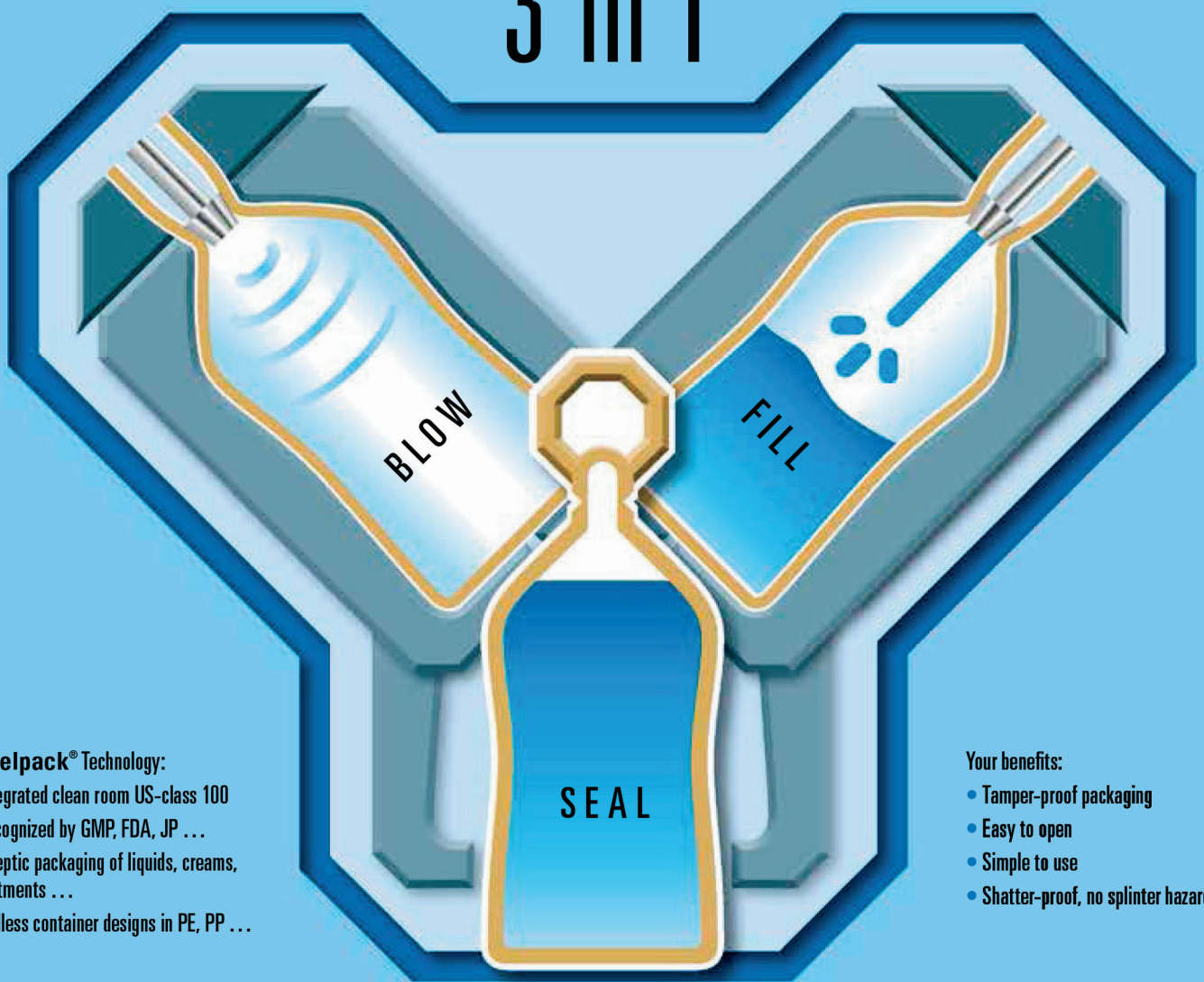

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Packaging Delivers

By Steven E. Kuehn, Editor in Chief

IT'S HARD to understate the critical role pharmaceutical packaging plays in ensuring the efficient distribution and eventually, the safe consumption of the world's drug supply. Much of where the category is today (and all that it brings to Pharma) stems from an amazing confluence of operational and technological wisdom gained from years and years of applicational experience across all sectors of the industrial landscape.

Seriously essential, packaging has always delivered, but in 2015 it's being asked to deliver even more to meet Pharma's ever-expanding demand for packaging solutions. From the materials and science associated with primary packaging, to the increasing sophistication and integration of drug delivery platforms and single-dose-unit forms, packaging is playing an increasingly integral role supporting the medical success of a given compound.

World pharmaceutical packaging demand, says The Freedonia Group, will increase 6.4 percent annually to $90 billion in 2017. According to Freedonia's "World Pharmaceutical Packaging" report, "Based on the operation of extensive and diverse drug-producing industries, Western Europe, the U.S. and Japan will account for nearly 60 percent of this amount." Not surprisingly, the report notes countries like India and China will experience the fastest product demand growth from "rapidly expanding pharmaceutical manufacturing capabilities, burgeoning drug exports, and the phasing-in of an extensive government program designed to upgrade the quality and integrity of nationally produced medicines." Who's coming up the fastest? Brazil, Mexico and Turkey were identified as fast-growing pharmaceutical packaging product markets.

For Pharma, what's on the outside counts as much as what's on the inside

As per usual, the U.S. will remain the largest market for pharmaceutical packaging "as its advanced drug-producing sector introduces new, sophisticated therapies with specialized packaging needs." Freedonia notes growth in West European demand will reflect government standards requiring unit-dose, high-barrier and security packaging for many types of medications. Japan, says the report, will also continue to provide a large, diverse market for pharmaceutical packaging.

FAST GROWTH PREDICTED FOR PREFILLABLE SYRINGES

Global demand for primary pharmaceutical containers, says Freedonia's analysts, will increase 6.6 percent annually to over $57 billion in 2017. Prefillable syringes, notes the report, will be in high demand, and the list of suppliers and vendors pursuing the potential revenue from this category are becoming legion; Becton Dickinson , Gerresheimer, SCHOTT, Vetter and West (to name just a few top players) are all positioning themselves strategically and operationally to deliver solutions to meet this burgeoning demand.

Demand for prefillable, injectable, single unit dose forms is being driven by a number of factors but Freedonia and others point out the advances in the biotechnology sector will mean a steady stream of parenteral therapies requiring prefillable solutions to deliver these therapies to consumers. West Pharmaceutical Packaging Systems' Mike Schaefers notes his company is seeing growing demand from customers for pure, high-quality packaging components for injectable biologics and biosimilars. "Many biotech and sensitive drug products have unique requirements, and polymer systems provide key solutions for patient safety and compliance," says Schaefers. "There are a variety of products on the market that can help mitigate these risks, including barrier films for elastomer components that help to reduce potential extractables and leachables formation," he says, but "for materials that are sensitive to glass, cyclic olefin polymers can be molded into a variety of shapes and sizes to accommodate not only the drug product, but also large-volume doses. In addition, cyclic olefins can be molded to suit innovative delivery devices, offering differentiation in the market." Ultimately, says Freedonia, that megatrend will also fuel "above average growth" in demand for parenteral vials and ampoules because the category will increase demand for those vessels as well.

MESSAGE IN THE BOTTLE

Despite increasing competition from highly engineered, unit-dose and prefillable solutions, plastic bottles will "remain the most widely used package globally for oral drugs distributed in bulk," notes Freedonia's report. Plastic bottle's penetration into Over-the-Counter (OTC) packaging will continue because many OTC medicines are sold in oral solid dose forms and in quantities of 50 or more.

Single-dose unit prefillable syringes are an increasingly popular primary packaging form when offered pre-sterilized and ready to fill in machine-ready trays like these units from Gerresheimer. (Photo courtesy of Gerresheimer)

Blister packaging is a rising star and Freedonia's study confirms this. Blister packaging of single doses are at the forefront of how Pharma is responding to the market and regulator's demand to improve dose compliance and therefore safety — not to mention the overall efficacy and improved outcomes of therapies administered this way. "Blister packs are becoming more popular as they can improve patient compliance and can be customized to fit a product design due to the availability of a broad range of materials and multiple configuration options," notes Gordon Haines, Rottendorf Pharmaceuticals' CEO. Rottendorf packages more than 3 billion tablets, capsules and pills a year on nine blister lines and two bottle lines. "Blister packs also protect product integrity, allowing patients to select one pill at a time while leaving the others untouched," says

West's SmartDose system is an excellent example of how West collaborates with biotech companies to offer fully integrated drug delivery systems designed to meet patient needs.

(Photo courtesy of West)

Haines, "as opposed to bottles where a patient might dump out a handful of pills in order to select just one."

Freedonia's report says it has become the second-largest selling group of primary pharmaceutical containers "and will generate above average growth in demand based on adaptability to unit dose and clinical trial formats with expanded label content, high visibility, and built-in track and trace features."

Tee Noland, CEO of Pharma Tech Industries (annual sales ~$80 million) notes customers are looking for innovation from a cost and quality perspective. "We are … seeing a lot of interest in unique delivery systems as line extensions, says Noland, "and more emphasis on single-dose forms from a portability and ease-of-use perspective." Noland also notes his customers are showing more interest in vertically integrating production points like packaging, manufacturing and molding, as well as onsite testing.

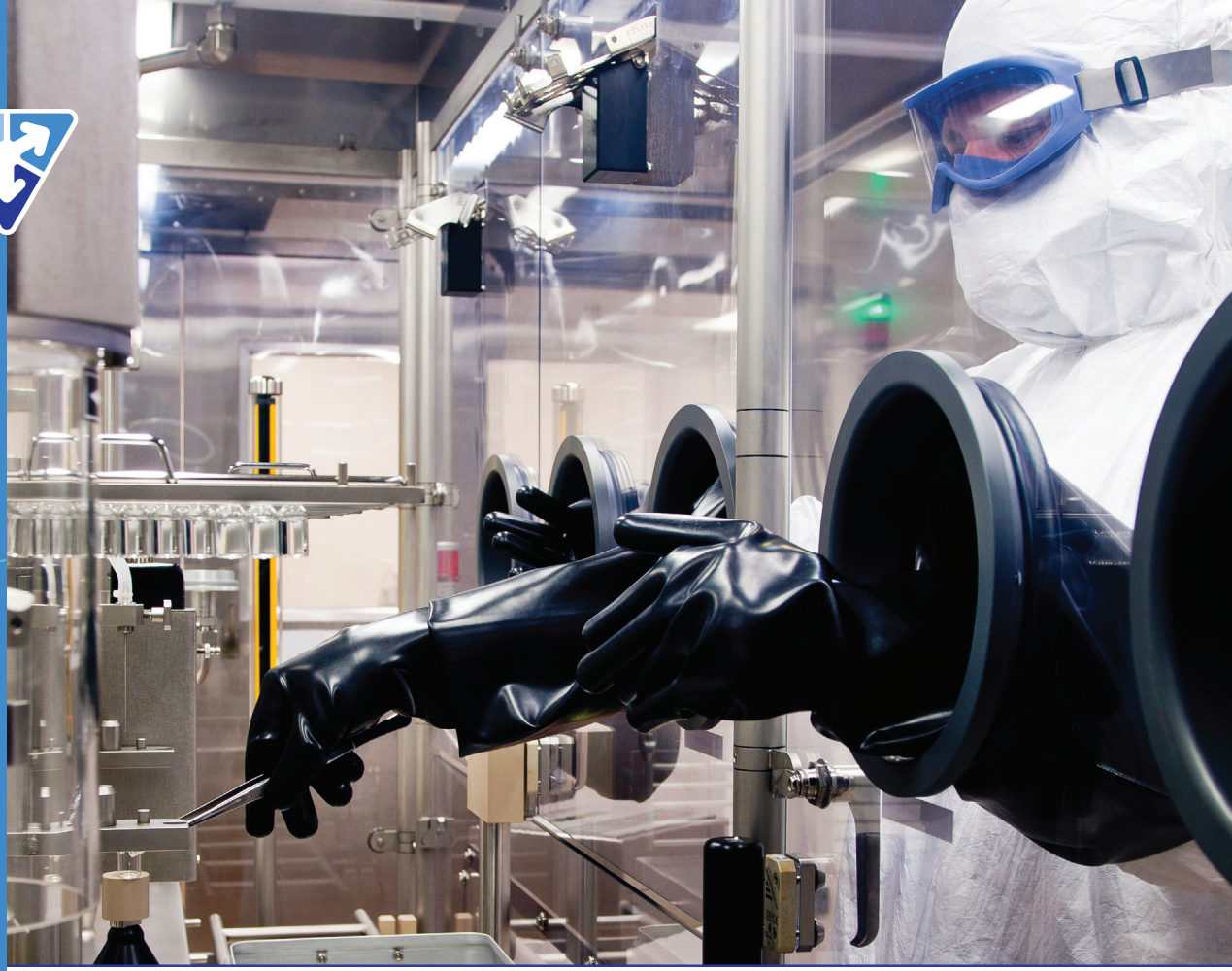
Prefillable inhaler's stock is rising, too. Due to the increasing number of patients diagnosed with COPD, chronic asthma, and allergy related respiratory symptoms, Pharma's introducing and regulators are approving new inhalable therapies at a pretty good pace. Further, some of these medications are going off-patent and Generic Pharma will not be ignoring the potential in this category any time soon.

West Pharmaceutical Delivery Systems' vice president Graham Reynolds illuminates how Pharma, and more importantly consumers, are pushing for increasingly sophisticated delivery modalities. "Historically," says Reynolds, "the primary focus of pharmaceutical manufacturers has, appropriately, been on the efficacy and safety of their drug product. However, with more drugs coming onto the market as combination products — drug products paired with delivery devices — pharmaceutical companies are paying closer attention to the design, function and efficacy of integrated delivery systems." Reynolds says a successful integrated system will combine the needs of the patient at a variety of stages during the patient journey with the drug, its primary containment system and its delivery system.

SECURITY FROM THE OUTSIDE IN

Beyond packaging's broadening role as the means and medium if you will, to provide both physical and virtual security in the supply chain, packaging is also being called on to help solve the knotty problems of dose compliance. According to the Healthcare Compliance Packaging Council, pharmaceutical noncompliance is a tremendous problem in the U.S.: "Estimated annual costs [associated with] patients not taking their medications approaches $300 billion. It is also estimated that 125,000 Americans die annually (342 people every day) due to poor medication adherence and 10 - 25 percent of hospital and nursing home admissions are also caused by people's inability to take their medications as prescribed."

Tom Hubbard, the New England Healthcare Institute's VP of Policy Research noted in a PMP.com report last year "There is no question that packaging is a part of the overall strategy to addressing medication adherence," noting medication adherence is a metric in the quality ratings for Medicare drug plans. "Payers and providers are thinking more strategically about adherence, said Hubbard, "Healthcare plans are trying to figure out the right mix of steps to keep patients adherent and head off overall medication spending. Packaging is part of that response."



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(Photo courtesy of Pharma Tech Industries)

Tee Noland, CEO of Pharma Tech Industries (packaging line operator shown here) notes customers are looking for innovation from a cost and quality perspective.

Mike Schaefers, also a marketing VP with West Pharmaceutical Packaging Systems, says his company is seeing strong growth in creative collaborations between drug manufacturers and packaging and delivery systems manufacturers much earlier in the drug development process. "To achieve the best possible patient outcomes, pharmaceutical companies developing injectable therapies must consider how the drug product will interact not only with the primary container, but also with the delivery system and the patient to help ensure compliance to prescribed regimens and loyalty to specific brands," explains Schaefers. According to Schaefers, by partnering with a component manufacturer early in the drug development process, pharmaceutical manufacturers can identify and mitigate many of the risks associated with hasty or poorly vetted containment selection.

SUPPLY CHAIN SECURITY OFFICER

Packaging is also being tasked to deliver improved supply chain security. "Implementing a Pharmaceutical Serialization and Traceability System in the United States," a study by consultancy Booz | Allen | Hamilton, noted in its executive summary that the U.S. pharmaceutical supply is considered one of the world's safest and the distribution system was well regulated. But on the other hand, critics note that the bulk, wholesale distribution of medications to and through pharmacy distribution networks, while proven safe and effective in the past provide an antiquated system that just isn't up to the task of interdicting the activities of very bad and sophisticated actors looking to profit from the nefarious trafficking of counterfeit, substandard and outright fake drugs.

Last year Walter Berghahn, The Healthcare Compliance Packaging Council's Executive Director, offered testimony before a House Energy and Commerce Subcommittee Hearing on Supply Chain Security. In his letter, he concluded that supply chain security should include the "patient" and noted the following about packaging's role in drug security and safety:

- Driving the serialized container through the pharmacy to the patient will virtually eliminate dispensing errors that occur regularly in today's "count, pour, lick and stick" environment.
- Putting an original manufacturer's container in patient's hands will allow them to authenticate the package.
- That same container, or more appropriately the serial barcode, will allow patients to link to a variety of compliance tools which will allow them to track their individual performance and link them to a variety of reminder tools.
- Serial numbers could create the opportunity for direct-to-consumer notification of recalls, unlinking the dependency on pharmacists to track the lot and then research which patients' scrips were filled from that lot, etc.
- Serial numbers could be used in reverse logistics to prevent the re-issuance of a container that was already delivered into the market place and left the care of a professional controlled environment.
- Serialized containers would ease the process of reverse logistics, returns. No more diverted returns.

Vetter, a well-known contract manufacturer and complex secondary packaging specialist, offers serialization at the carton (sales unit) level and aggregation at the carton (sales unit), shipping case, and pallet levels. Like others in its peer group, Vetter recognized that fundamental serialization services at the point of secondary packaging operations is something its existing customers need right now and something potential customers will likely want well into the future. Vetter says its serialization and aggregation services are seamlessly integrated into its primary packaging processes. Vetter says this service helps its clients establish "the 'parent-child' relationships among components and understand the exact contents of a product package at any point."

The point is, most of the physical aspects of serialization, the marking of primary and secondary packaging, and most of its associated data are gathered at this point in Pharma manufacturing operations. It's here where enterprise data and the physical manipulation of the products meet and the point where the handoff to logistics providers and others take possession of these goods. The prevailing wisdom is that there is much opportunity to optimize supply chain operations. Serialization, explains UPS Healthcare marketing director Robin Hooker, offers Pharma tremendous opportunity. "Every bottle will have its own birth certificate, passport and social security number, and in essence, once that happens you've got a tremendous way of visualizing the supply chain." Hooker explains that "if this transaction data gets handed off through every supply chain actor from the manufacturer, to UPS Freight [and on] to a distributor, then from distributor to drug retailer or specialty pharmacy, those handoffs and that visibility and that information is going to do amazing things for supply chain optimization."

FUNCTION JUNCTION

It's at this junction where the integration of data and production systems simply cannot be an afterthought. Most MES platform suppliers including Rockwell, Siemens, SAP, Werum and others know that information technologies, well integrated with packaging line production equipment, all married to machine vision and marking and labeling technologies will deliver efficiency gains that have far-reaching positive effects operationally.

CONTRACT PACKAGERS

Across Pharma's operational landscape, contract manufacturing organizations (CMOs) are doing the heavy lifting associated with packaging and packaging operations. For many drug owners, there's plenty of incentive to bring in contract packaging solutions providers from both a design and commercial packaging operations standpoint.

"Our customers want a reliable, high-quality operation that will help them meet new serialization requirements without having to make the capital investment themselves," says Rottendorf's Haines. To accomplish this, he says, Rottendorf works consultatively to design packaging to cost targets, "by providing more cost effective and efficient materials and operations," notes Haines.

"Consumers want a package that is easy to use and straightforward," says Pharma Tech Industries Noland, "you are seeing this with some of the new virtual companies that are developing certain OTC products. In terms of our organization, we have made more investment into our unit-dose capability suite to support these opportunities."

West's Schaefers explains that everything in the value chain cannot be a core competency, "so outsourcing makes sense on many levels. Quality

(Photo courtesy of Rottendorf)

Blister packs, says Gordon Haines, Rottendorf Pharmaceuticals CEO, are becoming more popular as they can improve patient compliance and can be customized to fit a product design due to the availability of a broad range of materials and multiple configuration options.

expectations are increasing, and as a result customers seek solutions to improve product quality and ensure drug integrity." Schaefers says West continues to make significant investments in vision inspection systems as more customers demand 100 percent inspection of components.

THE EARLIER THE BETTER

With packaging playing such a significant role in the commercial success of today's pharmaceuticals, it makes tremendous sense to include CMOs and contract packagers in on product development as early as possible. "Packaging choices can have a significant impact on the finished cost of a product," says Haines. "If packaging suppliers are involved early in the process, appropriate packaging can be designed and optimized for dependability and cost." Yet it's not all peace and harmony out there, he says. "While the mindset of companies is starting to change, many pharma companies still treat packaging as an afterthought. We try to make our customers aware of the potential impacts of incorporating packaging design early, to try to move it up on their list of priorities, but practice is still behind where it needs to be."

"In some cases," says Noland, "we are seeing this collaboration at the early part of the drug development cycle because packaging can comprise a significant part of a product's cost. Not only are we looking at specific packaging projects, but also technology transfers of entire operations or even entire sites. These more strategic activities allow our customers to rationalize their supply chain and simplify their business exponentially."

LET'S GET RATIONAL

The complexities of Pharma's supply chain, its limitations and its contributions to drug safety are well recognized by the industry, its contract services providers and its technology suppliers. Best practice involves getting resources and technologies aligned early for best effect. Noland's comment regarding rationalizing the supply chain has everything to do with successfully fielding well-integrated packaging operations and leveraging them to answer the halo of issues associated with supply chain security and dose compliance by consumers. Yes, packaging is bringing a lot to Pharma, and it appears it is ready to take delivery.

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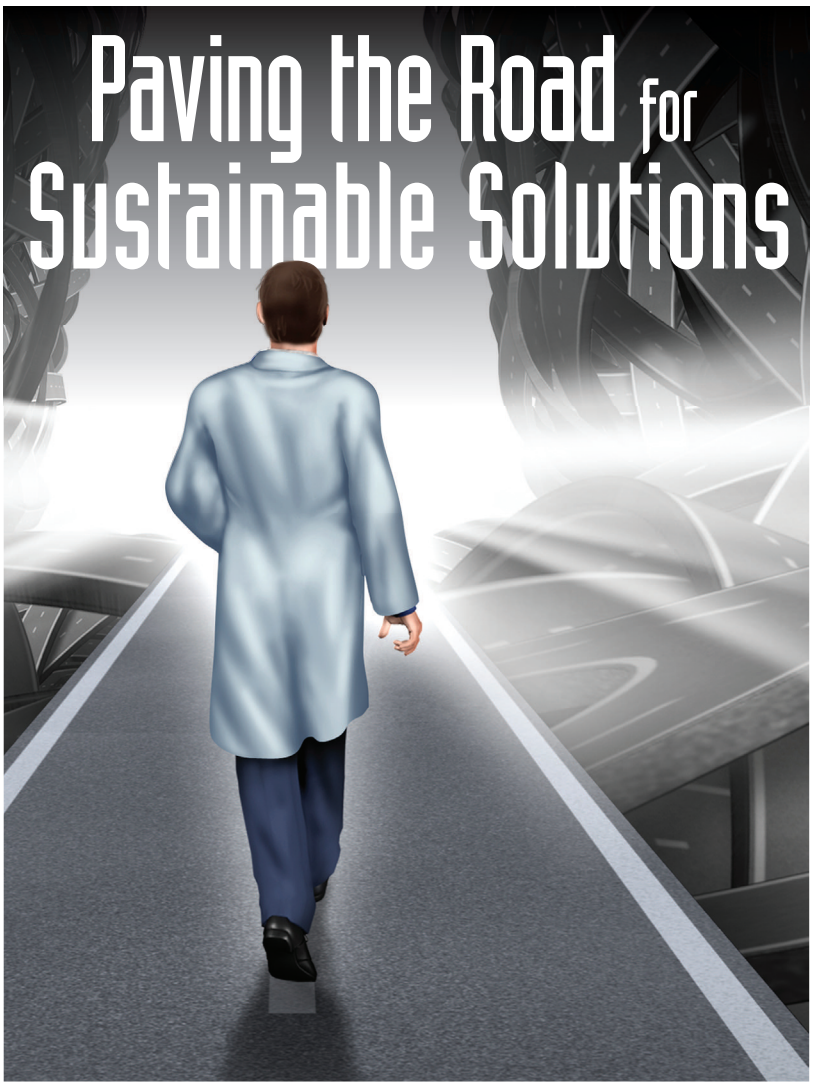

DESIGN & IMPLEMENTATION OF A COMPLIANCE PROCESS WITH GLOBAL GOVERNANCE

A CASE STUDY

BY ARNE BUTHMANN, PHARMA PRACTICE AREA LEAD, VALEOCON MANAGEMENT CONSULTING

WHEN PHARMACO (fictitious name) launched its Asset Change Control (ACC) project, the company faced a highly fragmented situation where physical asset changes were managed non-homogeneously across the manufacturing sites of one of its divisions. For instance, some sites would only include GMP equipment in the scope of change control but not utilities and facilities. At other sites the ACC's scope covered all equipment, but would only evaluate the GMP impact and not the HSE impact. Some sites were operating fully paper-based systems; others used partially automated or self-developed IT applications. The objectives of the project were therefore to establish a global harmonized asset change control process and to implement a global tool to support the electronic execution and management of asset changes.

Previous efforts to design and roll-out global processes had followed a strict top-down approach, which had led to a lot of resistance and, ultimately, inconsistent local implementation. The project team, therefore, decided to apply concepts and methods from the PharmaCo Operational Excellence and Change Management methodology, something guided by three questions:

- How to design a standardized global compliance process that fulfills business needs and leverages manufacturing site best practices?
- How to implement the process consistently while establishing global governance and maintaining local engagement?
- How to develop and deploy a global IT system that fully supports this process and is well perceived by its users?

PROJECT ROADMAP

Phase 1: Collaborative Process Design Leveraging Site Best Practices

A collaborative approach (See Figure 1) taps into the potential of all impacted associates while building the right capabilities to make the new process work. A truly participative approach with focus on knowledge sharing and mutual learning is more sustainable over time as employees engage into the proposed change and work together to achieve success. There is a big difference between mandating compliance to end-users versus engaging them in problem analysis and solution development. By providing employees with a stake in the outcome and developing ownership of their local site's accomplishments, a company as a whole will benefit immensely.

The emphasis on collaboration needs to be consistently applied from project beginning. The first step on this journey was to design a global business process that would work in reality and not just

in theory. Taking the collaborative approach, subject matter experts from the sites were invited to the 1st project workshop in 2011, which aimed at developing the new change control process together. The team aligned on typical process outcome problems such as incorrectly or not completed or lost change requests and long process lead times. Subsequently, they collected Voice of the Customer requirements and analyzed causes of poor change control process performance. The latter impressively demonstrated that the majority of root causes was related to knowledge and skills as well as process issues but not, as initially believed, to the lack of an electronic workflow tool.

The team also tried to establish a baseline for process capability. However, the team had to recognize that due to the fragmented situation actual process data was merely accessible. What came from the workshop and the following design phase was a basic four-step

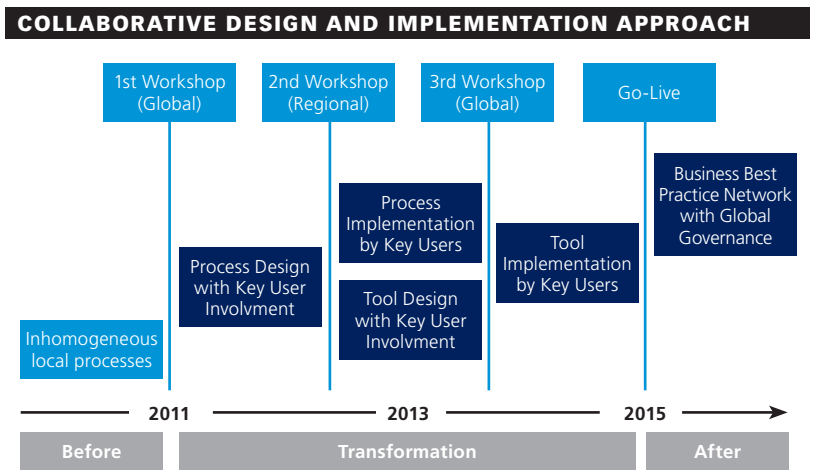

Figure 1

ACC process that ensured good engineering practices while being efficient and compliant at the same time (see Figure 2). The individual process elements were largely based on identified good practices from different sites; the new global process and responsibilities were established in the form of a global standard operating procedure.

Phase 2: Process Implementation with Global Governance and Local Engagement

Many companies have the tendency to focus on the technology aspect of the people/process/technology equation and try to develop a state-of-the-art platform that addresses all of the problems, presuming the new system will be quickly adopted

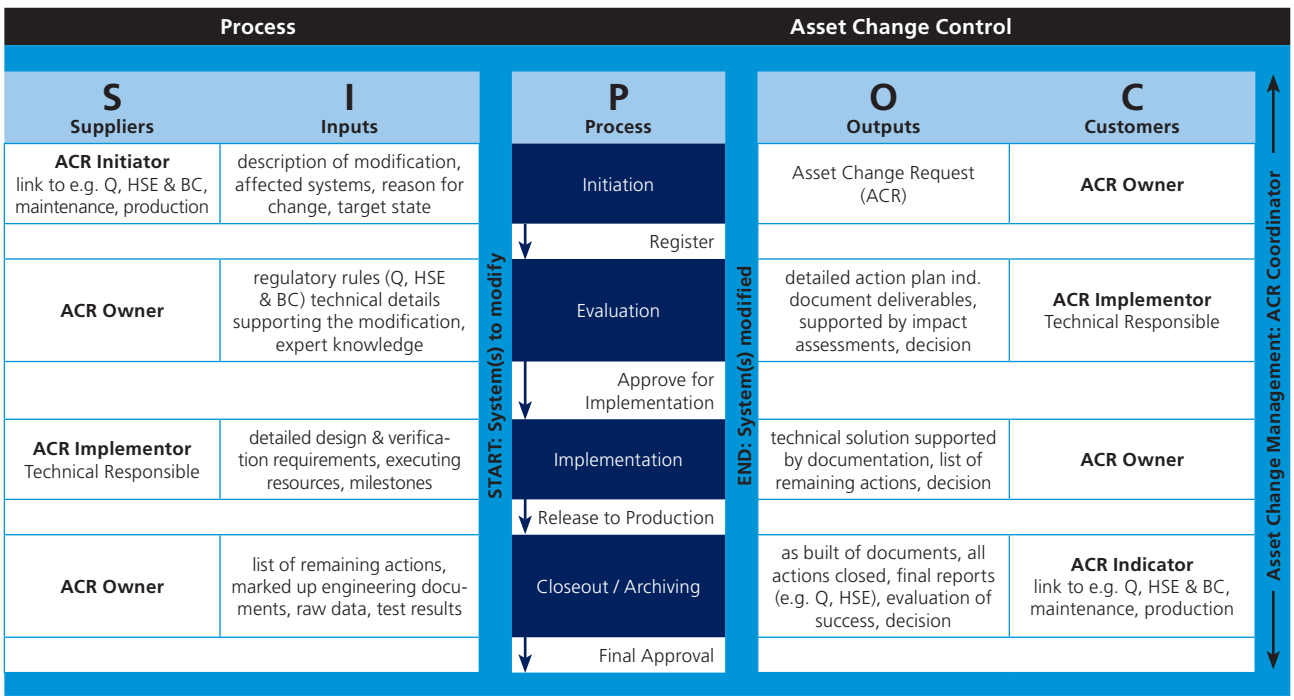

Figure 2

BEFORE – AFTER COMPARISON – EXAMPLE RESULTS

Metrics	Before	After
PROCESS # of sites managing both GMP & non-GMP ACRs	40%	100%
ASSESSMENT # of sites doing interdisciplinary impact assessment	70%	100%
TOOL # of tools in use across TechOps for ACC	6	1
HSE COMPLIANCE % of HSE critical changes (average)	<10%	<50%
TRACEABILITY link of asset changes to process/product changes	undefined	mandatory

Figure 3

and implemented. However, most technology-focused efforts fail to deliver the expected results: Developing the system often takes twice as long as planned, important business requirements are sacrificed when in a rush, and users reject the new system outright or fail to use it properly. The need for "employee engagement" is often considered too late in the process. By implementing on a robust business process first, the gaps in the organization can further be identified and closed before any system is developed, thus, the risk of creating an IT system that does not solve the real business problem is significantly reduced. Achieving compliance does not rely on a tool to be rolled out, but requires the stabilization of the current system.

Following these principles, the project team decided to implement the ACC process and ensure compliance before developing an IT solution. A second workshop was organized, this time on a regional basis in Americas, Europe and Asia. Two to three representatives from quality, engineering & HSE from each site were invited to participate as key users in this workshop. Before arriving at the workshop they had to complete a self-assessment questionnaire.

This preparation helped facilitate better understanding of the global procedure on a principle level, while also forcing the site representatives to start to think about what the gaps between global requirements and local practice were. The results from this self-assessment were also used to establish — for the first time — a real baseline for current site practices. For example, it revealed that 60 percent of the sites manage only GMP relevant systems via asset change control, only 56 percent of all sites involved subject matter experts from all disciplines in assessing the impact of changes, and overall six different tools were used.

At the process implementation workshop the key users were asked to map their current site processes in detail versus the new change control process and minimum compliance requirements from the global SOP. By doing so, the representatives created a detailed gap analysis and generated an action plan for subsequently closing those identified gaps. This tactic provided them with the opportunity to realize themselves what needed to be done rather than being told. As they presented their findings to their peers at the workshop, they learned how others were closing their gaps.

Key users from historically disconnected sites could hear directly from their peers the real differences existing between sites and realize opportunities for themselves. As mentioned earlier, some sites had more advanced ACC processes in place. Allowing key users from these sites to explain the day-to-day experiences, others were able to acquire key takeaways as quick wins for their work on site. This regional peer-to-peer support and mutual learning built the foundation for the later established best practice network.

Last but not least, all key users were equipped at this Regional Workshop with fundamental people change and influencing skills such as stakeholder mapping and elevator speech to help them successfully bring the process

ASSET CHANGE CONTROL

Technical or asset change refers to the modification of any defined automated or manual technical system or its documentation. The modification may impact production processes or product characteristics. As a result, Asset Change Control (ACC) is a key regulatory requirement (see ICH Q7A, ISO or FDA Pharmaceutical cGMP Regulations) for the operation of pharmaceutical manufacturing plants both from a GxP and from an HSE (Health-Safety-Environment) perspective. ACC is a central element of the asset life cycle management process as it ensures that production systems, which are modified during their life cycle, remain in a defined, verified and compliant state. A lack of appropriate asset change management increases the risk to both invalidate the qualified status of manufacturing plants and, worst case, to lead to batch contamination, rework, and product recalls.

to their site and to manage possible resistance of their colleagues towards the new way of working.

The second workshop was followed by a six-month period during which the sites had to close the gaps by implementing at least the minimum requirements from the global process. In doing this, they obtained a certain level of autonomy as they could implement the mandated process in line with their systems. The minimum requirements clearly defined "what" needs to be done, but with the local expertise, key users controlled "how" the process would succeed. For example, one of the minimum requirements advocates that a local ACC coordinator be in place. However, it provides the sites with the flexibility to assign the best fit to the role, whether it was an engineer or a member of QA. Or, for instance, another requirement states that every change needs to be assessed by an HSE expert. However, as some sites struggled to have enough central HSE resources, they decided to train more people with HSE expertise and, thus, expanded the skill set of the overall team.

The importance always relied on acceptance of "what" needed to be done, while providing autonomy for "how" it was completed. This increased the feeling of local control and ownership dramatically. Throughout the implementation phase, the global team stayed in regular contact with the key users, assessed performance, implementation progress and adjusted based on continuous feedback loops and a two-way communication.

The result of this approach was that even prior to the go-live of an IT tool, some of the expected ACC benefits in terms of compliance to Good Manufacturing Practices (GxP) and Health, Safety and Environment (HSE) aspects of the asset lifecycle management have been realized and could be confirmed in ongoing inspections.

SUMMARY OF SUCCESS FACTORS

Challenges	Key Success Factors
Global Solution Development	• Global policies, standards, and business processes developed together with entity representatives to ensure fit-for-purpose solution
	• Leveraging good practices from within the organization to avoid "not-invented-here" syndrome
Local Implementation	• Bring key users from each entity together to help them understand "what" gaps to close to successfully implement the global solution
	• Coach them to identify an effective approach for "how-to" that reflects local needs
	• Equip them with methods, tools, and skills to become change a gents in their entity
	• Key Users engage their local colleagues in the implementation of the global solution
	• Provide ongoing coaching and conduct regular „health-checks"
	• Establish business reference group for operational governance, best practice sharing and continuous improvement
Tool Development and Deployment	• First implement the new process and change behaviors accordingly
	• Apply agile system development approach with regular end user feedback
	• Provide key user with a "sandbox" version of the tool to allow them to play with it and experience "look & feel" long before go-live
	• Train-the-trainer approach helps key users become real experts in the tool

Figure 4

Phase 3: User-centric Tool Design and Deployment

In parallel to the process implementation, the global project team started the design of the supporting IT tool. The company took a strategic decision to use a global change control platform to create synergies between related change control processes and to keep the IT architecture slim, benefit from a global validation and a joint system operation with no local efforts.

In order to create the IT tool, the concept to focus on collaboration with the key users was continued. User feedback to the tool was collected through different development sessions. Early involvement helped the future users to already understand the tool and to be much more willing to work with it. A "sandbox" version of the tool was made available to all key users to experience the "touch & feel" and to be able to play with it and to give feedback to the global team.

For the tool deployment, a pilot site approach was selected in order to be able to implement potential lessons learned before go-live with all other sites. During the third workshop, the final tool was presented to the key users of 5 selected pilot sites. Since this was not their first time they saw it, the focus of the workshop was on capability building instead of questioning its design. The key users were trained to become trainers for the tool for the end-users on their site. In addition, the key users worked on their entity deployment plan. This included all relevant actions required before go-live such as updating local SOPs, defining user roles and

responsibilities in the tool, and preparing master data to be uploaded into the tool. The pilot sites were given another four-month window to implement their plans. Again the global team stayed in weekly contact with them to monitor progress and to clarify any upcoming issues and questions. The involvement of the global team in local deployment preparation activities facilitated the leverage of best practices among all sites and the global business and IT owner. In this way, detailed insights and effective solutions could be easily shared for the benefit of all teams.

The ACC tool smoothly launched with only minor adjustments after two months of hyper care phase.

Based on the pilot site experience a fast-track deployment in only four months to the remaining sites was possible, which finally helped realize the full project benefits (see Figure 3). Among other results, all sites are now managing both GMP & non-GMP ACRs, interdisciplinary impact assessments and ensure the link of ACC and asset maintenance. The percentage of HSE critical changes went up from below 10 percent to greater than 50 percent, which is a significant increase in HSE compliance. Eventually, for the first time, all sites are now using the same tool to manage Asset Change Control.

ESSENTIAL APPROACH

With more and more corporate companies aiming at standardizing the way they work across their entities, it becomes essential to select the right approach. This approach must guarantee both:

- Developing global business processes and supporting IT systems in synchronization that actually work and support the entities, and
- Deploying process/tool in a harmonized way that creates engagement and ownership for the transformation on the entity level.

As outlined in this article, the key success factor (see also Figure 4) for this was replacing a top-down design and deployment of a technology to fix a business process with a collaborative approach to maximize local ownership for the transformation. Those mindset changes make resounding results possible, exemplifying the insight of Einstein saying, "We can't solve problems by using the same kind of thinking we used when we created them."

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BIO PHARMA MANUFACTURING'S

TOP 15 TRENDS for 2015

The quest for efficiency continues as demand fuels capacity growth and process throughput

By Eric S. Langer and Jean-Claude Lupis, BioPlan Associates Inc.

WHAT'S DRIVING Bio Pharma manufacturing production in 2015? To get to that answer and rank the industry's Top 15 trends for 2015, we drew insight from our "12th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production" as well as input from BioPlan's Biotechnology Industry Council, a panel of more than 500 biopharma industry subject matter experts.

1 Manufacturing efficiency and productivity — where biomanufacturers are putting most of their attention.

In an effort to reduce costs associated with bioprocessing, launch biosimilars and address other strategic issues, the top trend this year involves "productivity and efficiency." Of the 13 key areas studied, more than 27 percent of respondents to our annual study noted these, along with cost reductions as their primary focus in 2015. This is demonstrated in areas including:

- Improvements in productivity from bioreactors, where average titer for clinical-scale biologics rose to 3.4 g/L this year, compared with 1.9 g/l in 2008.
- Average mammalian titer at commercial scales is 2.50 g/L and 3.41 percent at clinical production scales.

Titers will continue to increase. Downstream continues to be the area requiring technological improvements, with 19.1 percent of respondents citing "Chromatography columns" as currently causing significant or severe capacity constraints. However, downstream productivity is getting better, and key indicators like capacity constraints have declined dramatically; this year only 45 percent expected moderate or worse capacity problems, compared with 88 percent of the industry back in 2005.

2 Budgets for Biomanufacturing operations up as much as 6.1 percent; all operational budgets have increased this year.

Budgets for operational aspects of bioprocessing have increased across-the-board, from 1.9 percentage average budget increase for R&D, to 6.1 percent for new capital equipment, and 5.3 percent for process development. Budget areas can be considered an indication of where facilities are focusing their attention and resources in the coming year(s).

3 Single-use systems and disposable devices in hot demand: 7 out of 10 top new bio-innovations are single-use.

A large majority of biomanufacturers are demanding better single-use devices, disposable chromatography, downstream purification and throw-away sensors, which lead the pack in what buyers want. More than a third are demanding more and better devices today. The most urgent problem with adopting more single-use devices is simply breakage, and loss of production material. With breakage a fairly rare occurrence, this suggests that adoption hurdles are becoming increasingly less of a problem.

Essentially all, 90 percent, of respondents report using single-use bioprocessing equipment, with "Disposable filter cartridges" cited the most, used by 94.2 percent, followed by "Tubing" and "Depth filters." Single-use bioreactors were reported as used by 73.6 percent of respondents. The single-use products with the highest reported growth in annual adoption rates (1st use in facility) were "Membrane adsorbers" with annual growth of 16.8 percent, "Mixing systems" 16.2 percent and "Bioreactors" 14.9 percent; with the lowest reported adoption rate, 1.5 percent, for "Disposable chromatography devices." Both single-use "Mixing systems" and "Bioreactors" have seen more than a 50 percent increase in adoption since 2006. More than two-thirds (68.8 percent) cited single-use equipment as improving their bioprocessing in the past year, including 73.9 percent of U.S. respondents. More than one-third of respondents cited their desire for improved single-use downstream purification equipment, including 35.7 percent citing the desire for improved chromatography equipment.

Downstream continues to be the area requiring technological improvements; Sartorious agrees, developing this single-use clarification system that eliminates centrifuges.

4 Healthy, 14-percent Bio Pharma industry segment growth.

Growing consistently at ~14 percent and based on sales of biologics over the past 18 years, sales of biotherapeutics are currently at $200 billion. In manufacturing, current capacity utilization is a healthy 70 percent for mammalian production; facilities expect to expand their mammalian production by 49 percent on average over the next 5 years (2020); and by 25 percent for microbial facilities.

Bioprocessing-related budgets are expanding. Companies are investing more in biomanufacturing R&D, including hiring staff and expanding manufacturing capacity. Budgets for new capital equipment continue to grow; respondents report their budget up this year by an average of 6.1 percent versus 4.4 percent last year. Budgets for process design up 5.3 percent; new facility construction budgets are at an all-time high. Overall, companies appear to be investing in increasing productivity with what they already have, e.g., process development and new technologies for downstream manufacturing receiving high budget increases.

5 Bioprocessing capacity, including among CMOs, is at a healthy level, with no capacity crunches expected. Many new facilities and expansions are recently completed, underway and planned.

Survey respondents reported an average 69.9 percent capacity utilization for mammalian cell culture and 57.9 percent for microbial fermentation. These rates are in a healthy range — not too high (with bottlenecks) and not too low. But despite this, 56.7 percent of respondents reporting having experienced at least minor capacity constraints in the past year, mostly with commercial manufacturing (a factor driving capacity expansions and new facilities). CMOs reported higher capacity utilization — 81.8 percent for mammalian cell culture and 68.3 percent for microbial fermentation — and also much higher "significant" constraints, 32.7 percent versus 10.3 percent for product developers. U.S. mammalian capacity utilization rates are higher than for Europe — 72.3 percent versus 51.4 percent, while Europe has higher microbial capacity utilization, 65.8 percent versus 55.3. Overall, 60.1 percent expect "facility constraints" as likely to create capacity constraints at their facility within the next 5 years. Respondents projected an average 5-year planned increase of 49 percent in their facility's mammalian bioreactor capacity and 25 percent increase in microbial capacity.

6 Purification/downstream processing continues to be the most problem area.

However, DSP problems appear to be slowly abating. Today, 41 percent of industry feels better DSP technologies will re-

duce capacity problems. Nearly half the biopharma industry (41 percent) point to downstream purification as the cause of their most significant capacity problems. Easing these will involve developing more efficient, cheaper, single use disposable filtration and chromatography devices. Survey respondents reported an average 5.2% increase in their "Process development" budgets this year. Respondents noted that improvement in DSP technologies is highly desired. "Chromatography Products" and "Disposable Products: Purification" were the top-cited areas of interest in new bioprocessing equipment, both cited by 35.7 percent and rising to 43.5 percent among CMO respondents. But industry is adapting and finding ways to increase downstream productivity. Purification is no longer a continually worsening bottleneck for much or most of the industry. Use of Protein A resins will remain the dominant initial monoclonal antibody capture step, with only 7-16 pecent of respondents reporting expected to use other products for existing bioprocesses, but there is high interest in alternatives, with a majority (54.4 percent) considering alternatives for new bioprocesses.

7 Biosimilars to add more products and competition; cost-effective bioprocessing becoming even more essential.

FDA finally approved its first biosimilar, and biosimilars will, in coming years, outnumber their reference products, changing the underlying nature of the biopharmaceutical industry, with everything becoming more like mainstream drugs, with generics dominating. BioPlan's Annual Survey indicates that the industry recognizes the top two critical trends to biosimilars success include efficient bioprocessing and the ability to cost effectively produce these follow-on products; this will likely include the applications of novel technologies for production.

China, India and other ROW countries are rapidly developing domestic, mostly biogenerics-oriented, biopharmaceutical industries. These are the fastest growing geographic areas for biopharma R&D and manufacturing. But these countries pose no threat to U.S. and other major market dominance in biopharma, particularly in terms of adopting innovations/manufacture of products for major markets. With biosimilars increasing competition, including with their reference products and other biosimilars, biobetters and biogenerics, it will become more important to cost-efficiently manufacture products.

Manufacturing efficiency and productivity are top of mind for biopharmaceutical producers; this EMD Millipore 2000 liter single-use reactor was designed to meet this need.

8 Hiring new staff creating serious problems in bioprocessing; 46 percent of U.S. facilities can't fill their process development jobs.

The most difficult-to-fill positions this year continue to be associated with process development, where 39 percent of the industry cannot fill their upstream PD positions, and 37 percent cannot fill their downstream PD jobs. The U.S. has the greatest problems, where nearly half of biomanufacturers (46 percent) report inability to fill downstream PD jobs.

9 Innovative bioprocessing technologies and products still needed; suppliers are increasing their R&D and focus on improved productivity.

End-users' budgets are up 5.2 percent this year for acquiring better downstream technologies, and up 4.1 percent for improved upstream technologies. Factors contributing to better bioprocessing have been attributed to a broad set of attributes, but single-use devices were noted by 69 percent — the greatest of all 15 areas measured. Many deficiencies in bioprocessing, particularly, involving downstream technologies/equipment, are increasingly being addressed. Among supplier/vendor respondents, the leading areas where they report developing new products are "Bioprocess development/optimization services/bioprocess modeling" (39.8 percent), and "Disposable/single-use bioreactor bags/consumables" and "Disposable/single-use bags/films" both tied at 26.6 percent. However, problems with vendors continue, with 52.7 percent of vendor respondents citing demands for "Better customer service."

10 Fill-finish operations going high-tech/single-use.

The most critical fill-finish trend in 2015 was the introduction of innova-

tive, single-use devices, where 75 percent of this segment believes industry change will have the greatest impact (and 36 percent of the segment has developed plans to adopt SUS technologies in 2015). In addition, innovative RABs and isolators were indicated by 33 percent of this segment as hot trends and opportunity.

11 International growth in biomanufacturing continuing; China and India maturing biomanufacturing locations, with 15 percent concentration, employment increases over 5 years. China, India and other ROW countries rapidly developing domestic, mostly biogenerics-oriented, biopharmaceutical industries.

China and India have shown growth of up to 15 percent, according to BioPlan's top1000bio.com website, which has tracked biomanufacturing concentration (capacity, employment and # products) on a regional basis over 5 years. Offshoring of various bioprocessing operations to these areas is an indication of opportunity. Outsourcing costs are rising, and quality problems in many developing countries are becoming more apparent. Offshoring using ROW CMOs has increased, with 14.3 percent of respondents reporting offshoring bioprocessing in the past year.

Among all respondents, the U.S. and Germany were the leading expected future outsourcing destinations, both cited by 27 percent, while 22 percent cited China and 12 percent cited India. Among U.S. respondents, Germany was the leading expected outsourcing destination over the next 5 years, cited by 50 percent, followed by Singapore at 38.6 percent. China was indicated by 25 percent of U.S. respondents as a likely "outsourcing" destination, up from just 2.8 percent in 2009. India, as a destination for outsourcing, has held steady at around 11 percent among U.S. respondents. Among European respondents, the U.S. and China were similarly tied with 36.4 percent citing this as their expected outsourcing destination.

12 Flexible facilities: More flexible, multi-product, hybrid and even whole modular facilities are coming.

Bioprocessing is becoming more flexible; multiple-product and stainless-steel facilities are being upgraded to hybrid, and fully modular facilities are starting to have an impact. More bioprocessing technology vendors are developing modular approaches. Companies will be able to assemble systems using off-the-shelf or customized modules ready for plug-and-play with other modules. This modular trend will likely accelerate worldwide proliferation of commercial manufacturing, including to lesser-developed countries. Flexibility may be warranted as more biopharmaceutical R&D is done on more, but smaller market drugs. The percentage of biopharmaceuticals in R&D versus small molecules is increasing, while the size of targeted markets is generally decreasing. More products and smaller markets means more bioprocessing facilities and process lines, but these increasingly at smaller scale.

13 Continuous Bioprocessing emerging as a critical new technology: GMP issues, around consistency and reproducibility, and process complexity are critical factors.

GMP issues associated with continuous bioprocessing ranked highest in a recent comparative analysis of Continuous BioProcessing (CBP), versus Batch operations. Process operational complexity was a primary concern to 77 percent of biomanufacturers. And of the 19 comparative areas evaluated, the Top 3, where respondents reported perfusion/CBP as presenting more concerns (versus fed-batch) included: 1) Process operational complexity, 2) Process development control challenges, and 3) Contamination risks.

Perfusion is the leading continuous bioprocessing technology, but perceptions concerning implementation persist, e.g., 77 percent of respondents cite more "Process operational complexity" with perfusion versus 3.6 percent with fed-batch processing; 76 percent cite more "Process development control challenges" versus 3.6 percent for fed-batch; both values for perfusion are at record highs. Despite this, 51 percent of respondents noted they would likely specify perfusion for a new clinical process, with 37 percent using single-use equipment.

14 New and better assays are needed to improve industry performance.

Thirty-two percent of the industry is demanding better analytical assays, and 66 percent believe that such analytical testing improvements will improve their biomanufacturing performance.

15 Bioprocessing getting better; failure rates reduced by nearly 50 percent over past 8 years.

Fewer failed batches in biomanufacturing are occurring, based on time between failures; the average weeks between failures declined steadily since 2008 when the frequency was one every 40.6 weeks. By 2015, that rate had declined to one failure every 60.2 weeks.

By David Benderly, CEO, PhotoScribe Technologies

PHOTONICS FOR IMPROVED PHARMA PROCESS

From tablet marking to quality assurance, lasers and machine vision are boosting functionality and efficiency

IN THE multidisciplinary pharmaceutical industry, photonics plays an increasingly crucial role in the manufacturing process. From quality assurance to marking, the scope of photonics is wide-reaching. Specifically, the use of lasers and machine vision in oral solid dose (OSD) manufacturing is revolutionizing functionality, security and speed while reducing costs and boosting efficiency.

In certain regions of the world a growing problem concerns medication quality, stemming from poor manufacturing processes. For example, drugs manufactured with a lower dosage of active ingredients than approved by regulators is a dangerous situation that can lead to patients not receiving a medication's full benefit. Worst-case black market scenarios involve nonpharmaceutical-grade or harmful ingredients resembling medication being used as substitutes, such as chalk and talcum powder [1].

The gray market, on the other hand, manifests itself in several ways, but with reselling, importing and exporting that ultimately can have high costs both for the end consumer and the manufacturer[1]. ("Gray market" goods are also termed parallel imports. This is when someone other than the designated, exclusive importer buys genuine trademarked goods outside the U.S., for example, and imports them for sale in the U.S., in direct competition with exclusive U.S. importers.[1])

Gray market companies acting as secondary wholesalers are a growing problem within the industry as well. When a pharmaceutical wholesaler sells to a secondary wholesaler, limited-availability prescription drug pricing can become inflated, with pills passing through the hands of numerous wholesalers[2]. In anticipation of a shortage, these gray market companies incite panic and are able to resell drugs to consumers at higher prices[3,4].

Pharmaceutical manufacturers should express concern over the gray market, particularly since it most commonly affects their bottom-line profit. When medicine is inexpensive in less-developed countries, but moves through the gray market to be resold in countries without drug pricing regulation, such as the U.S., the availability of cheaper drugs in developed markets can take away from a manufacturer's margins and profit[5]. Laser marking of unique product identification, both overt and covert, helps control and promote an orderly supply chain.

LASERS FOR PHARMA

Lasers now are used in several ways for pharmaceuticals, particularly where traceability and security are important considerations. Packaging is being laser-marked with a unique identification number, allowing for manageable tracking through the supply chain. A given product can be traced to a specific manufacturing facility, batch number or manufacturing date, providing transparency and accountability, and ultimately boosting consumer confidence. With OSD tablet marking, high-speed lasers have the capability to mark on the fly with a unique identification number, if desired — even down to individual tablet level — without slowing down process speed.

For many years, lasers have been used for tablet drilling, with one of the most important applications of this technology being the osmotic controlled-release oral delivery system. This technology uses osmosis pressure as the driving force to dispense medicine in a controlled time-release manner[6]. This drug delivery system, in the form of a tablet, usually consists of a semi-permeable outer membrane, the medicine and an osmotic core as the driving force that delivers medicine through the laser-drilled hole.

Laser in place to inspect tablets as they are conveyed to their next processing step.

Several other methods for time-release drug delivery exist, with the commonality being a semi- or insoluble outer layer and either single or multiple laser-drilled holes. Recent years have seen a significant increase in demand for improved manufacturing methods for time-controlled drug delivery systems. With the expiration of several primary patents for osmotic pump delivery, the adaptation of this technology has grown. Laser drilling also is used in fast medicine release, not only in slow time-release. In this method, a tablet's protective outer layer is laser-drilled with a multi-hole pattern, causing the outer shell to collapse once the pill comes into contact with water in the digestive system.

As with tablet drilling, direct laser marking has become an important application for lasers in the pharmaceutical industry. Before lasers, OSD forms were traditionally imprinted using one of two methods[7]. In the first method, a mark is molded into a tablet during the compression of the powder in the manufacturing process. This method is limited, however, as it allows only for marks that are simple and large in composition, usually containing two to five characters or an elementary symbol. The second traditional method is offset rotogravure printing, which has significant drawbacks including cleanliness of operation, the use of solvents and extra downtime to clean and maintain equipment. Overall print quality can also be limited.

Laser marking was introduced to combat these problems. To accommodate the large volume usually required by pharmaceutical manufacturers, the mark-on-the-fly method is well-suited, during which the laser follows the product on the production line and marks with precise placement, allowing for continuous marking at extremely fast speeds with rates of up to hundreds of thousands of tablets per hour. The most common setup for such an operation includes a quadrature encoder, which gives the controller data on the conveyor speed and direction. In addition, a sensor mounted on the conveyor gives the controller a trigger signal that tells the laser when to fire.

Several types of sensors are in commercial use today, including inductive, photoelectric, fiber optic, ultrasonic, magnetic and camera-based vision systems. Some sensors can identify not only the location of the conveyor but also the presence of the OSD form, directing the laser to fire when the tablet is properly placed. The combination

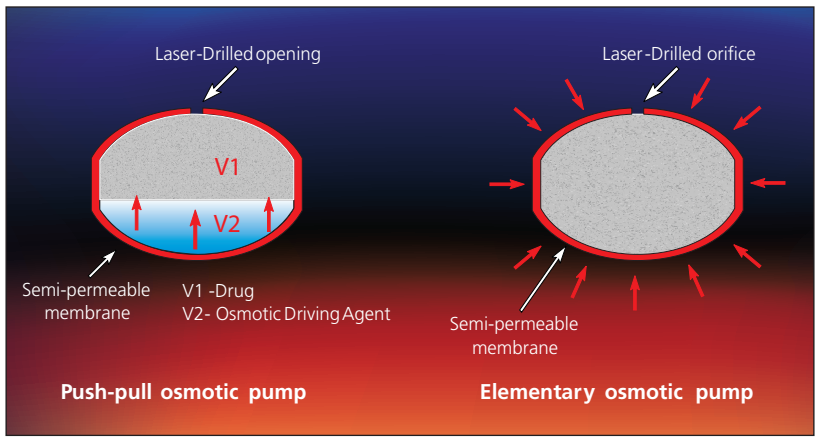
of both devices allows for real-time feedback, ensuring accurate mark placement on the pill. In high-speed laser marking, delays of only a few microseconds can make the difference between a successful mark and a failed one. However, with correct and careful selection of system components, these systems have been shown to be extremely robust and highly reliable.

When considering color in OSD marking, laser wavelength and optical beam delivery are carefully selected based on the type of tablet being marked. In most cases, OSDs interact with a laser producing sufficient contrast. However, on other dose forms like transparent gelcaps, laser markings appear to be a white, frosted color. Several methods can be employed to enhance this contrast or even to introduce contrasting color, if desired.

In one method, FDA-approved laser-sensitive additives are combined during the manufacturing process, allowing production marks based not on the ablation of the dose form, but rather on a thermal chemical reaction with laser energy. This method allows the usage of lower energy density, sufficient for the production of high-contrast, high-resolution markings without material ablation.

In another method, the tablet's protective outer layer comprises multiple layers of different colors, and the laser selectively ablates the outer layer, revealing the contrasting color below. This method allows the mark to appear in color, rather than being limited to the black or white usually associated with laser marking.

Lasers have the significant advantage of being a non-contact marking technology, reducing contamination, breakage and rejection rates. In addition, no tools or dies need to be changed, as the indicia are computer- generated and can be modified easily. Because



An osmotic pump drug delivery system.

of laser marking's advantages as a non-contact printing method, older equipment in the industry could, in many cases, be retrofitted with lasers, adding capabilities to machines currently in use.

Pharmaceutical companies are taking advantage of the technology also to imprint branding on a pill. The logo or alphanumeric or another identifying mark adds functionality beyond the rudimentary FDA requirements. Advances in laser technology and beam-delivery systems make it possible to mark on the fly with serial numbers, batch numbers or logos down to a single-unit basis. FDA regulations do not allow drug products in solid oral dosage form to be introduced (or delivered for introduction) into interstate commerce unless they are clearly marked or imprinted with a unique code. In conjunction with the product's size, shape and color, this code permits the unique identification of the drug product and its manufacturer or distributor. Product identification requires that active ingredients and dosage strength be documented.

Machine-readable code, such as data matrices, can also be marked onto dose forms and used for automated identification. Codes on pharmaceutical packaging identify the manufacturer, date of production, expiration date, and serial and batch number, allowing for full transparency in production. Encrypted information could be connected to a database that would follow a pill along its supply chain travels. This tracking system could help battle the huge global problem of counterfeit medicine, which has resulted in fatalities.

MACHINE VISION FOR PHARMA

Laser-based machine vision technology truly automates pharmaceutical manufacturing, making the process systematic, highly efficient and cost-effective. Lasers significantly increase production uptime, streamline the process and reduce costs, all while delivering new and improved capabilities ranging from product identification to functionality.

Adding identifying marks and barcodes to tablets, other dose forms and packaging is important, but without automated inspection and quality assurance, this process would be inefficient. Across companies, machine vision systems are being added to printing devices, ensuring that dose forms are complete and unbroken, while also verifying print quality.

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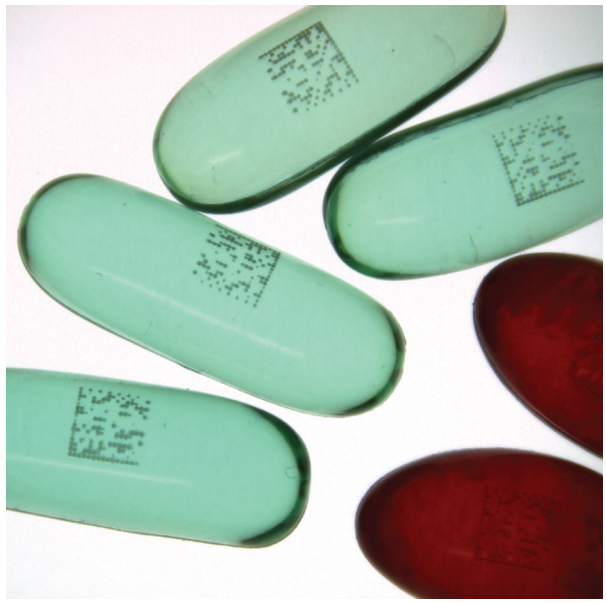
Pharmaceutical-adapted machine vision cameras are mounted on printing devices to inspect pills in real time. Cameras are mounted on production lines for several purposes. First and foremost, the camera inspects the pill's integrity. If the pill is incomplete or broken, machine vision will send a signal to initiate a burst of air that can push any single pill toward the rejection bin (several rejection mechanisms exist, but the burst of air is the most popular).

A camera also is used to verify that tablet marks are correct and of good quality, again sending a command to reject any single unit that is not up to standard. For tablets marked with a unique identification, this scan is also the first in the product's supply chain tracing. Information about the tablet, such as its manufacturing date, batch number and factory location, is saved to a database.

Machine vision also can analyze shape and color to identify proper placement. For example, on a bicolor tablet where only one of its colors should be drilled, machine vision identifies the color and sends a command for the laser to mark the correct side. From capturing an image on camera, to analyzing product features, to making decisions based on predefined criteria and information sent to multiple devices (such as rejection/ejection and laser marking), complex interactions such as these are done in real time. In a cycle as short as microseconds to a few milliseconds, a pill is instantaneously and seamlessly processed.



Data-matrix code, laser-inscribed on gelcaps with encrypted manufacturing information. Images courtesy of PhotoScribe.

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ENVIRONMENTAL MONITORING IN PHARMA LABS

By Stew Thompson, CAS DataLoggers

Data Logger FAQs reveal application insights

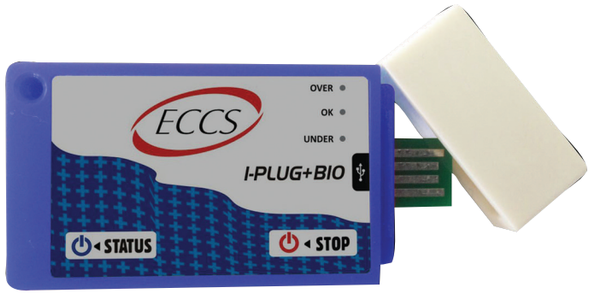
MONITORING TEMPERATURE and/or humidity in a pharmaceutical laboratory? Data loggers are a technology that offers a viable way to automate environmental measurement. Finding the best data loggers to monitor samples and/or equipment in the laboratory application has its challenges, and many are new to data logging and may not be sure which technology and manufacturer to choose. If specifying a monitoring solution is in your near future, consider the following Pharma Environmental Monitoring FAQs, which may help find the right logger for a given application.

Q: Which data loggers are designed for lab use?
A: Data loggers can measure nearly any physical or electrical value, so they're used in many laboratory applications, whether to record data from experiments or to handle measurement of the required temp and humidity for equipment such as refrigerators and freezers, incubators, climate chambers, autoclaves, etc. While there are many different manufacturers and models, one can narrow down their search with a few questions about the product, equipment to be monitored and its location.

Q: I don't know what sensor types I'll be using — which loggers are flexible?
A: When this is the case, or when multiple sensor types are being used, it's often more cost-effective to use a datalogger with universal analog inputs which can connect with many different sensor types. Universal input dataloggers can record and store temperature readings from thermocouples, thermistors, RTDs and many other kinds of sensors.

Q: I know which sensor type I need — which data logger connects to it?
A: If the sensor type to be deployed is known beforehand, that will quickly narrow down any search. For example, many data loggers are designed to record data from thermocouples, significantly lowering your cost, while others can connect to a broader range of temperature sensors such as RTDs and thermistors.

Q: What type of data logger can I get at my price range?



CAS Dataloggers offers temperature data loggers with a small footprint and low temperature range.

A: Data loggers are available in a wide variety of models from many different manufacturers. CAS Dataloggers offers temperature data loggers with a small footprint and low temperature range for laboratory and life science monitoring applications. Certain applications such as biorepository storage or cleanroom monitoring demand more sophisticated systems with the advanced functionality to protect valuable products and specimens.

Q: Should I go with a wireless or wired logger?
A: The answer depends on several factors including a given facility's network, the physical layout and resultant wireless range, and where the datalogger is to be installed.

The wireless technology available from suppliers, including CAS Dataloggers, automatically sends data to secure cloud servers. Operations staff can view data and alarms any time from a mobile device. Cloud Storage offers:

- Completely Automated Operation
- Online Access for Multiple Users
- Logs, Graphs, Charts
- Secure Data Storage
- Local and Remote Alarms
- Product Protection 24/7

Q: How can we prove compliance with our specific regulations?
A: Dataloggers perform continual monitoring, alarming and electronic documentation to aid with compliance and best practices in the pharma industry. If you need to record and archive data for FDA and other compliance reporting, monitoring solutions are available.

Q: Where will alarms be sent?
A: For many callers with temperature-sensitive products, alarm capability is the most important factor to consider. When storage units have a temperature excursion, operators likely want a device that shows its alarm state by an audible alert, or perhaps sent by email directly to one's mobile device to alert the fault after hours or on the weekend.

Using a wireless data logger, operators can view data online from any web-enabled device — desktop, laptop or smartphone. It's easy to check the condition of valuable products no matter where one is when a situation arises. There are devices that can send out SMS text messages, emails, and even sequentially dialed voice messages as well the ability to design custom callout lists.

Universal input dataloggers can record and store temperature readings from thermocouples, thermistors, RTDs and many other kinds of sensors.

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BY KATIE WEILER, MANAGING EDITOR

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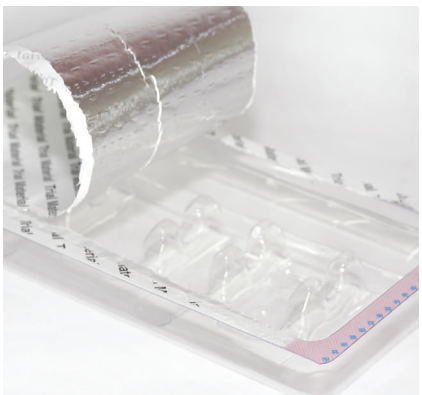
This new, servo-driven machine from Changsung offers a solution to mass-production needs. The big brother to the 650-R machine, the 880-R provides 6 RPM maximum speeds, bigger die rolls than before, as well as a user-friendly, touchscreen interface. The unit provides low noise and vibration, fast encapsulation, quality control and high accuracy. Machine size is 2396 x 1269 x 2059mm.

CHRIS HILLSETH ENTERPRISES

www.changsungsoftgel.com 818-495-3038

TAMPER-EVIDENT OPENING SYSTEM

Constantia Flexibles has developed CONSTANTIA TEOS, a new tamper-evident opening system for packages containing medical devices. The key feature is a tamper-evident, peelable cover foil that is functionally destroyed during initial opening. As such, the cover foil provides reliable protection against the packaging's illegal reuse, the company says. Constantia TEOS also can incorporate a variety of optional features that further assist with tamper evidence. Possibilities include holograms, customized security foil, special security pigments and inks, and security printing such as microtext, hidden graphics and built-in pattern deviations.

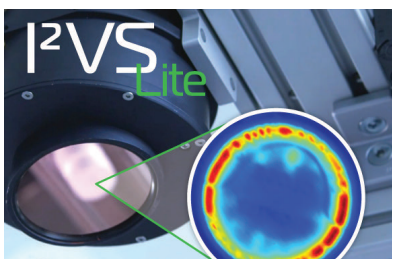


CONSTANTIA FLEXIBLES

www.cflex.com • 803-404-6581

THERMAL IMAGE INDUCTION SEAL INSPECTION

DIR Technologies will debut a simplified version of its Induction Integrity Verification System (I2VS) for bottles, which is said to employ a pioneering application of thermal imaging for induction integrity assurance. I²VS Lite uses the same thermal imaging technology as the original I²VS and, in terms of both machines' primary purpose of induction seal inspection and analysis, is identical to its predecessor. According to the company, the systems provide induction sealing integrity analysis for 100% of bottles without packaging line slowdown by performing inspection through the closed cap, without physical contact in an entirely passive, non-destructive fashion.



DIR TECHNOLOGIES

www.dir-technologies.com • 201-961-4740

CUSTOM EQUIPMENT AVAILABLE

Harro Hofliger is a supplier of production and packaging equipment, primarily for pharmaceutical and medical device industries. In addition to its standard products, the company can provide innovative, custom equipment

to meet customer needs. Standard and special solutions to assemble and package an array of applications include: capsule filling, capsule and tablet weighing, powder handling and dosing, liquid and powder inhalers, wallet packs for blisters, blister stacking, transdermal patches, dissolvable oral film strips, aseptic assembly and more.

HARRO HOFLIGER PACKAGING SYSTEMS

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MULTI-PURPOSE, ASEPTIC FILLING

The Steriline Cartridge Filler Model VKSFCM50 is a filling solution designed to achieve flexibility for multi-purpose filling under aseptic conditions. It enables users to handle all components on a single machine in a single room, resulting in a reduction in capital cost as well as validation and operational costs. The cartridge filler has

controls for no-container, no-fill, reject of any container with missing stopper, missing alu-cap or wrong fill volume, and includes a user friendly touch screen HMI.

MG AMERICA

www.mgamerica.com • 973-808-8185

PRECISION EJECTION SYSTEM

Optel Vision TabletProof 360°, is a high performance inspection system (top, bottom and 360° surface) that ensures every tablet or capsule is inspected while maintaining product integrity and quality control. A precision ejection system allows each defective product to be discarded without interruption. Running at speeds of up to 2,000 products per minute, TabletProof 360° reduces downtime and rework. This inspection is achieved using Optel Vision's camera and software combined with Aylward's patented product-handling technology. It provides shape, size, color, print and logo verification.

OPTEL VISION

www.optelvision.com

418-688-0334

BLISTER PACK ANTI-COUNTERFEIT SOLUTION

Romaco will showcase its blister solution Noack 960 with a special anti-counterfeit technology from solutions provider NANO 4 U. The solution can be applied to any Romaco blister machine with a heatable coding tool. It is based on a banknote authentication system to protect the primary packaging of pharmaceutical solids, and can be integrated into all blister machines equipped with coding stations. An individual hologram stamp gives a unique indication of originality — in-line and without the use of additional materials. The Noack 960 Blister Line can produce up to 700 blisters per minute.

ROMACO

www.romaco.com • 609-584 2500

FULLY ELECTRIC ASEPTIC PACKAGING SYSTEM

Rommelag's bottelpack bp430, which uses blow-fill-seal technology, is a fully electric aseptic packaging system. The mold is designed so that the point of filling within the parison is completely encapsulated from the environment. The modular system allows the

separation into dark/white sides, so that a minimal cleanroom size is needed. Filling is carried out using standard time-pressure dosing or a disposable filling system with peristaltic pumps. This disposable system eliminates the need for CIP validation and guarantees almost no product loss.

ROMMELAG

www.rommelag.com • 303-674 8333

REDUCED DELAMINATION RISK

SCHOTT Vials DC combine an optimized production process with a reliable chemical test procedure: superior inner surface homogeneity; high inner glass surface homogeneity decreases the tendency for delamination, especially at the bottom near delamination risk zone. Conventional SCHOTT vials can be easily replaced by SCHOTT Vials DC without re-registration because of an unchanged glass composition and glass surface.

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The Videojet 7810 2-Watt UV laser marking system delivers high-contrast, permanent codes enabling product lifetime track and trace for pharmaceutical, medical device and cosmetic manufacturers. Prevent the risk of counterfeiting and meet industry regulations with crisp, vision readable 2D codes on white HDPE and LDPE plastic, and other synthetic fiber materials such as DuPont Tyvek.

VIDEOJET

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DECONTAMINATION AND DEPYROGENATION

The ASEP-TECH Model 628 BFS machine from Weiler Engineering Inc. is now available with STERI-Shroud, a patent-pending option for non-aqueous gas sterilization of the critical fill zone shroud. Combined with the NOX FLEX Rapid Bio-decontamination system from Noxilizer, the STERI-Shroud technology can provide both decontamination and depyrogenation of the critical fill zone shroud on Weiler BFS machines. These benefits will result in improved manufacturing efficiency and process control, according to the company.

WEILER ENGINEERING

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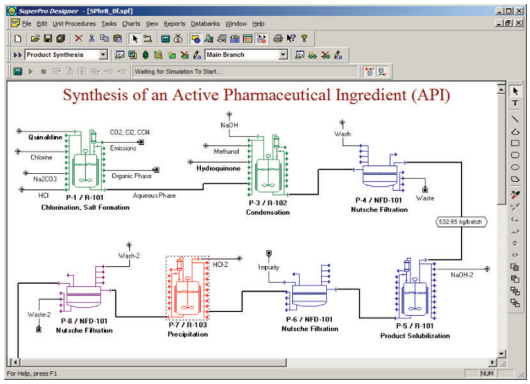
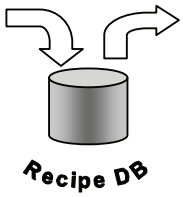
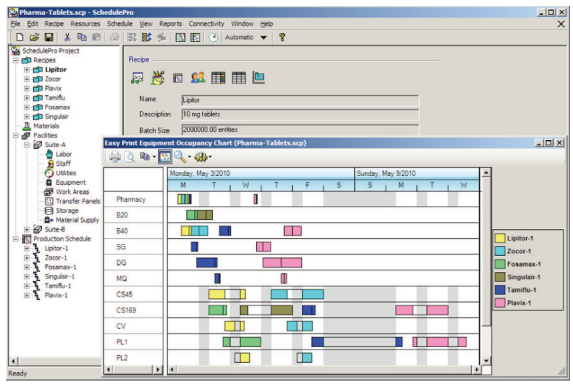
SuperPro®



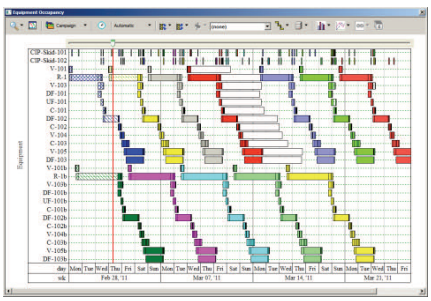
Use SuperPro Designer to model, evaluate, and optimize batch and continuous processes



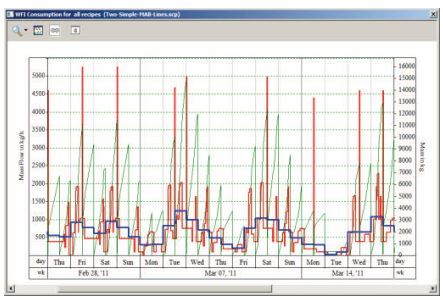
SchedulePro®



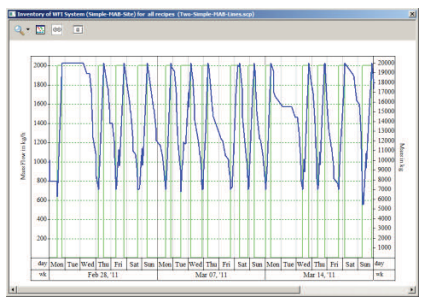
Migrate to SchedulePro to model, schedule, and debottleneck multi-product facilities



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.

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EQUIPMENT & CUSTOM SERVICES

The Forgotten Segment in PAT

What can a PAT program bring to the packaging party?

BY EMIL W. CIURCZAK, CONTRIBUTING EDITOR

EVER SINCE the U.S. FDA embraced the idea of PAT (even prior to its 2002 Draft Guidance), many, including myself, have attempted to define exactly where PAT begins and ends in a Pharma process. My personal view is that EVERYTHING about the process of making and delivering a quality product is covered, including packaging.

At my first Pharma job in 1970, I was hired to determine, with methods I was supposed to devise, the interactions between pharmaceutical dosage forms and polymeric materials. The industry was moving to distributing drugs in plastic bottles, not knowing what kinds of polymers to use, how thick the walls, or what shape the bottles should be, and what additives were safe or could protect the polymers.

I was guided by regulators to use "best scientific judgment" (cGMPs were not yet in effect) to measure interactions. Vapor transmission (both water and organic solvents) was one simple test, followed by light transmission (adding TiO2 wasn't for esthetics), shoulder angles (to avoid chipping or cracking during filling), and cap tightness. We also needed to see what went into and is extracted from the polymer; plastics were suggested to save money and improve safety. A plastic dropper for nose drops was chosen. After initial success with testing, it was decided that the dropper could be packaged in the bottle. Eureka! We had a smaller and lighter package — what could possibly go wrong?

Well, no one thought of testing the preservative (thimerosal) over time with the dropper in the bottle. As it turns out, thimerosal went into the plastic rather rapidly at room temperature. So after using the dropper and inserting it back into the bottle, the remaining solution became a petri dish for cold "germs." Another instance involved hand cream. The bottle's PVC antioxidant was tetraethyl zinc … which migrated into the cream over time and ultimately killed the product.

Though this was happening in the '70s, as recently as two years ago a major Pharma company was forced to recall its products because of "an organic odor." It was discovered that the wooden pallets the bottles were stored on emitted fumes from the preservatives used on them. These emissions permeated the bottles and "adulterated" the products. Unfortunately, the company also had a spate of recalls for shipping mislabeled batches of product, all of which finally brings us to what PAT can bring to the packaging party.

It seems that even a company with a thriving PAT program (i.e., well monitored and documented) can make some false assumptions. At one outfit, we had labels specially made for high humidity climates with "heat seal" mucilage and "wet seal" for dry climates; on several occasions these were mixed, ultimately causing the batch to be rebottled. Another case involved a bi-layer polymer that was heat-sealed to the base of a blister pack. We found that if the polymer is wound on the roll upside down, the polymer will melt onto the heated roller that seals capsules to the packs. What a mess.

A SMALL NIR OR RAMAN UNIT COULD DETERMINE ID AND POTENCY OF A PRODUCT **AS WELL AS CHECK PLASTIC SEALING.**

Such problems may be obviated by simply conducting a last-minute check in the packaging area. A small NIR or Raman unit could determine the ID and potency of a product, as well as to ascertain that the plastic sealing material is correct. That simple step brings packaging into the PAT paradigm of the company.

Keeping sterility is a major problem when packaging liquids, since the drug product is a solution and by definition, homogeneous, confirming content uniformity is generally a matter of weighing the containers. One interesting approach is Blow Fill Seal (BFS) technology, often used for volumes from 0.1mL to >500mL.

If you are not familiar, the basic concept of BFS is that a container is formed, filled and sealed in a continuous process without human intervention, in a sterile area inside the machine. BFS reduces personnel intervention making it a more robust method for the aseptic preparation of sterile pharmaceuticals. Generally, the containers are polyethylene (PS) and polypropylene (PP). PP is more commonly used to form containers which are further sterilized by autoclaving as it has greater thermostability. Notably, the plastic containers can be easily checked with a Raman monitor, thus allowing them to remain sealed and sterile.

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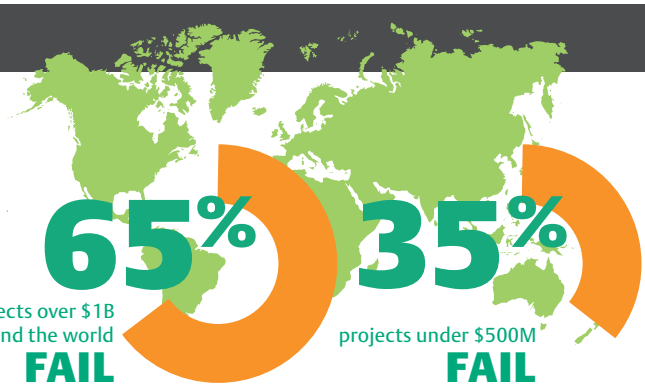
For every $1 billion spend on a capital project, $135 million is at risk. 56% of that ($75 million) is at risk due to ineffective communication.

–2013 Pulse of the Profession, Project Management Institute.



65% projects over $1B around the world **FAIL**

35% projects under $500M **FAIL**

A project is considered to have failed if the schedule slips or the project overspends by more than 25%, the execution time is 50% longer, or there are severe and continuing operational problems into the second year of the project.

–Speed Kills, Klaver, Ali. 2012 Project Manager Magazine.

40 percent of projects in the oil and gas industry are subject to budget and schedule overruns.

–Capital Project Execution in the Oil and Gas Industry. M. McKenna, H. Wilczynski, D. VanderSchee. 2006 Booz Allen Hamilton survey from 2006 of 20 companies (super-majors, independents and EPC firms).

budget & schedule **OVERRUNS** **40%**

30% anticipated value **DISAPPEARS**

Up to 30 percent of anticipated value disappears during the turnover/ commissioning and ramp-up phases of new asset lifecycles.

–Deloitte. Effective Operational Readiness of Large Mining Capital Projects - Avoiding value leakage in the transition from project execution into operations. Article, 2012.

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Good front end planning leads to as much as 20% cost savings and 39% schedule reduction for total project design and construction.

–Construction Industry Institute: Adding Value Through Front End Planning. CII Special Publication 268-3.

PERSONNEL

50% expected to **RETIRE**

50% of experienced and managerial personnel in national and international oil gas processing companies are expected to retire in the coming decade.

–Society of Petroleum Engineers, "The Great Crew Change: A Challenge for Oil Company Profitability", April 16, 2011.

6 TO 7 YEARS

It takes an average of six to seven years to develop new employees into autonomous petrotechnical professionals who can make non-standard, original technical decisions.

–2010 SBC Oil & Gas HR Benchmark, Schlumberger Business Consulting Energy Institute, March 2011.

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