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Pharmaceutical MANUFACTURING

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Better by Design

Intent on making the virtual manufacturing model work, pharma's collaborating in new ways to drive risk out and quality into extended supply chains

SEPTEMBER 2013

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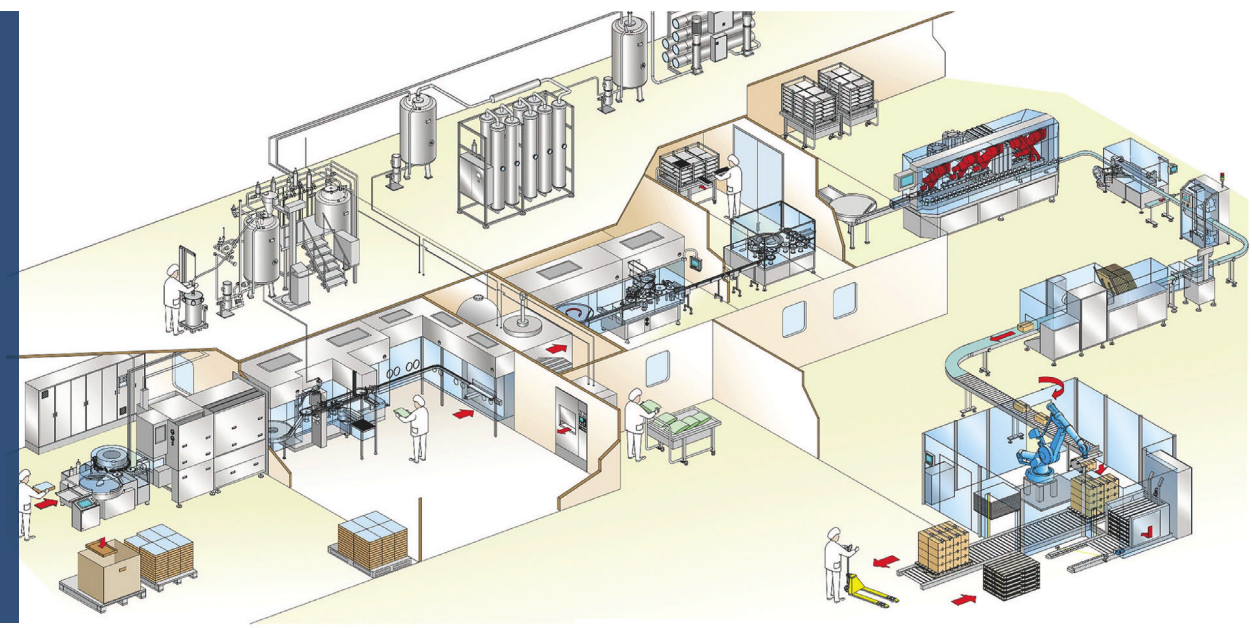


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Better by Design

Intent on making the virtual manufacturing model work, pharma's collaborating in new ways to drive risk out and quality into extended supply chains

BY DOUG BARTHOLOMEW

20

Features

30

Departments

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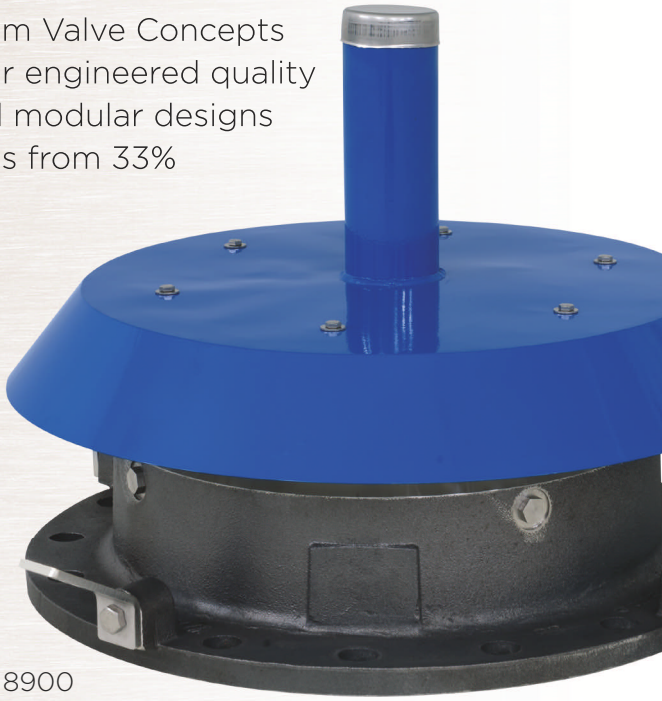

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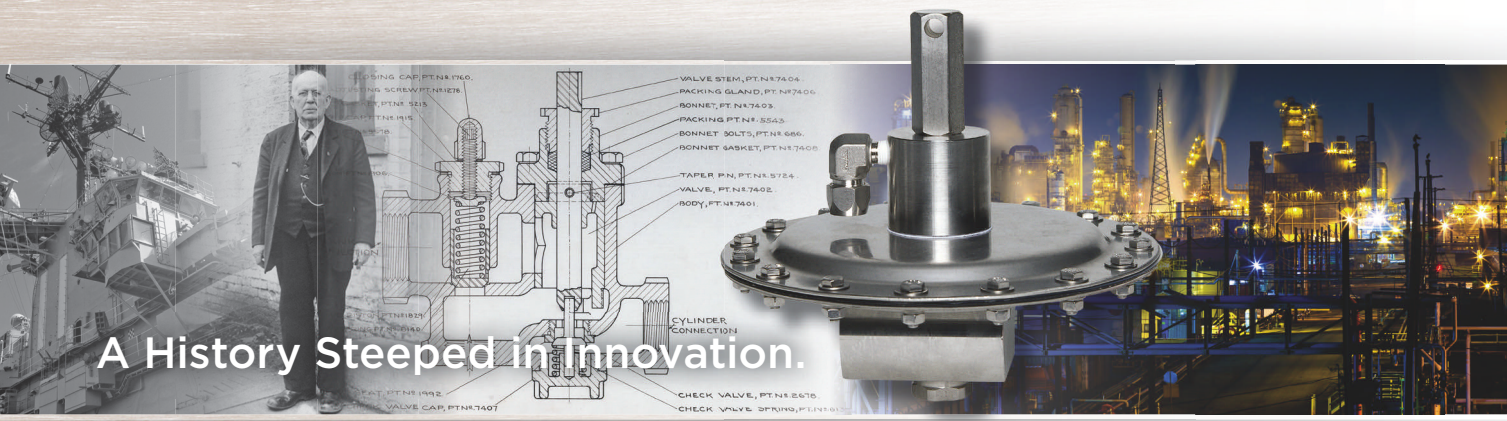

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Chasing the Dragon in China

China's crackdown may ultimately prompt better, more ethical behavior by capitalist and communist alike

THE ALLURE of fast-growing markets and equally bountiful revenue streams continues to attract the world's most prominent Pharma suppliers to China. But to anyone current on the news and events coming out of this region will attest, making and selling drugs in China has just gotten a whole lot riskier, especially in light of the bribery scandals involving GSK, Sanofi, Novartis and now Lilly dominating the industry's news cycles this summer. In a recent CNBC.com editorial, Benjamin Shobert, Rubicon Strategy Group's managing director, finds that regardless of what narrative may ultimately prove best to explain China's recent crackdown on Pharma — backlash from lax internal enforcement, Chinese intimidation of foreign-owned pharma companies, or the extension of the country's emerging regulatory regime to control its own industry, "The fact remains that doing business in the sector for multinationals will never be the same."

As all drug makers are likely aware, to play in emerging global markets like China, new strategic business models are required — ones designed to exploit opportunities while addressing the increasing complexities and risks of extended global supply chains and operations. These strategies are ultimately made more successful with the careful implementation of technologies, processes and procedures — something contributor Doug Bartholomew confirms in his Special Report on p. 20. Unfortunately, even the best-implemented business strategies and technologies can be derailed when the internal dynamics of the market's political and economic systems create commercial environments that only survive financially from tacitly sanctioned corruption, and I mean that from both sides.

The fact is, doing business in China will never be easy — the struggle to reform its collectivist-based political and economic systems and adapt to the realities of free global market generates an instability that may never be fully reconciled. However, in spite of suspicions that this is just more of the same self-serving political theatre, it does appear that regardless of what is motivating it, the state is attempting to institute reforms and disrupt the cycle of corruption that grew from the effects of its waning centrally controlled economy and the resulting neglect of the country's maturing health care sector.

Rubicon's Shobert gives China's government credit for what it has accomplished and posits that, "For China's health care reforms to be successful, something along the lines of the GSK scandal had to happen." China's State Food and Drug Administration (SFDA) announced in July that it would be conducting a six-month inquiry into the marketing, distribution and sales practices of foreign and domestic pharmaceutical companies within its borders. "In the long-term, the GSK scandal has the potential to become an important event that actually stabilizes the country's health care system by ensuring that limited funds get allocated more efficiently and directly ..."

PERHAPS IT'S PHARMA WHO'S BEEN CHASING THE HIGH OF BIG PROFIT IN CHINA, **TOKING ON THE PIPE OF CORRUPTION.**

Unfortunately, like opiates, corruption can be addictive. Users, once hooked, are loath to give up the certainty of financial reward without some serious disincentives. It can all be so tawdry — what's interesting is that these and similar scandals often involve the middle/lower layers of a given multi-national's local sales and business development staffs hard pressed to meet overambitious financial goals without ascribing to bribes and other illegal incentives required to compete successfully.

Call it what you will, this type of corruption is intensively corrosive to free markets and creates perverse incentives that tend to sustain it — especially in centrally controlled economies like China's.

The phrase "Chasing the Dragon" generally refers to an addict's unending attempts at pursuing the next, better high. In this instance, perhaps it's Pharma who's been chasing the high of big profit in China, toking on the pipe of corruption at least regionally (in a global market sense) to meet sales targets. This cycle is being interrupted and GSK its first target, but it might have been avoided if it looked a bit deeper into how its local business units were meeting the business goals it was mandating in a region known for its institutionalized corruption.

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Big Data Hangover?

Why Pharma shouldn't stop drinking

BY KAREN LANGHAUSER, DIGITAL CONTENT MANAGER

BIG DATA'S existence is nothing new. The changing digital landscape, especially the rise of mobile and tablet platforms, has made big data even bigger, exponentially. Research and information is pouring in from so many different sources that it's easy to become a bit overserved with information. With so much on tap, it's likely some are experiencing a Big Data hangover.

Social media represents only a small segment of the big data pie, and even those stats are overwhelming: On a daily basis, there are 4.75 billion pieces of content being shared on Facebook, and 400 million Twitter tweets. More specific to pharma, the National Institutes of Health, per the ClinicalTrials.gov site, reports that in 2012, there were a total of 138,893 studies registered on the site; that averages out to approximately 380 clinical trials registered daily.

When it comes to pharmaceutical research, companies are definitely facing big data overload. Perhaps the area in which drug makers are under the most is pressure is drug innovation. Speeding drug development could clearly help with the innovation crisis, but the traditional clinical trial process is slow and costly. (Statistics indicate that the average drug developed by a major pharmaceutical company costs anywhere from $4 billion to $11 billion. In the event you were wondering, $4 billion will buy you over $220 million cases of good beer, which, true to my headline, would give you quite the hangover.)

I recently watched a TED talk by Dr. Bertalan Mesko — Ph.D, author, lecturer and "Medical Futurist." In his talk, Mesko discusses medical information overload from the Internet, and the importance of filtering it. Mesko recognized that he had to build specific medical communities, thereby crowdsourcing medical questions and curating information from the most relevant group of individuals. The right people can be amazing filters. But if you don't know your community, your efforts are ineffective. The same idea can be applied to the pursuit of innovation in the pharma industry. By using new ways of analyzing and organizing "big data," companies like AstraZeneca are utilizing a different kind of philosophy to understand drugs better in the early stages of clinical development and tailor this to the right patients. This "translational science-based" approach utilizes technology to better analyze data from the beginning, creating a more customized drug development process.

Berg Biosystems, a systems biology company, has developed software platforms to analyze pre-existing data sets and illuminate the full use of that data. This enables researchers to leverage big data analytics to create an assortment of drugs targeting very specific diseases. While this new era of medicine has brought with it even more data, it also brings the tools to better utilize this data. In terms of drug innovation, researchers now have the power to decrease the time it takes to bring drugs to market because they can focus on specific patients who are more likely to benefit from certain kinds of drugs and treatment options.

Big data is getting bigger, but Big Pharma is getting smarter. I'll drink to that.

Scan the QR code for additional info, links and fun stuff related to Big Data.

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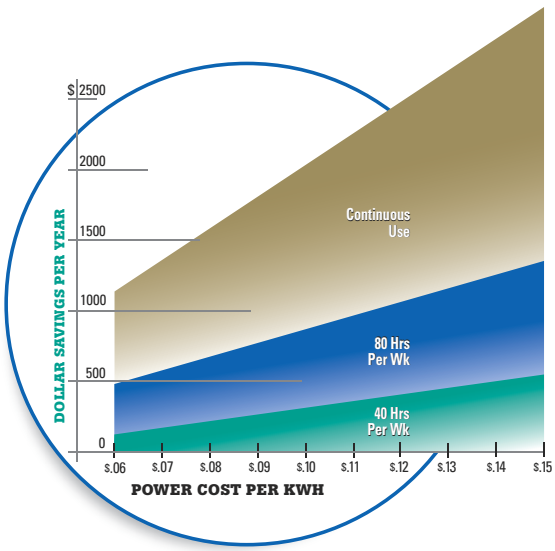

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APPLICATION: Research & Development facility

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"Grooving also takes a lot of time," O'Keefe continued, "from one hour to an hour-and-a-quarter compared to just 15 minutes with Viega ProPress. Given a choice between Viega ProPress stainless or grooving, there's not even a question. It's Viega ProPress. I won't groove any pipe that's 4" or less if I don't have to."

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FDA and EMA Offer Lessons "Learnt"

The agencies provide feedback from the results of their Quality by Design applications pilot program

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

NEAR THE end of August, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) provided a solid dose of feedback concerning the results from the agencies' pilot program for parallel assessment of Quality by Design (QbD) applications. The pilot program was launched in 2011 to asses market-authorization applications using the QbD method "which are relevant to QbD such as development, design space and real-time release testing," said the joint FDA/EMA announcement. According to the regulators, "Both agencies experienced the pilot program as extremely useful to share knowledge, facilitate a consistent implementation of the ICH guidelines and to harmonize regulatory decisions to the greatest extent possible."

As a result of the pilot, says the EMA and FDA, the agencies reached agreements on a wide range of QbD aspects, of which guidance was revealed in the Q&A segment of the joint announcement. Among the key findings is the fact that manufacturing process descriptions require the same level of detail regardless of development approach.

In answer to "What are the Agencies' expectations in a regulatory submission for manufacturing process descriptions?" Regulators responded, saying: "The same requirements apply to the level of detail in the manufacturing process description irrespective of the development approach. For the U.S. FDA, a comparably detailed process description be submitted in lieu of a Master Production Record for drug product manufacturing for 505(b)(1) products." The answer concluded by offering this: "The process parameters that are included in the manufacturing process description should not be restricted to the critical ones; all parameters that have been demonstrated during development as needing to be controlled or monitored during the process to ensure that the product is of intended quality needed to be described."

Another question the agency offered an opinion on was whether or not the agencies would accept a three-tier classification of criticality for process parameters:

The response was: "The Agencies do not support the use of the term Key Process Parameters (KPP) since it is not an ICH terminology. Furthermore, experience reveals that different applicants use the term 'key' differently, leading to more difficult internal communication. The fact that a risk of failure is mitigated by applying a robust proactive control strategy should not allow for the underestimation of assigning criticality." The response went on to say, "The Agencies are amenable to the applicant using this terminology in the pharmaceutical development section to communicate development findings. However, in the 3.2.P.3.3 "Description of the Manufacturing Process and Process Controls" and 3.2.P.3.4 "Control of Critical Steps and Intermediates" sections, the description of all parameters that have an impact on a CQA should be classified as critical."

FUNNY PHARM

"Sir, your application looks to be highly evolved."
— Randy Zeitman

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

Pharma EXPO Debuts in November 2014

ISPE ANNOUNCED it has formed an alliance with PMMI, the Association for Packaging and Processing Technologies, to develop an all-new trade show — Pharma EXPO, which will debut November 2-5, 2014, in Chicago.

Pharma EXPO will be held in conjunction with PMMI's PACK EXPO, one of the world's most successful manufacturing and packaging events. The new joint event will be held annually and take place in Chicago and Las Vegas on alternating years.

Pharma EXPO will present the opportunity to see and compare new and emerging technologies, processing and packaging equipment and other products and services that advance the pharma manufacturing industry. Seminars and mini-sessions planned will also deliver education and information specific to the pharmaceutical manufacturing industry.

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As like-minded, not-for-profit associations with related missions, ISPE and PMMI share a commitment to advance the manufacturing industry. ISPE and PMMI will collaborate in the planning, promotion and execution of Pharma EXPO. The event will be a new platform for educational sessions for pharmaceutical development, manufacturing, packaging, supply chain and other professionals working throughout the product lifecycle. By aligning the new event with PACK EXPO, they anticipate exciting opportunities for member education and networking, as well as a new opportunity for supplier members and exhibitors.

This new initiative is anticipated to provide many additional benefits to ISPE Members, Communities of Practice (COPs), Affiliates and Chapters and the global industry. They envision that this new program will offer members and their companies new opportunities for education, networking and for viewing and comparing the latest in world-class equipment and technology.

For more information, or if interested in speaking or exhibiting, please email PharmaEXPO@ispe.org.

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ONLINE FEATURES

- Quality by Design has become a focused initiative by many of the life science companies that are highly regulated. John P. Helfrich of Accelrys Inc. says the goal is to link manufacturing intelligence to product and process research and development data in order to streamline the operational changes required to produce a quality product at the lowest manufacturing costs reliably and consistently in a variable environment.

- Pharmaceutical manufacturers should think beyond California as they evaluate and implement serialization strategies, says Scott Pugh, Verify Brand. Any manufacturer that wants to be active in global markets will need to have a flexible serialization solution that can meet varying standards and requirements. Furthermore, manufacturers should understand that countries' regulations will more than likely evolve over time, making flexibility in their serialization solutions all the more important.

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Better Wiping,Less Griping

DID YOU know there really is a "right" cleanroom wipe? One size does not fit all. According to ERC Wiping Products, the range of cleanroom wipes on the market is vast and the options are many. Choosing a material, size, weight, manufacturing process, treatment, sorbency, as well as how the wipes are to be packaged, can be confusing and time consuming. Here are five, fun facts about wipes, courtesy of ERC:

1. Cleanroom wipes have their origins in the nuclear industry, specifically to "control the release of radioactive particles."
2. The characteristic of a wipe greatly affects its performance. Make sure to discuss in detail with your vendor about the exact application.
3. The wiping method can impact how well the surface area gets cleaned. Specifically, wiping in circular motions can smear dirt from a dirty area to a clean one; instead, wipe "towards you in straight horizontal lines, each time overlapping the previous one by 10-25%."
4. Not all microfiber cloths are clean room compatible.
5. The cleanest wipe option out there is a laundered, sealed edge polyester wipe, but polyester is less absorbent. So, if absorbency is your main issue, then go with a natural fiber or microfiber wipe.

Viega Names Exec Team

AT A recent media event held August 21, Viega introduced its new executive management team at a venue near and dear to Chicago Cubs fans' hearts — a rooftop overlooking Wrigley Field. Viega's "Boys of October," include new CEO and president Dave Garlow and new COO Robert Boots, both of whom officially begin their roles in October. According to Viega, Garlow succeeds former president Dan Schmierer who has led the company since its founding in 1999.

With 14 years at Viega under his belt, including most recently as vice president of sales, Garlow's no stranger to the Viega executive team and has been an instrumental part

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of the company's growth and success over the years. New COO Boots is also a company veteran with experience managing the company's manufacturing facilities. In 2009, Boots was promoted to vice president of Supply Chain Operations. Formerly with Vanguard, which Viega acquired in 2005, Boots has covered supply chain management and operations for some 23 years.

Garlow (top, right) paid his respects to the company's former leader and his successful legacy running the company. In his remarks to attending media, Garlow made it clear that the company's transition to its new executive team would be seamless and they were well equipped to not only assure the continued performance of the company, but usher in a new era of innovation while paying particularly close attention to its customers. "Even though leadership of our company is changing," said Garlow, "our customer focus won't change. Our mission will continue to be enhancing lives by providing innovative piping systems for our industry; rest assured that a lot of the things we built our success on won't change."

Similary, Boots (top, left) shared his excitement and said he was looking forward to getting involved in the sales side of the business. "In a lot of companies the tradition is that the sales and supply chain sides don't work well together ... And what I think makes Viega so special is that … not only do we work well together, we're partners. I view the supply chain as an extension of the sales division, and we are all here to serve our customers in the best way possible."

It was a perfect night for a ball game and a great venue to better understand the depth and abilities of Viega's executive bench. Bringing in the wins for Viega will be their job #1.

Maximizing the Value of CRO Relationships

Open collaboration, commitment and mutually agreed upon goals will accelerate the value of CRO alliances

BY JOSHUA SCHULTZ, CORPORATE VICE- PRESIDENT, PAREXEL INTERNATIONAL

STRATEGIC PARTNERSHIPS with clinical research organizations (CROs) can deliver multiple benefits for biopharmaceutical companies of all sizes by reducing direct and indirect costs, improving efficiencies and accelerating speed to market. However, such relationships require open collaboration; mutual investments in time, process improvements and technologies; robust, multi-level governance; and a commitment to long-term success to achieve their maximum potential.

COST SAVINGS AND STRATEGIC PARTNERSHIPS

Until recently, biopharmaceutical companies engaged CROs in project-by-project, transactional relationships to lower costs, utilize internal resources more efficiently and decrease risk. These relationships were similar to outsourcing relationships that have been used for decades in other industries. Although transactional models can reduce fixed costs and improve operational efficiencies to a degree, they typically cannot deliver the high levels of operational efficiencies needed to meet the challenges of today's changing biopharmaceutical research and development (R&D) landscape.

In recent years, sponsor relationships with CROs have evolved into more committed and complex multi-year strategic partnerships designed for multiple studies. These partnerships leverage the CRO's resources and experience and deliver broad-based solutions across the clinical development continuum. In these partnerships, CROs generate direct cost reductions by establishing rates that incorporate expected partnership efficiencies or volume discounts that enable shared savings driven by the long-term nature of the relationship and a larger amount of work. Streamlined contract structures and pre-negotiated rates dramatically reduce study delays associated with completing contracting activities, request for proposal (RFP) completion times and competitive bidding. Additional cost-savings result from dedicated staffing, training efficiencies, better utilization of resources, up-front study design and innovations.

QUANTIFYING INDIRECT COSTS SAVINGS

Direct cost savings represent only a fraction of total savings possible from a well-constructed, long-term strategic partnership. Most savings can be derived from reducing the level of sponsor project oversight, improving cycle times, building trust and accountability and having easier data access.

Compared to traditional transactional models, oversight cost reduction can be dramatic. Partnership-level agreements that define key project management criteria — such as agreed-upon quality standards, project metrics, governance, shared incentives and improved communications — can dramatically reduce the need for extensive hands-on management, while still assuring a high level of information exchange about each project's progress. Duplication of effort can also be reduced because the CRO can take over many of the day-to-day project tasks, allowing sponsor employees to focus on other priorities. As a result, strategic partnerships can increase the average sponsor-to-CRO oversight ratio from 1:3 to 1:8 and even 1:15 — equivalent to saving up to 20% of a CRO's professional fees for a typical project.

THE CHALLENGE IN MAXIMIZING A STRATEGIC PARTNER'S VALUE IS THE INVESTMENT OF DOLLARS AND TIME.

ACCELERATING CYCLE TIMES

One of the greatest areas of potential savings in a strategic relationship results from reducing development timelines driven by operational improvement and the streamlining of the processes necessary to develop the study protocol. Compared to transactional outsourcing in which the CRO relationship typically starts later in the development process, in a strategic partnership the CRO's experience and expertise can be accessed before the protocol is approved. Early CRO involvement can also help with designing trials that focus on results that support regulatory approval, reimbursement and market access.

The CRO can help develop more efficient protocols or operational plans that can significantly reduce a study's overall time and cost. In addition, CRO partners can increase speed by investing in operational improvements such as clinical report form (CRF) libraries, study start-up templates, data transfer

specifications, contract backup language, automation and technology integration. All of these documents can be approved before a study begins.

The time and costs of product development can also be reduced by using technology to automate tasks and improve visibility to data, leveraging the CRO's global presence to access patients and expertise that might be difficult to access locally, and the bundling of services across a program or a compound.

MEASURING DRIVERS OF VALUE

Strategic partnerships have become a value-driven approach to clinical development focused on reducing sponsor oversight while retaining quality, accessing innovation and driving faster cycle times. Metrics to accurately measure and demonstrate a partnership's value should be defined at the beginning of the relationship, and then measured throughout the course of each project to demonstrate their health and progress.

Among metrics that should be defined and measured at the beginning of an engagement are: financial success, operational improvements (study milestones, cycle times, productivity, quality, etc.), innovation metrics around improvements in processes and technology, and stakeholder analyses to provide an overview of partnership goals and progress.

MAXIMIZING VALUE OF A CRO RELATIONSHIP

Maximizing the value of a relationship with a CRO requires addressing the following four steps:

1. Understand that mutual investments are necessary. Both sponsor and CRO must invest in processes, technology and systems alignment. Investments aren't necessarily financial in nature and are often based on defining goals, anticipating issues and measuring results. In addition, investments in partnership-level agreements that define how teams should interact and effectively manage change can help build the trust necessary to advance the relationship.
2. Define commercial terms to align incentives. Fees, prices and expertise-sharing must be aligned at the beginning of each project. As a relationship matures, this becomes easier because both sponsor and CRO understand the necessary approaches to align incentives. In short-term transactional projects, it is often difficult to align incentives because of the more limited nature of the transactional relationship.
3. Ongoing refinement. Both sponsor and CRO must be willing to define what constitutes success and prioritize key value drivers to measure a partnership's financial, stakeholder and innovation value. Planning should include a robust, multi-level governance structure that includes GMP and manufacturing colleagues, and a communications plan that encourages ongoing, open dialogue, rather than ad hoc, issue-centered discussions. These definitions and planning should start at the relationship's beginning, with the understanding that partnership improvements will continue throughout the life of the relationship.
4. Work on the partnership. Successful strategic partnerships begin with an understanding that there will be challenges along the way. When issues arise, the partners have already defined how to address them. Experience shows that the more time the sponsor and CRO invest in building the partnership, defining success metrics and communicating frequently and openly, the greater the return. For this reason, partnerships designed for multiple studies over an extended period of time tend to be the most successful. Generally, it can take 12 months to reach an initial steady state and two years to see the full value and benefits of a strategic partnership. Such benefits are difficult to realize in a one-study, transactional relationship.

EVOLUTION CONTINUES

Strategic partnerships between biopharmaceutical companies and CROs will continue to evolve from the traditional transactional model toward integrated relationships that drive value through increased alignment and efficiencies. The greatest challenge in maximizing a strategic partnership's value is the investment in dollars and the time needed to create a deep, integrated and meaningful relationship and the patience for those investments to pay off. A strong commitment by both partners in the relationship's long-term success, along with greater alignment of commercial terms and true collaboration, will maximize benefits and minimize risks.

ABOUT THE AUTHOR

Joshua Schultz is corporate vice- president, Strategic Partnerships, at Parexel International. He leads the Strategic Partnership group at Parexel, which is focused on developing and executing innovative relationships with key pharmaceutical companies. He has held a number of roles within Parexel, including building a group dedicated to efficient operational design and launch of clinical studies (START) and another focused on pharmacovigilance. Prior to joining Parexel, Schultz served as vice-president of corporate development at Veritas Medicine, which he co-founded. Previously, he worked at Mercer Management Consulting, where he developed growth strategies for Fortune 500 companies.

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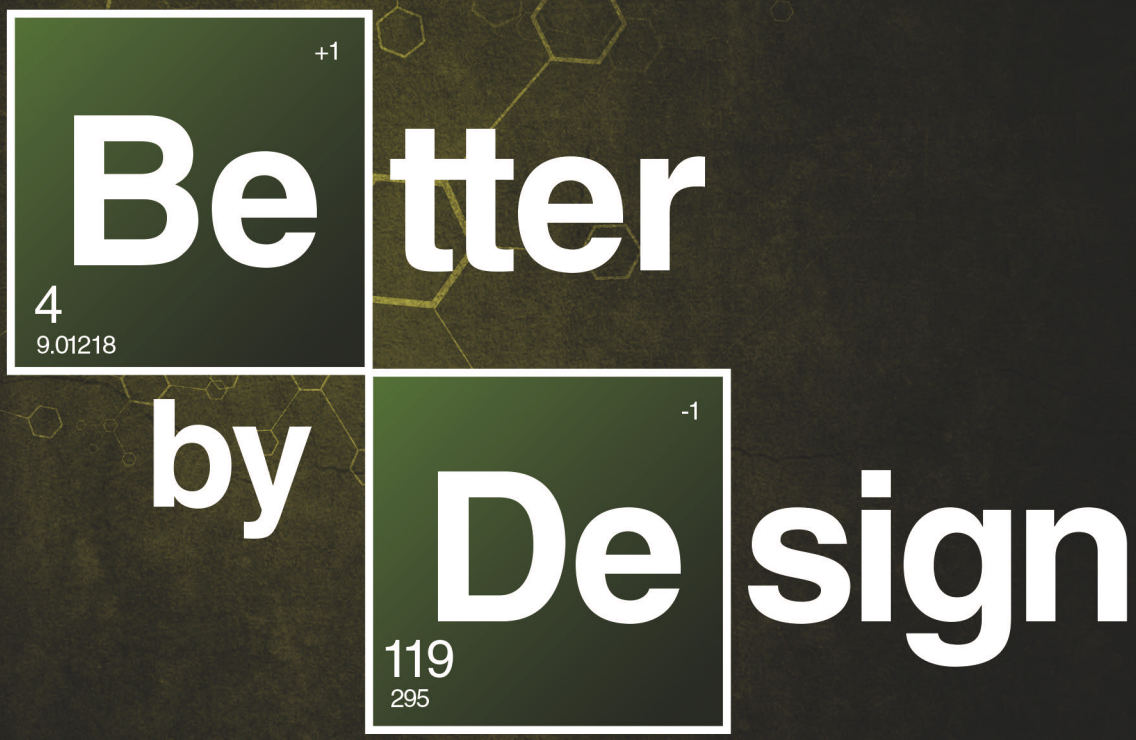
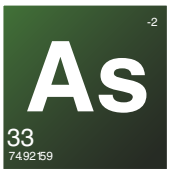


Intent on making the virtual manufacturing model work, pharma's collaborating in new ways to drive risk out and quality into extended supply chains

by Doug Bartholomew



THE PHARMACEUTICAL business moves closer to the virtual manufacturing model, the need to manage quality and risk across the extended supply chain has emerged as a front-and-center challenge to the industry.

Today the virtual model is embraced on a grand scale by the large OEM drug firms. The giants of the industry view it as a cost-effective approach to extending their supply chain to serve emerging markets. At the same time, it enables them to quickly and cost-effectively add new manufacturing capacity worldwide.

"Over the last three to five years, pharmaceutical companies have started moving 30% to 50% of their manufacturing to contract manufacturers," says Hussain Mooraj, director, Life Sciences Supply Chain Practice at Accenture. "But as these strategies were adopted, the companies needed a new way of operating."

In fact, many pharmaceutical firms are struggling to manage their suppliers. "Every company I visit is struggling with this — it's going to be the issue du jour for the next couple of years," says KR Karu, director Pharmaceutical Industry Solutions, Sparta Systems, a quality management systems vendor.

He cites the experience of a drug firm that recently received an FDA warning for not properly managing its suppliers — specifically, not properly evaluating them, and failing to verify that they had a corrective and preventive action (CAPA) system in place. "All suppliers need to be following GMPs and need to provide proof of that," Karu says.

COST REDUCTION THE CHIEF GOAL

It's no secret that most drug manufacturers made the decision to outsource production to a CMO as a way to reduce costs. But product quality can suffer as a result, if proper safeguards — in the form of processes and technologies — aren't put in place. The rub here is that all too often, the connections between drug manufacturers and their suppliers dealing with quality problems often consist of emails, spreadsheets, faxes and phone calls — not exactly the kind of cutting-edge technologies one would expect multi-billion-dollar companies to depend on in a real time, digital age.

"It's so much harder to manage a business that way, because if you have a quality issue or some other supply problem, days can go by before all the relevant knowledge gets to all the people," says Brian Daleiden, senior vice president, marketing at Tracelink Inc., a provider of supplier collaboration tools for the life sciences industry. "The result is that quality issues fall through the cracks."

"We ask the question, 'Shouldn't you have the same level of data for your outsourced product as you do for data on product you produce yourself?'" Daleiden says. "But the problem is that it's really hard to build the infrastructure to do that."

According to some, that's an understatement. "There can be information sharing enabling a pharma to engage a CMO as if it were its own facility and recall batch, training, maintenance and cleaning records, view analyst notebooks, and review process KPIs," says Ramana Reddy, associate vice president and Practice Leader for Life Sciences at Cognizant Business Consulting. "This would make the client/CMO relationship almost completely transparent and enable partnerships on a much deeper level. This is easier said than done, and we are not aware of any partnerships with this level of integration."

IDENTIFYING SUCCESS

Given that level of partnership is the goal, what are some best practices for quality monitoring and risk management across the virtual manufacturing and supply network? What does outsourcing success look like, and what technologies can help make it a reality?

One challenge the industry continues to wrestle with is the need to integrate a variety of different information formats and information systems. While the typical pharmaceutical firm has an enterprise resource planning (ERP) system in-house, it may or may not have any kind of smooth communication links with the various different ERP systems in use at the company's suppliers. "There is an underlying technology gap out there," Daleiden says. "For companies that may have 30 to 50 different external supply relationships, you could have the same number of unique technology environments for bi-directional information sharing."

On the technology side, some pharmaceutical companies have extended their ERP systems to communicate key production data with suppliers. Still others use online portals as a platform for exchanging inventory, batch and other information. "ERP is an excellent tool inside your organization, but there are tremendous challenges to extend it into a network," says Mooraj. "That's the hurdle these pharmaceutical companies faced."

Cognizant's Reddy agrees, adding, "Most ERP systems and best-of-breed MES (manufacturing execution system) tools offer the possibility of achieving a 'virtual enterprise'. However, achieving this in practice requires more than the underlying technology, but the experience of successfully deploying these systems across a global network."

But Joseph Miles, vice president for SAP's Life Sciences Solutions Group, points out that SAP's vertical solution for the pharmaceutical industry offers rich functionality for drug companies. "We are a leading provider of serial track and trace capabilities," Miles says. "Because all the product and sourcing data are kept in the back-end systems, that information is critical to producing high-quality products," he adds, pointing out that the technology is critical to both prevent counterfeiting and ensure the security of drugs as they move through the supply network.

In a similar vein, John Danese, senior director, Life Science Industry at Oracle, another major ERP software provider, says pharmaceutical companies are using its ERP and product lifecycle management (PLM) systems to manage and monitor their suppliers. He recounted a recent incident in which a contact lens manufacturer discovered through the Oracle PLM that a series of complaints had been logged over lens reservoirs that were low or dried out altogether.

"The case was logged in the PLM as a quality event," he says. It turned out the problem was caused by sharp edges resulting from out-of-specification tooling at the CMO. "The company put that supplier on hold and assigned production to another vendor until the problem was solved," Danese says. "The company managed it all through the PLM system."

Many pharmaceutical firms are struggling to manage their suppliers. According to Accenture, over the last three to five years, pharmaceutical companies have started moving 30% to 50% of their manufacturing to contract manufacturers.

VARYING TECHNOLOGIES POSE CHALLENGE

Another issue drug manufacturers' face when managing CMOs is the variety of technology platforms in use throughout the industry. The typical pharmaceutical business may work with a small manufacturer with a totally heterogeneous IT environment and that may not have a shop floor system (MES) integrated with an ERP system. Or there may be several different versions of the same ERP system that have yet to be consolidated.

Then there is the need to carefully "vet" any new CMO. "You may have an initial cost savings, but doing the due diligence and assessing how this supplier may impact your company from a risk standpoint is essential," says Deb Kacera, Regulatory and Industry Strategist at Pilgrim Software, a provider of quality and compliance management systems. "You have to have somebody with feet on the ground" checking out the CMO's manufacturing site, she adds.

An example of a pharmaceutical manufacturer coming to grips with these issues is Merck. Seeking to establish a global supplier network to more economically serve emerging markets as well as mature ones, the company has had to find ways to sharpen visibility into the activities of suppliers and third-party logistics providers. Merck also is using information technology to share information with its supplier community, thereby promoting greater collaboration on important issues such as quality.

"We aspire to have a world-class supply chain," says Steve Hydzik, executive director, Merck Manufacturing IT. Hydzik described Merck's plans for the virtual supply chain in a July 2013 webcast at http://bit.ly/18Ahnum with Merck's technology partners; Tracelink, a software firm; and Amazon Web Services, which hosts the public cloud on which the supplier network management software runs.

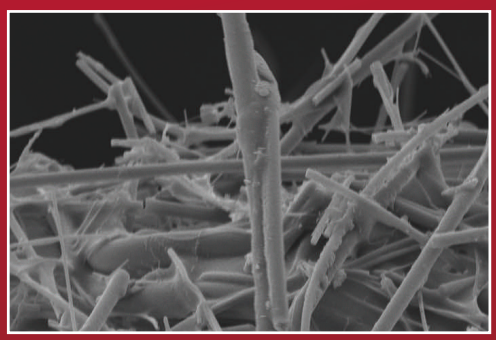
Merck wants greater visibility and collaboration with suppliers, Hydzik says, with the goals of driving down cost, shortening time to market and meeting ever-increasing customer expectations. "We've established a vision of an end-to-end supply chain capability," he says. "You really need visibility into these business processes. You need to

Air Quality Related Contamination Risk Reduction

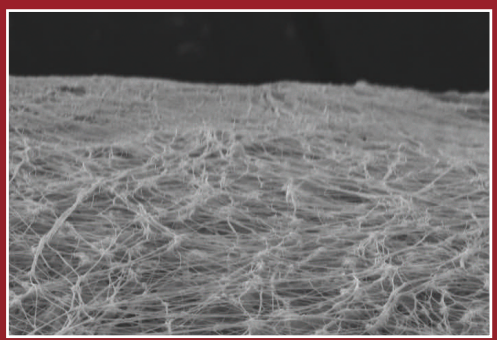
in Biotechnology & Pharmaceutical Processes

Downtime during manufacturing from terminal air filter failure does not only result in substantial revenue losses and costly recoveries, it could also mean that a consistent quality of medicines cannot be guaranteed, so patient health and safety are at risk. Product quality, therefore, needs to be at an indisputably high level. During manufacturing, any risk of contamination has to be minimized, and no concessions to sterile conditions can be accepted in the most critical processing areas. Adverse effects on medicinal products need to be prevented and GMP compliance guaranteed. Choosing the right cleanroom terminal air filter is vital for safeguarding the required conditions and reducing process risks.

Until recently, these air filters were predominantly made out of micro-glass making them very fragile, prone to damage, and potential leakages. Technological advancements in filtration media now offer higher durability resulting in reduced contamination risk. These high-durability HEPA and ULPA filters are made of the same inert material deployed for decades in filtering pharmaceutical fluids; ePTFE (expanded PolyTetraFluoroEthylene). Demonstrating high tensile strength and abrasion resistance, with a burst pressure substantially higher than traditional air filtration media, ePTFE membrane media is extremely durable. Air filter integrity is retained and fiber shedding risk in cleanroom environments is eliminated. The result is a high robustness for significantly improved filter life expectancy and reliable operation.



Micro-glass fibers are damaged and fracture when folded.



AAF's ePTFE media is 8x stronger than micro-glass media, and bends rather than breaks when folded.

make problems visible to achieve operational excellence."

To realize that strategy, Merck "has embraced the concept of an air traffic controller in a collaboration tower with the ability to see all the necessary information," he says.

Although the company is in the fifth year of implementing a corporate-wide ERP system using SAP, Hydzik says ERP isn't designed with collaboration at its raison d'etre. "The things ERP does well are inventory management, demand management and purchasing, but what it doesn't do well is share information with other types of solutions," he explains.

to be able to log corrective actions against those suppliers to see which ones are impacting products on a recurring basis," Dahod says. "This information, in turn, can be fed to a planning group, and they can work with procurement to get an alternate supplier in place."

He cites the case of a major pharmaceutical firm that had a product in short supply due to a time-consuming quality review process. "They were not releasing batches fast enough to be able to deliver to market on time and in full," Dahod recalls. "By having a technology platform to share that information, they can solve it much faster

The most advanced pharmaceutical manufacturers are working with CMOs to integrate their information platforms to facilitate collaboration.

MERCK'S SEARCH FOR A SOLUTION

In a careful search for the right software to perform the collaboration function, Hydzik says Merck considered three possible approaches — a custom-built system, the purchase of an off-the-shelf software package, or something totally different, such as a cloud-based technology. "We decided to embrace the cloud and move fast, and if necessary, bail fast. We decided to go with Tracelink as an enabler to do that."

Tracelink, which runs on Amazon Web Services' public cloud, offers a supply chain collaboration platform enabling manufacturers to share information with business partners on supply, production and distribution. "This technology links brand owners and their CMOs, providing visibility into inventory information and compliance information, which mitigates the risk somewhat," says Mooraj.

The ability to aggregate key performance metrics by supplier is an essential capability for pharmaceutical firms with extended supply chains, says Shabbir Dahod, president and CEO at Tracelink. "For instance, if there is a recurrence of quality issues among suppliers, it's helpful

than if they had to collaborate via fax or email. With their planners aware of the problem, they were able to plan around the shortage and solve it by sending batches of product where they were most needed."

In Merck's case, the company wanted both greater visibility and agility when it comes to managing the various processes in the virtual supply network. "We want to enable our relationship managers to fine-tune the timing of each and every order in the supply chain," Hydzik says. "The cloud provides that speed and agility. And it allows us to drive a better return on investment."

One of the secrets to Merck's success in moving to the cloud-based solution to manage its virtual supply network was the company's recognition that the project was business-driven, as opposed to IT-driven. "The key fundamental principle was that this was not an IT project — it was all about business outcomes," Hydzik adds.

Another essential ingredient was supplier buy-in. "We saw it as an opportunity for a win-win with our suppliers, because it was anchored in driving out inefficiency in business processes." But prior to moving

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to the new platform, Merck had varying approaches for managing processes such as purchasing. "Each business manager had his own way of purchasing management with his suppliers," Hydzik points out. "The ability to drive standardization, eliminate waste and make the information visible to Merck and the CMO was a win-win."

The benefits to be obtained by suppliers quickly became apparent. "It allowed suppliers to trade up," Hydzik says. "Instead of having a CMO focused on inventory position or 'Where's this purchase order,' it was, 'How can we improve the packaging line?' It wasn't a tough sell, and we are actually finding an amount of support from CMOs."

IDENTIFYING STRATEGIC PARTNERS

The most advanced pharmaceutical manufacturers are working with CMOs to integrate their information platforms to facilitate collaboration, Mooraj says. "The new approaches to collaboration in the extended supply network have to do with how to develop shared processes," he says. "A first step is to segment suppliers to identify those that are strategic, and then find ways to integrate platforms with them to exchange information and provide end-to end visibility." The idea, he says, is to "develop a bi-directional feedback culture with your partners."

Perhaps more important than the technological links are the organizational and cultural changes required to bring about this level of collaboration. "You have to have the focus to eradicate the barriers that exist, including the people, process and organizational challenges," Mooraj says.

He recommends that pharmaceutical firms first adopt the necessary over-arching strategy. "They need to develop a holistic strategy for

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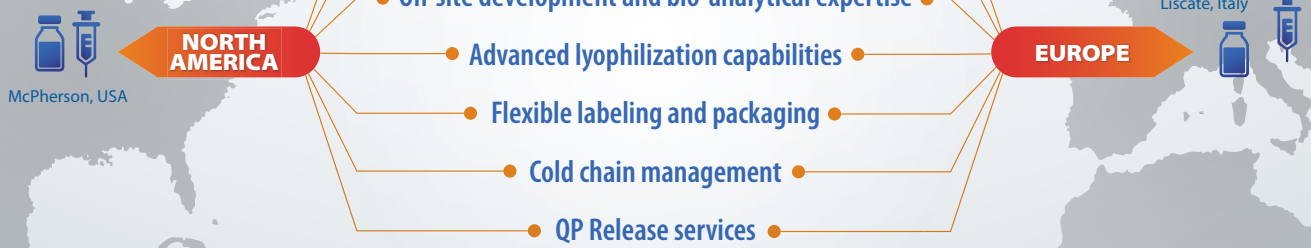

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contract manufacturing that will take their relationship with their suppliers from 'arm's length,' to a collaborative relationship," Mooraj adds.

Instead of treating all CMOs and other suppliers alike, pharmaceutical companies should adopt a segmented approach, focusing on establishing a close collaboration with a handful of strategic suppliers. Mooraj recommends developing a set of bi-directional metrics so that results are measured and people are held accountable for those results.

SITE VISITS AND COMMUNICATION

Another best practice to ensure successful outsourcing of production from a quality and risk view is to conduct regular site visits and audits to verify that the contract firm is following good manufacturing principles and has employees who are trained to adhere to the client's standard operating procedures.

"One of the big differences between a contract facility and a company facility in terms of quality is that the client's product is rarely the only product being manufactured at that site, and often the client doesn't know what the other products are," says Reddy of Cognizant. "Aside from the biggest concern of cross-contamination, there are issues such as ensuring that equipment is not being swapped around, or if it is, that it is validated. The best practice is vigilance. Random batch inspections and verification of the CMO's analysis by the client firm's analysts should be part of any partnership."

Not surprisingly, communication also looms large when trying to keep a tight and accurate pulse of the virtual supply chain's health — not only for operational or logistical reasons, but also for managing quality and risk. As an example, quality incident reporting can suffer if communication is not totally candid. "For example, cultural issues at the CMO facility may prevent bad news from moving up the chain, so that the client is not aware of delays or failed batches until it's too late to head off the problem," Reddy adds.

When dealing with suppliers that have recurring production issues, it may be necessary to institute more careful and frequent product inspections. "The client can use a risk-based approach to inspect incoming products," says Kacera of Pilgrim Software. "The inspections can be based on the level of risk for that supplier, or on the level of risk associated with the product," she adds.

Ultimately, though, it's better to catch manufacturing deviations early on via some electronic means of reporting from the CMO to the pharmaceutical company. As Kacera puts it, "You need real-time feedback from suppliers to see where their non-conformances are and see if there is a trend."

Finally, driving many of these concerns is the industry's need to comply with FDA requirements. "The regulatory environment for contract manufacturing is getting tougher," observes Accenture's Mooraj.

For example, in May the FDA issued a draft of new guidance governing drug manufacturers' relationships with CMOs to ensure product quality. The FDA recommended that pharmaceutical companies and their contractors implement written Quality Agreements to delineate their responsibilities to ensure the quality, safety and effectiveness of the drugs they produce.

"The FDA says the pharmaceutical companies need to be auditing their suppliers, and that they are fully accountable for that product," says Miles of SAP. "You can outsource the process, but not the accountability."

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FORMATTED ACTIVE CARBON FILTERS

Cartridge style activated carbon filters offer advantages over loose carbon in pharmaceutical ingredient production

■ Part 1 ■

BY DENNIS G. BATTERSBY AND MAJID ENTEZARIAN, 3M PURIFICATION INC.

THE EVOLUTION of charcoal from its earliest uses in ancient Egypt and India for the clarification of curatives and drinking water to its present activated carbon form is characterized by the selection of carbon sources, methods of activation, materials design and complex formations. Concomitantly, uses of activated carbon have expanded to include in vivo medicinal treatments, toxic waste remediation and catalysis to cite a few examples.

Although water purification utilizes the largest quantity of activated carbon, clarification and purification of pharmaceutical intermediates and products still remain a significant application. Although these latter applications may, by virtue of scale seem less daunting — an application may be unique and used only in a single campaign — they have peculiar requisites: As a general rule, animal sources are undesirable, chemicals involved in activation must be absent or readily removable, and regulatory support material concerning the activated carbon materials should be available. Table 1 lists essential aspects of activated carbons in terms of their sources, activation methods and available formats.

CARBON SOURCES	ACTIVATION METHODS	AVAILABLE FORMAT
COCONUT SHELL	CHEMICAL TREATMENT	FINE POWDER
ANIMAL BONE	ACID TREATMENT	PELLETS
ANIMAL BLOOD	STEAM	BLOCKS
WOOD		DEPTH FILTERS
COAL		
PEAT		

Table 1. Partial listing of essential aspects of activated carbon

While the characteristics of various grades of activated carbon in terms of porosity and general adsorption capacity are well understood, the phenomena of chemical adsorptions and predictive behaviors are oftentimes enigmatic. This circumstance partially explains the large number of commercially available activated carbon offerings and something that usually necessitates the testing of representative carbon samples with one's product.

CONSTRUCT AN ISOTHERM

One usual method of evaluating the efficacy of a powder carbon sample with a given product is to construct an isotherm by adding graduated concentrations of a given powdered carbon sample to a product, agitating it for a given time then analyzing it. While not particularly difficult, this process can be tedious and time consuming. Moreover, the realized affect of the carbon may be quantitatively different when small samples are tested in the laboratory and scaled-up processes are actually run in production under quite different fluid management techniques. In contrast to working with powdered activated carbon samples, 3M depth filters impregnated with specific carbon types support both activated carbon selection and production scale-up calculations. For example, Table 2 lists five grades of depth filter media of differing effective porosity, for use with products of differing viscosity. Media with larger porosity are appropriate for viscous samples, while the denser or tighter media are recommended for use with aqueous or solvated samples.

3M Depth Filter Grade	Nominal Pore size (µm)	Viscosity Range (cp)
R-1	0.8 - 4.0	60 - 80
R-2		
R-3	0.6 - 2.0	20 - 60
R-4		
R-5	0.5 – 1.0	1 - 20

Table 2. Partial Listing of Depth Filter Media Grades, Effective Porosity and Viscosity Range.

Additionally, five different types of activated carbon are available in each of the grades as shown in Table 3 below.

Carbon Source	Activation	Surface Area (m^2 / g)
#1 Bituminous Coal	Steam	800
#2 Lignite Coal	Steam	650
#3 Peat	Steam	1200
#4 Wood	Acid	1400
#5 Wood	Acid	1400

Table 3. Five Standard Activated Carbon Types Available

OPTIMIZING CARBON EVALUATION

For initial evaluations, small disposable filter capsules of 25 cm^2 area, or 13.5 cm^2 disks for use in reusable stainless-steel test cells can be used. Using a simple arrangement of filter, holder and a pump for control of sample

flow rate, it is possible to optimize both carbon evaluation and operating conditions for scale-up. Figure 1 shows the simple set-up for use in various activated carbon filter media trials. Qualitative analyses of the developing filtrate fractions determine the end point of the testing, and the filtrate pool constitutes the throughput.

Using a known filter area and selecting a product flow rate establishes the flux:

$$\text{flux} = \frac{\text{flow}}{\text{area}}$$

generally normalized to L/min/m2.

Given that the filter media area is fixed by the test filter size, the flux will be controlled by the pumped flow rate. The lower the flux, the longer the product residence time within the carbon matrix; and as a general rule, the longer the residence time, the more effective the carbon-product interaction. Once an effective carbon type is selected, generally only one or two flow rate evaluations are required for flux optimization. Following these determinations, it is a simple matter to relate product volume, available processing time, flux and throughput to predict the necessary filter area for a scale-up process. Likewise, existing processes that use loose activated carbon can be easily converted to the depth filter activated carbon format.

It is worth mentioning that the presentation of the activated carbon to the product in the depth filter format is quite intimate and the fixed carbon particles provide consistent interactions with the product. In contrast, the loose carbon powder suffers random packing and is prone to channeling and the selection of preferential pathways.

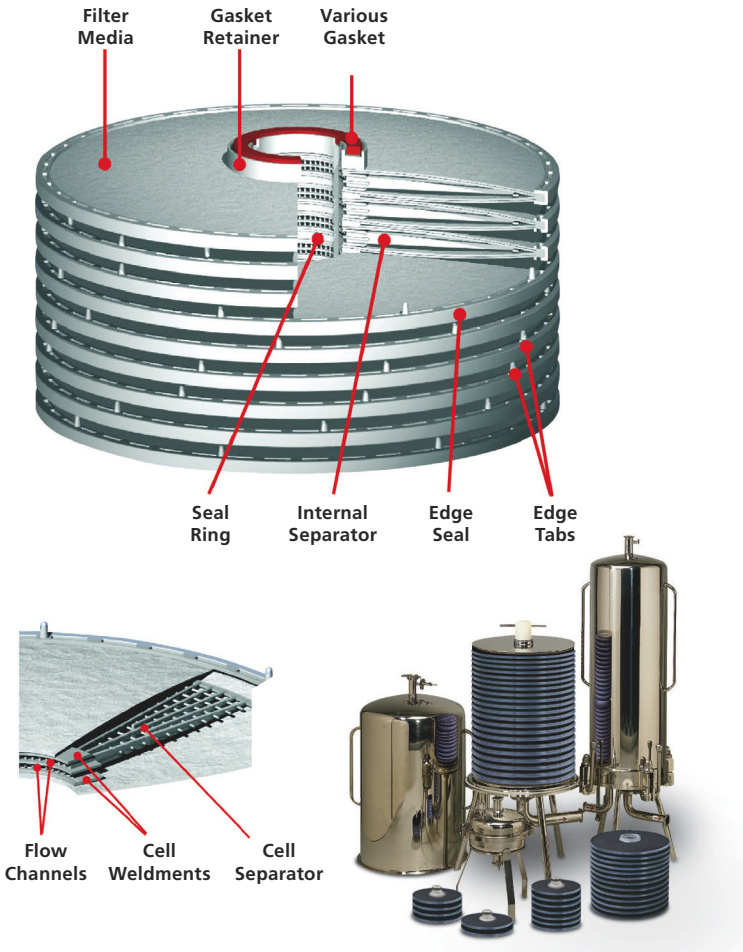

Figure 2. Carbon Depth Filters, Anatomy of Lenticular Filter Cartridges and Housing. Notice the bilateral convexity of the individual filter elements.

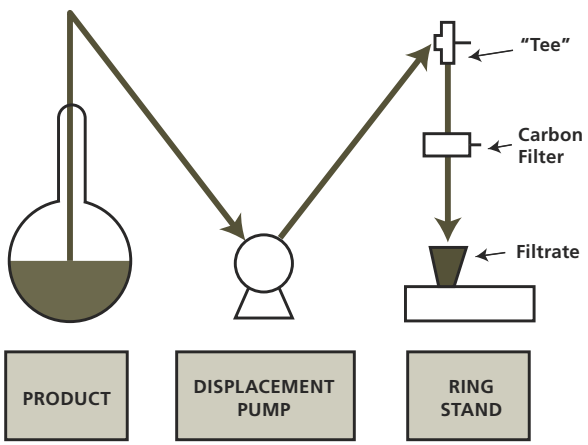

Figure 1. Essential Activated Carbon Filter Testing Set-up.

In addition to simplifying the activated carbon selection and scale-up processes, the lenticular activated carbon filter cartridges obviate the handling of bulk powdery carbon and the associated problems of health and safety risks due to dust, storage and handling as well as post-use clean-up and disposal.

ABOUT THE AUTHORS

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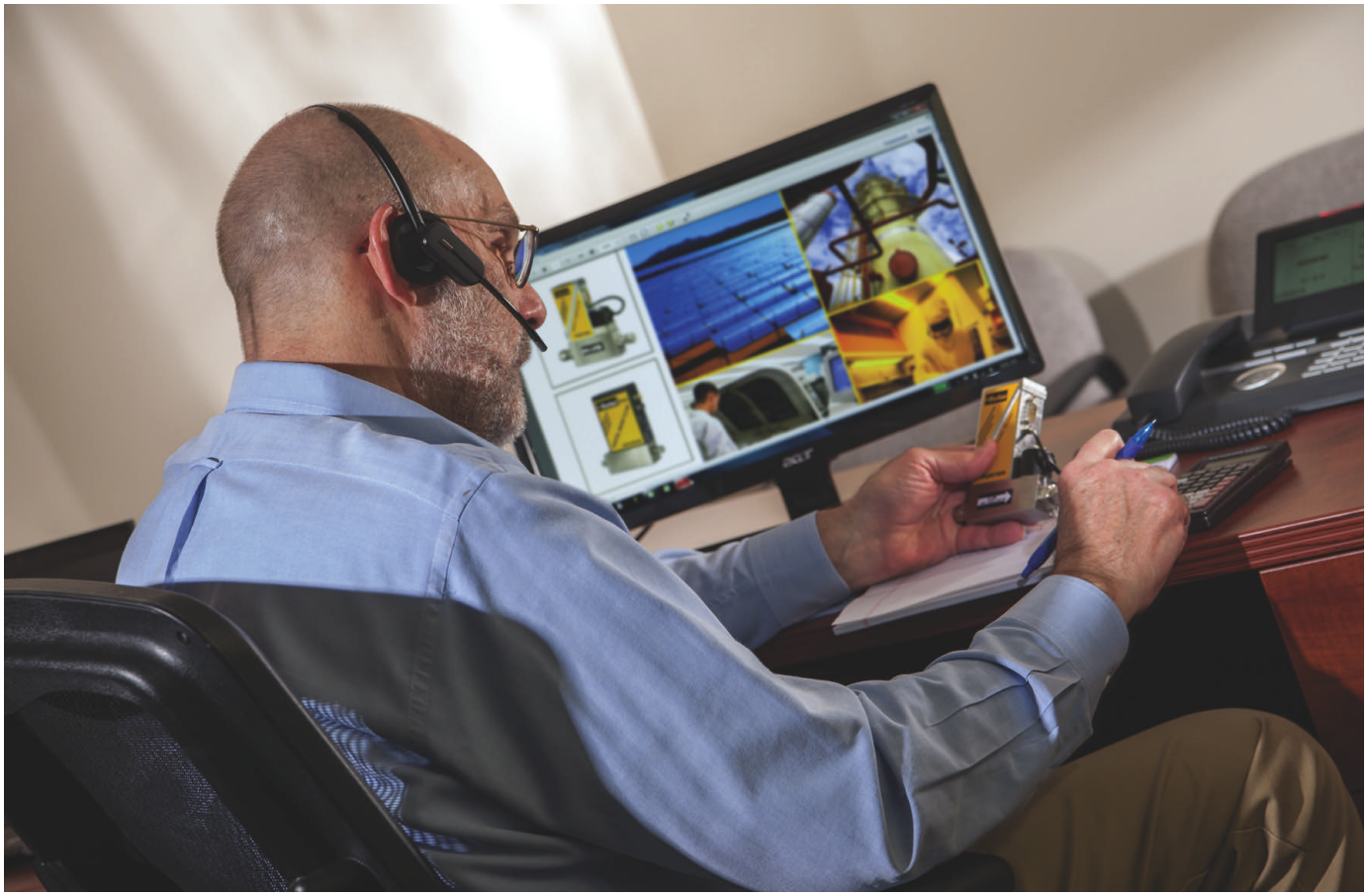

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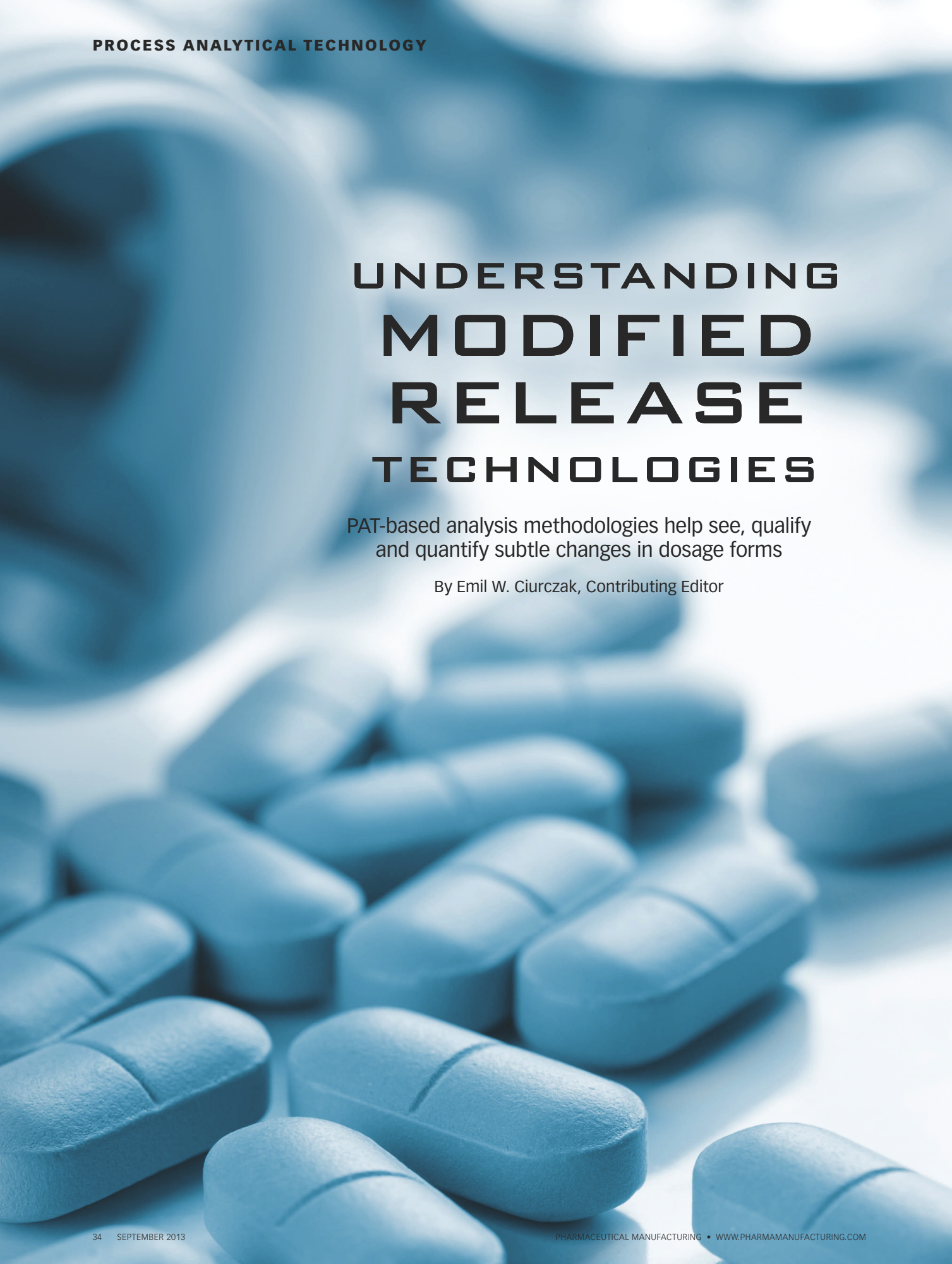

UNDERSTANDING MODIFIED RELEASE TECHNOLOGIES

PAT-based analysis methodologies help see, qualify and quantify subtle changes in dosage forms

By Emil W. Ciurczak, Contributing Editor

THERE ARE numerous mechanisms for delivering a drug to a patient. Whether tablets or capsules, sublingual solid doses or patches, injectables or suppositories, when it comes to drug delivery solutions, all may be modified for time of API release into the bloodstream. Among these, tablet-based dosage forms have particular complexities which, depending on formulation, can grow exponentially — depending on the modified release (MR) strategy chosen to correctly administer the tablet's therapeutic dose over time. Process analytical technologies (PAT), fortunately, can help drug makers better understand the choices they make and provide the data they need to better understand MR mechanisms relative to formulation and support a robust and effective QA/QC effort.

There are numerous definitions of MR. Modified release can be defined to mean any "un-natural" mechanisms used to change the bioavailability or rate of uptake of the API by a body. As a baseline, consider a mixture of API, excipients (bulking agents), lubricants and flow agents as the "natural" mode for tablets. That is, no chemical is added to modify the solubility of the API, in any manner.

When a dosage form is modified, it may be to either speed up or slow down the release from the matrix (all the non-active ingredients). The nearest analogy may be a military missile: a standard tablet may be seen as a ballistic artillery shell; the modified dosage form is a guided missile. A number of popular approaches will be covered with suggested techniques that could be used (in a PAT program) to assure proper parameters.

ACCELERATED API BIOAVAILABILITY

A number of APIs are known to have low or slow solubility *in vivo*. Physical and chemical modifications to both the API and matrix may be made to speed up the transport to the drug to the blood. One common approach is to keep the API in an amorphous state to aid in its solubility (Figure 1 shows the % crystallinity, followed through a blending process). In this case, a Raman or NIR scan during the granulation and pressing of the tablet can assure that the API was not converted to a more crystalline form.

Another approach is to add a solubilizing material, such as a surfactant, disintegrant or both. Again, a simple NIR approach may be used: a mere reflection spectrum to assure rations or chemical imaging to show distribution of materials.

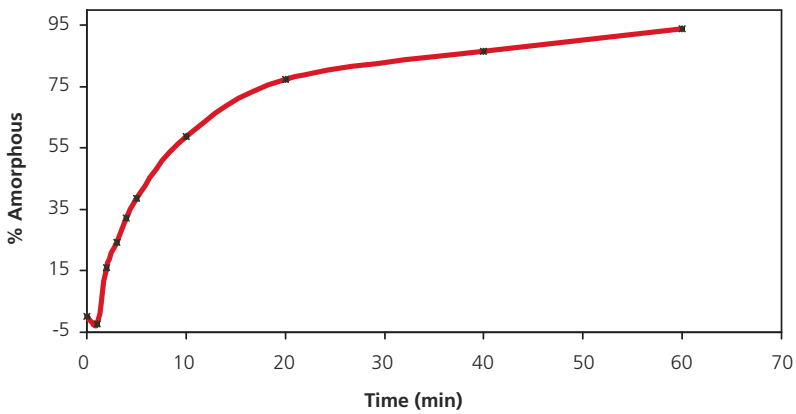

Figure 1. Using NIR to Determine % Amorphous Sucrose vs. Time of Blending

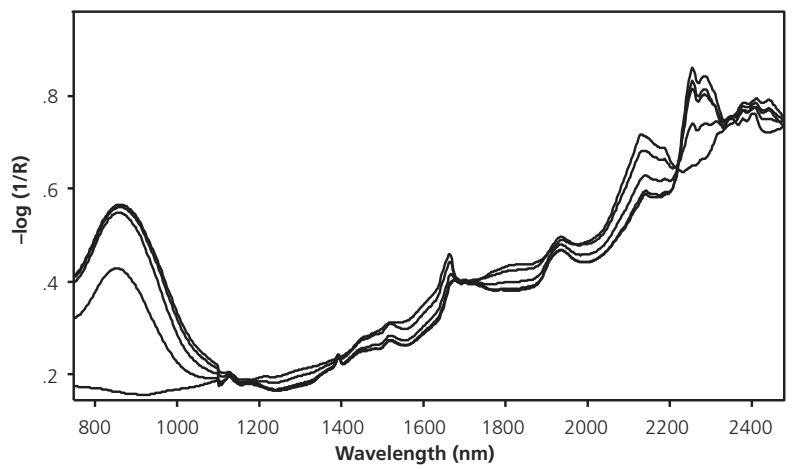

Figure 2. Using NIR to Determine Coating Levels

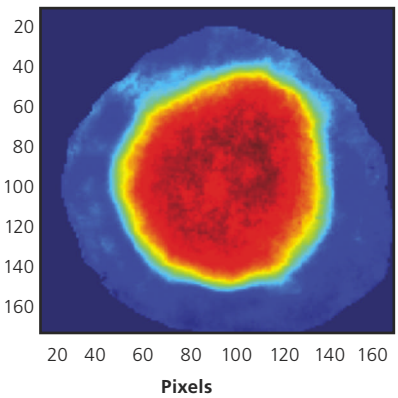

Figure 3. Cross-Sectional NIR Chemical Image of Time-Release Bead

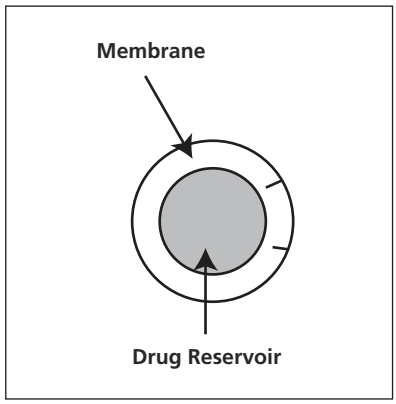

Figure 4. Drug Reservoir MR Dosage Form

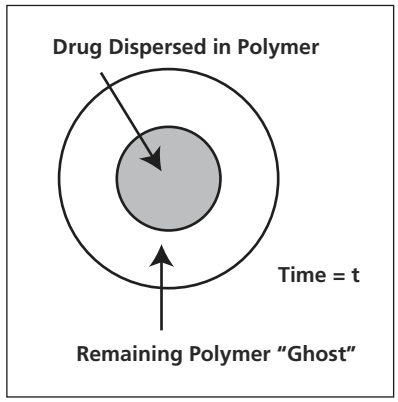

Figure 5. A Drug-Polymer Core, surrounded with a controlling polymer coating

CONTROLLED RELEASE (DELAYED)

A number of drugs are administered around the clock to maintain effective blood levels. In the "classic" approach, a tablet or capsule may be administered three or four times a day. This assumes patient compliance and, while effective, blood level graphs may resemble a roller coaster ride. To assure more even blood levels, continuous release dosage forms have been developed.

Entero-Coated Tablets: available since the 1960s, these dosage forms depend on an insoluble matrix, usually something like carnauba wax, in which particles of API and soluble excipients, such as starch, are mixed and pressed into a tablet. As the starch dissolves, the solvent reaches the API and slowly dissolves the particles.

It was seen, as far back as the early 1970s, that the rate of release could be predicted through thermal analysis (DSC or DTA). The faster the matrix was cooled or the harder it was pressed into tablets, the higher the energy of the wax polymorph formed. The consequence of the high energy polymorph was greatly slowed dissolution. Today, Raman or NIR can easily monitor (and control) the polymorphic state. Some other MR approaches include:

Film Coating: The most common method has been to modify the type and thickness of the coating. The coating could be designed to dissolve at a set pH (as in the intestine @ 7.5 instead of the gut @ 1.0) or remain intact and allow drug and solvent to pass through in a controlled manner.

Raman or NIR may be used in situ in the coating pan to monitor the correct application of the coating material(s) to the cores in real time. After the coating and/or during development, Terahertz is useful to show, not only the thickness of the coating, but whether or not the coating is properly adhering to the core (Figure 2 shows NIR spectra of a core being coated).

Timed-Release Beads: Or, as commercials put it, "tiny little time pills." These are usually inert cores, coated with drug, then coated with some coating material(s) (Figure 3, NIR chemical image of time release bead). The thickness of the coating determines the dose level and rate of release. Both NIR and Raman may be used in the spray pans or Wurster coater to control the coating profile.

Reservoir with Polymer Coating: This dosage form is, in essence, a liquid or semi-solid reservoir with a controlling polymer coating to control the release rate (Figure 4). Again, NIR or Raman as controls could allow real-time control.

Drug Dispersed in Polymer (with polymer coating): Figure 5 shows the similarity of this type to the two preceding types. However, mixing the drug with another polymer to give a controlled matrix allows the reproducibility to be somewhat better than the other two forms.

Bulk-Eroding and Surface Eroding Biodegradable Systems: Figure 6 shows the general form of these type of products. They are made from biodegradable (e.g., polylactate) matrices and can be ingested or placed subcutaneously for long-acting drug delivery. Once again, NIR and or Raman may be used for controlling the production of these forms.

Osmotic Pumps/Systems: This is a very interesting approach. The drug is sequestered in a non-soluble "shell," which has specifically set openings for solvent to enter and begin dissolving the drug. As the solvent is drawn in by osmotic pressure, it eventually forces the drug-containing solution out. As the pressure decreases, more

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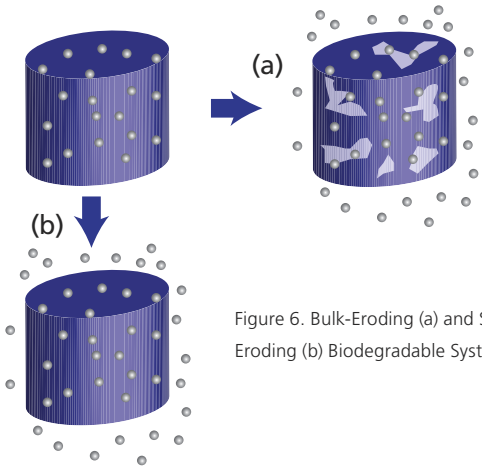

Figure 6. Bulk-Eroding (a) and Surface-Eroding (b) Biodegradable Systems

pure solvent is allowed in to dissolve more drug substance and the process continues until all the API is dissolved and forced out. This device is made quite precisely and is controlled by vision systems (pores), NIR or Raman. The device lends itself to the new generation of 3-D printers.

Transdermal Devices: Sometimes referred to as "patches," transdermal devices can be quite sophisticated. Figure 7 shows how a well-designed device looks in a cut-away picture. Of course, there are as many variables in skin as in gastric systems, so this device is often limited to drugs that could cause gastric distress or are poorly soluble in the gut and intestine.

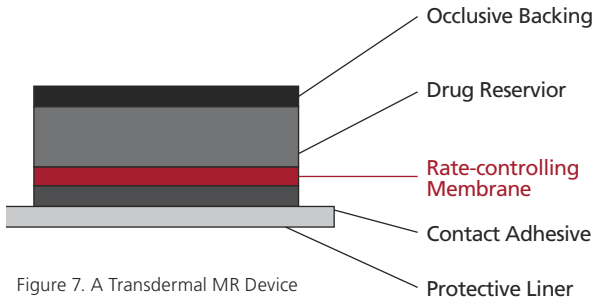

Figure 7. A Transdermal MR Device

MULTIVARIATE CORRELATIONS OF IVIVC AND ONLINE MEASUREMENTS

The correlation of *in vitro* or lab results (usually dissolution) with *in vivo* or clinical results needs to be demonstrated before an NDA or ANDA is approved by the appropriate Agency (FDA, EMA, etc.). When an appropriate dissolution method is approved for product release, then the company has a tool for both release and stability. However, since the dissolution method often takes between eight and 12 hours, it is hardly an appropriate method for a PAT or QbD program.

To perform in-process measurements (and modifications/corrections), a rapid and, preferably, non-destructive method needs to be found. What is needed is for the PAT group to find a method (i.e., near-infrared, Raman, light-induced fluorescence, terahertz) that will see, qualify and quantify subtle changes in dosage forms as they are produced. These (subtle) changes then need to be correlated with the approved release/stability methodology. To do this, multivariate algorithms, properly handled by a Chemometrican, need to be employed.

What must be done very, very carefully, is not to find a quick and easy correlation and assume it is appropriate. It is likely that this second-tier correlation will take far more samples from far more lots to assure both QA and the FDA (EMA, etc) that what we are reading is true.

These dosage forms are essential for many of the newer drug substances, yet, unless the manufacturing process is made better than the traditional four sigma approach to tablets, the costs will place them beyond most patients. The well-run QbD approach will make these clever, inventive products safe and effective.

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High Potency Tech Transfer

Alkermes successful approach to creating a high-volume process for highly potent APIs

By Fidelma Callanan, Senior Director, Alkermes Pharma Ireland

THE MANUFACTURE of a High Potent Active Pharmaceutical Ingredient (HPAPI) compound can present many challenges due to the complex handling required for toxic substances. The successful and safe manufacture of HPAPIs requires a highly skilled team with the right experience, the proper evaluation and training procedures being in place and state-of-the-art facilities. Recently, Alkermes Contract Pharma Services and a large pharmaceutical company collaborated to establish a high-volume process for Highly Potent (HP) Active Pharmaceutical Ingredients (APIs).

For the company in question, donor site capacity was an issue and the drug maker was seeking an outsourcing manufacturing partner to assure adequate commercial supply. Its product was classed as a highly potent compound and had an Occupational Exposure Limit (OEL) of 0.5 µg/m3, an Adverse Drug Event (ADE) level of 5µg/day and exhibited teratogenic and eco-toxic properties. Further, the product had a low Minimum Ignition Energy (MIE) of <3mJ and manufacturing required contained dispensing, high shear granulation with microwave drying, blending, compression and coating processes.

A SYSTEMATIC APPROACH

When taking on a HPAPI for final stage manufacture, it was important to follow a systematic approach to handle potent drugs safely. Other essential elements included the following:

- Defined standard operating procedures, developing and managing a staff training program;
- Using tools to evaluate and measure exposure;
- Designing and developing containment and controls;
- Developing systems to verify effectiveness, and

- Determining and assessing the environmental impact of the active substance and associated manufacturing.

Ensuring these steps were in place was particularly important due to the fact that the Alkermes site is a multi-product facility. Concern relating to cross contamination with other products being manufactured had to be considered.

The following steps were taken to ensure containment procedures were in place to manage the safe manufacture of the HPAPI product. First, OELs were determined and a compound categorization scheme was organized. Industrial Hygiene (IH) exposure assessment was conducted, and control verification and sensitive IH analytical methods were also instituted. General and specific handling guidance, procedures and training, as well as medical surveillance regimes were instituted as well.

THE RESULT

With these measures well understood and implemented the HPAPI product successfully tech-transferred onto the Alkermes Athlone, Ireland site. From Alkermes' involvement with this project, a number of significant milestones were realized, including the execution of a robust containment strategy:

- Primary: high containment primary processing areas, high containment transfers and sampling areas were built (or established)
- Secondary: segregated processing rooms were built
- Tertiary: dedicated segregated suite, security access controlled, Closed Circuit Television (CCTV) remote monitoring, Heating Ventilation and Air Conditioning (HVAC) single pass air (safe change in room), double High Efficiency Particulate Air (HEPA) exhaust, pressure cascade and fogging shower were all put in place.

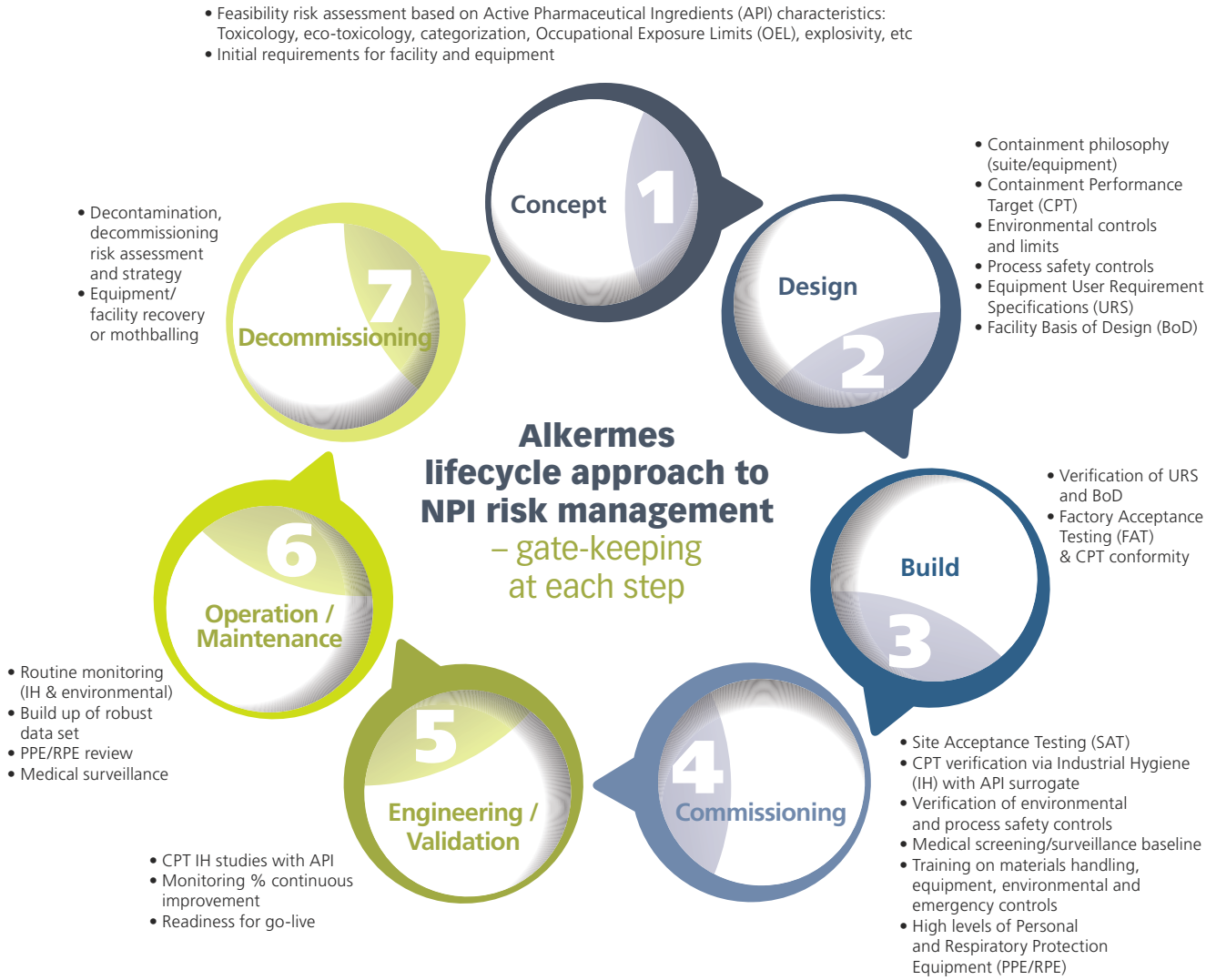

Figure 1. Integrated lifecycle risk management template for New Product Introduction (NPI) on-site applied by Alkermes.

Other significant actions included organizing contained and dedicated waste water facilities, and making available on-site personal protection equipment (PPE) and respiratory protection equipment (RPE) suitable for HPAPI handling. Alkermes also installed segregated, high containment dust extraction systems and implemented an extensive training and competence development program for all staff involved in the manufacture and handling of the highly potent product. Lastly, Alkermes established a medical surveillance, proactive IH and environmental monitoring regime.

Notable was the institution of a New Product Introduction (NPI) model (Figure 1) designed by Alkermes risk managers to enforce an integrated lifecycle risk management approach during all API-related operations.

EFFECTIVE APPROACH

The use of the NPI model allowed for a robust approach to be followed when bringing HPAPIs onto the site and proved effective in implementing tech-transfers and commercial manufacture of all products including highly potent compounds for partners.

As a result of this partnership, the Alkermes Athlone site now has the capability to handle APIs to potency of 0.1 µg/ m3 at development (Discovery to Phase III) and commercial high volume scale. Alkermes now successfully handles two commercially available potent compounds on its multi-product facility in Athlone for its partners.

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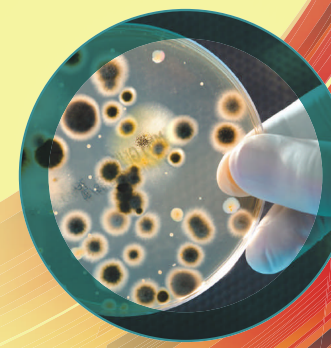

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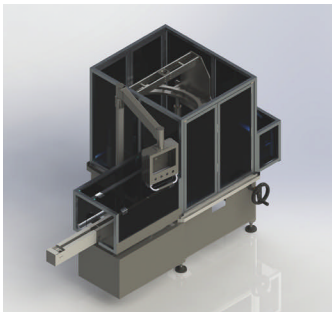

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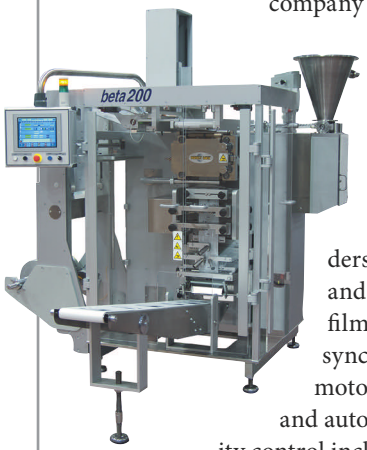

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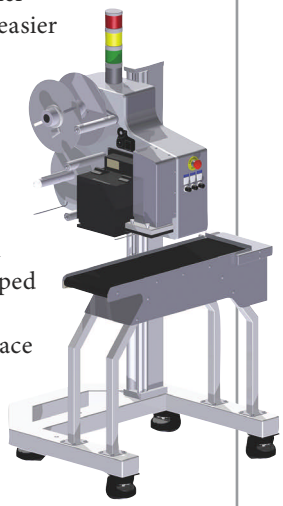

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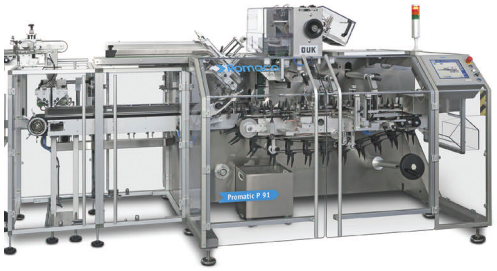

ducible format changes also mean less downtime. Servo-controlled systems like the patented carton pick-up with its positive opening system boost the productivity of the Promatic P 91 and improve the quality of the end product. It offers a maximum output of 100 cartons per minute. A wide range of product-specific feed units is available.

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WAGO Corporation's IP67 SPEEDWAY 767-1311 Fieldbus Coupler links the fieldbus level to Sercos V1.2 real-time Ethernet fieldbus system. Supporting all Sercos cycle times, WAGO's high-performance coupler integrates into a Sercos system via Standardized Sercos Profiles and Device Description. The machine-mount coupler features 10µs high-speed synchronization for harsh-environment motion control applications. The coupler is extendable up to 64 modules, which can be installed away from the Sercos coupler for system expansion up to 200m.

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I'm from the Government: Here to Help

Conflicting goals between the FDA and Congress are creating an interesting "tug of war" across the Generics space

BY EMIL W. CIURCZAK, CONTRIBUTING EDITOR

ONE OF the biggest problems with government oversight is the sheer size of the government; often a single agency speaks with several voices. The blogs and chat sites (like LinkedIn) are full of statements like, "One inspector told me my (QbD) plan was OK, but another wanted it more like cGMPs." In fact, no one at FDA is willing to comment (officially) on QbD now; it is rumored that they are attempting to come up with "something better."

When a large company I worked for received a 483 (back in the early '80s), one item was that the QC department reported to the director of production, a clear conflict of interest. So, the FDA believes that you can't enforce rules when the entity you are trying to correct is above you in the food chain? Let's follow that reasoning and apply it to Congress and its current relationship with the FDA.

Congress, motivated for many reasons but largely economic, has committed to the ideal of a large, ongoing generic drug presence in the market. They also oversee the FDA budget and can directly affect their lab space, equipment and personnel levels. Does anyone see a problem here?

Clearly, cGMPs ask for "meaningful in-process tests." The other "inconvenient" truth is that GMPs call for "statistically significant" numbers of final dosage forms to be tested. While the current paradigm of six tablets or capsules for dissolution and 20 tablets/capsules for assay may have been fine in the 1950s, when lots were only in the hundred-thousands; but, now, with lots routinely in the millions, these numbers seem insufficient.

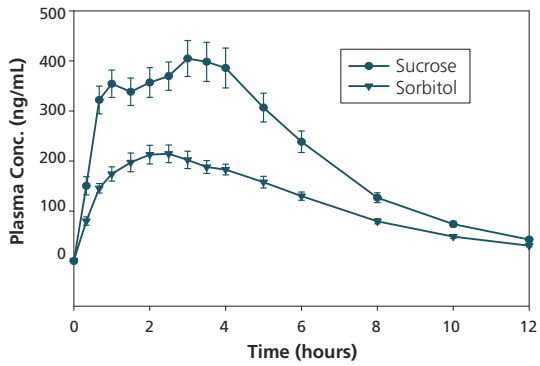

Figure 1. The effect of an excipient on the blood level of drug in "same" dosage form.

Source: A Modern View of Excipient Effects on Bioequivalence: Case Study of Sorbitol

Take a batch of 5 million tablets, for example; 20 units assayed would represent a 0.0004% sample. This leads to the question, "What do we do for continuous processing?" In that case, a drug maker may be producing many millions of doses over a week or so. How, then, do we sample this under GMPs? Of course, the answer is we can't; we must sample under QbD/PAT protocols. In that case, we are actually monitoring several tens of thousands of doses. By analogy, shouldn't we sample tens of thousands of doses under current GMP testing? Well, let's see what that could entail. A typical lot of product might have to have 20-25,000 assays to be considered "statistically significant."

ARE WE BEING PROTECTED ADEQUATELY OR DO THE POLITICAL INTERESTS OF CONGRESS CREATE AN UNTENABLE CONFLICT?

That number would be a crushing burden, even for the largest proprietary manufacturers and would be the death of a large number of small to mid-size generic firms. So, we have a case where we have seemingly conflicting goals: The FDA is tasked with protecting the health of patients, while the Congress is committed to keeping economically attractive generics available. In theory, generics are identical to the initial products they imitate. However, cases are mounting where clinical data is not generated and a given generic product receives a "biowaiver." That is, all a generic company needs to do is show the same dissolution profile as the original product (and assumes that it will show a similar IVIVC — in vitro/in vivo correlation). This is usually done for immediate release doses. However, the excipients can make a difference not seen in a standard dissolution test, as seen in Figure 1.

So, I must ask: At what expense in safety does this economic and political expediency come? Are we being protected adequately or do the baser political interests of Congress create an untenable conflict because it is currently the "boss" of the FDA? Would we be better off without politics dictating drug policy? My bet is that we would — perhaps it is time for the FDA to become an entity independent of congressional oversight.

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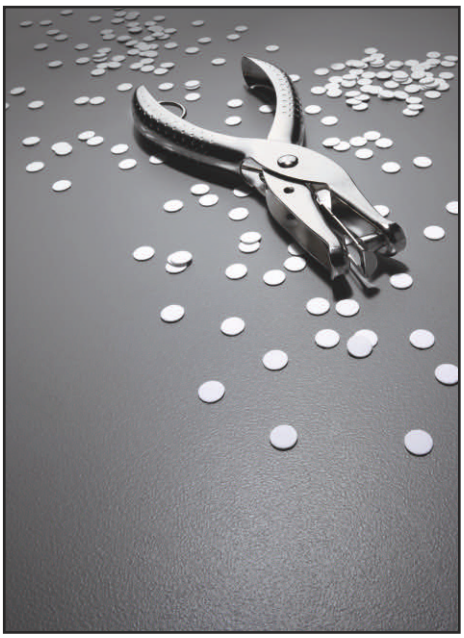

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