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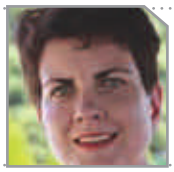


Ignorance: Too High a Price

Despite recalls and consent decrees, few companies are quantifying the cost of quality failures

FOR DRUG manufacturing professionals, these are especially trying times. At some facilities, even bench chemists and managers are being thrown into the breach, to keep production moving, according to our 2012 salary and employment survey.

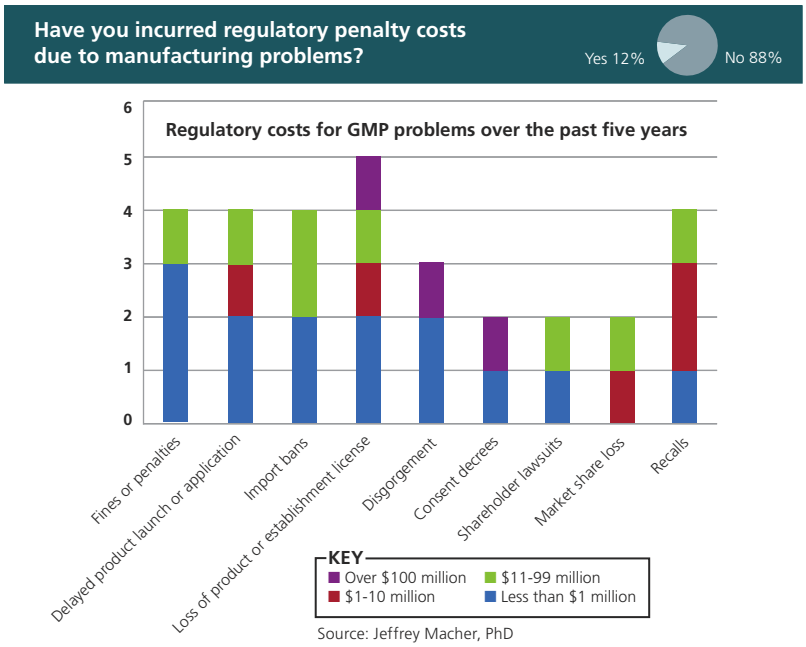
We see signs of strain everywhere. Today, a number of pharmaceutical manufacturers are in the midst of consent decrees, each of which, according to some estimates, can cost well over $2 billion.

Regulators are connecting the dots between staffing and potential noncompliance. PIC/S, the international pharmaceutical inspection authority, has suggested that downsizing be added to the factors that account for potential GMP risk.

For manufacturers, there are potentially huge external costs, not only delayed product launches or approvals and consent decrees (figure), but the less tangible costs of loss of reputation.

Less dramatic are the internal costs, of wasted raw materials, scrapped batches, investigations and remediations. They all add up. Do you know how, or can you quantify what they cost every day or every year at your line, facility, company, or corporation?

Last fall, at ICH conferences in the U.S. and Europe, Jeffrey Macher, associate professor at Georgetown University's McDonough Business School, presented results of a survey sponsored by PDA and ISPE, designed to clarify the cost of poor pharmaceutical manufacturing quality systems. As of last September, nearly 70 professionals representing



Source: Jeffrey Macher, PhD

19 companies had responded to the survey (you'll find slides on both PharmaManufacturing.com and PharmaQbD.com).

The findings might surprise you:

- Of those who responded, 12% had incurred regulatory costs due to GMP deficiencies;
- 62% did not calculate the cost of poor quality at their production sites; and only 11% had had such programs in place for five years or more;
- 53% used manual methods to collect, analyze and publish data, with 29% using ERP and 6% using control charts;
- Roughly 92% did not evaluate the cost of improving quality against the potential cost of failure.

In the survey, those who had begun efforts to measure the cost of poor quality had already begun to see some improvements, with 50% citing on-time delivery, 46% pointing to reduced internal failures and deviations, and 26% noting overall cost savings of over 15%.

The stumbling blocks? Training is one, Macher noted, so is the use of IT. Those companies that use IT to collect, analyze and report on the costs of poor quality tend to perform better than those who don't, he said.

Proactive companies also make corrective processes possible and easy to make for operators, and those doing the day-to-day work, during manufacturing. Are they accessible in your facility? Write in and let us know.

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No Guidance? No Problem.

Even without clear guidance, pharma digital marketing is plowing full steam ahead.

MICHELE VACCARELLO WAGNER, SENIOR EDITOR, DIGITAL MEDIA

YES, THE pharmaceutical industry received some sort of social media guidance from FDA in December of 2011. No, it did not actually provide clear-cut guidelines for social media participation or digital marketing for that matter. Regardless, it appears Big Pharma is plowing full steam ahead, testing the waters with innovative social media tools and new technologies to educate and market to consumers.

Pfizer, for example, is linking Google search ads, not directly to its site, but to its brand-specific YouTube channels which provide more consistent and streamlined results for users. A Google search ad that reads, "Counterfeit Pills Can Be Dangerous," now links to a Viagra YouTube channel where visitors can watch a series of investigative reports on how counterfeit drugs are manufactured, trafficked, and sold to consumers by illegal online pharmacies.

EVEN WITHOUT FDA GUIDANCE, BIG PHARMA IS PROVING THAT SOCIAL MEDIA CAN BE USED EFFECTIVELY.

Pfizer hopes to use standard search ads not just to drive traffic to its Viagra brand, but also alert customers to the dangers of counterfeit drugs and educate them to legitimate online pharmacies. The initiative also hopes to push down illegal pharmacies that appear organically on Google searches.

Boehringer-Ingelheim is also using social media tools in its digital marketing campaigns through the creation of an interactive game called Syrum. Still in Beta testing, Syrum will allow players to attack deadly diseases from virtual laboratories and work with friends to discover and market new drugs. The game will also allow players to learn more about drug patents and participate in clinical trials.

A recent ClickZ.com article cited Alison Woo, director of social media for Bristol-Myers Squibb, saying that the game initiative "shows a willingness to be in the space and test things out," and suggested it may also help the industry at large to "overcome reputation challenges," referring to the typically cautious approach taken by pharma brands using social media.

Even if FDA's recently published draft guidance for pharma marketers only somewhat satisfied requests for clearer social media rules, Big Pharma seems to be proving that social media can be used effectively. If FDA does have this guidance on a lower priority, pharmaceutical companies are finding ways to help and educate patients and consumers anyway.

Some points to ponder:

- Will marketing campaigns like Pfizer's Viagra YouTube channel and BI's Syrum help push the boundaries for Big Pharma's involvement in social media?
- Will FDA be quick to shut these initiatives down?
- Will FDA ever issue a more, detailed guidance for digital marketing and social media?

What do you think? Let me know your thoughts: mvaccarello@putman.net.

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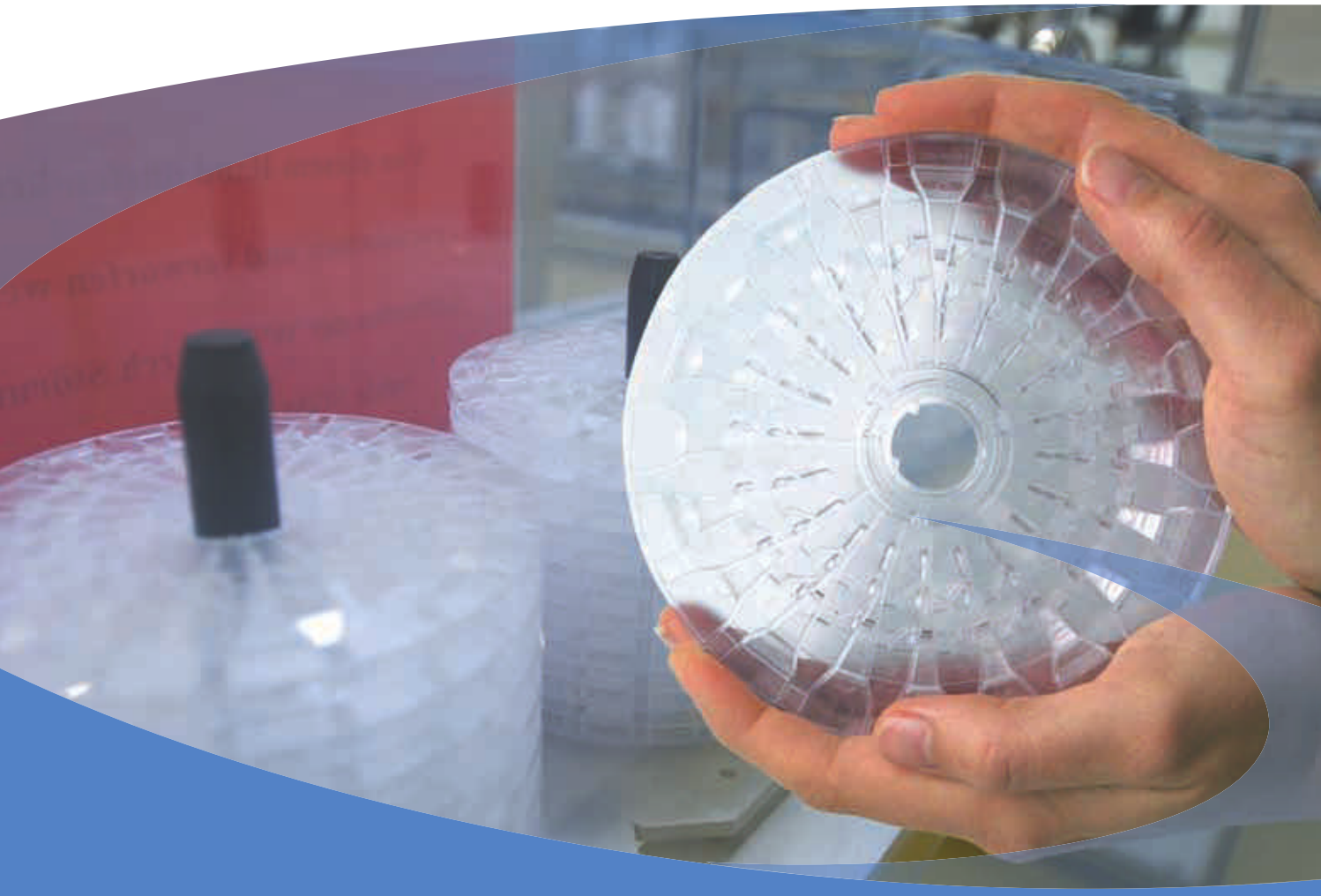

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FDA's Friedman's Challenge to Execs: Modernize!

Modernizing manufacturing and quality systems is good business, he told IFPAC attendees

BY AGNES SHANLEY, EDITOR IN CHIEF

AT IFPAC 2012, the 26th International Forum for Process Analysis and Control, Richard Friedman, associate director with FDA's Office of Product Quality, emphasized the need for pharmaceutical manufacturers to modernize the way they control manufacturing processes and quality risk assessment.

In so doing, he suggested, the industry would be embracing the true spirit of ICH Q10, with its emphases on change and knowledge management, and innovation.

Citing Jim Colton's article on statistical quality tools for pharmaceutical manufacturing in December 2011's issue of *Quality Digest* (http://www.qualitydigest.com/inside/healthcare-article/statistical-tools-pharmaceutical-manufacturing.html), Friedman quoted CDER director Janet Woodcock on the need to think of the primary customers, the people taking medicines, when manufacturing. He also noted the importance of reconciling the producer's risk, of rejecting product of adequate quality, with the consumer's risk, of accepting defective product.

The voice of the customer should be the foundation for quality efforts he said, and patient-focused quality systems require senior management commitment. "Quality is better assured when management recognizes that upstream controls make good business sense," he said.

With the right controls in place, he added, a proactive Quality Assurance culture will supplant the antiquated Quality Control paradigm.

The test of any Quality System is whether or not it can catch a problem in a batch during production rather than after the product has been placed on the market, he said. Today, he said, mistakes are not often caught by individuals who make the error but through QC tests, which are of limited sample size or sensitivity.

The industry needs a "redundancy of controls," or process analytical technology (PAT), Friedman said.

In order to get there, managers must see how GMPs align with basic business goals of process predictability and product dependability. Friedman referred to Deming's Chain Reaction, in which reducing variability and improving quality decreases cost, improves product quality and increases company competitiveness.

He also reiterated the fact that identifying gaps, and root causes, an area where recent FDA citations have faulted many facilities, is simply good business.

Friedman referred to last year's survey by ISPE and ICH on the cost of pharma non-compliance (p. 7), in which 51% of respondents found that cost was a "significant factor" in decisions on whether or not to fix potential quality problems, yet 41% of respondents noted that proactive fixes cost 1/10th as much as reactive ones to achieve.

Common causes of compliance problems, he said, were deficient facilities and processes, including old platforms, lines that require frequent stops and starts. He contrasted open vs. closed, manual vs. automatic, and emphasized the importance of facility design, especially for biopharmaceuticals, where issues such as viral clearance, containment, flow of materials, sterilizing and cleaning, and storage and handling are of critical importance. For drugs that aren't well characterized, there is a need for redundant controls.

In short, his presentation challenged pharma's risk-averse managers to view risk in a different light and to modernize operations. In the end, doing so will only lead to improved patient safety and corporate competitiveness, he suggested.

Inadequate CAPA, Root-Cause Analysis Cited in FDA Letters to Novartis, Merck KGaA

IN LATE January, Novartis received a 483 from FDA citing cGMP issues and inadequate investigation into 31 customer complaints stemming from products manufactured at its Lincoln, Nebraska, facility. The company is ramping up quality improvement efforts at its manufacturing facility in Boucherville, Quebec, and has temporarily suspended manufacturing of some products at the site. In February, FDA published a warning letter it sent to Merck KgaA regarding manufacturing at its Swiss and Italian plants, and citing inadequate analysis of 75 consumer complaints received in 2009 and 2010. For links to copies of the redacted reports, visit pharmamanufacturing.com.

PDA To Weigh in on Single-Use Systems

PDA WILL soon release a Technical Report on single-use disposable biopharmaceutical processing equipment. Robert Repetto, director of technology and innovation at Pfizer and a key member of the committee that drafted that consensus document, shared some information on what to expect.

PhM: There's been a lot written about single-use systems, of course, but what knowledge gaps will the technical report fill in for the industry?

R.R.: While there are hundreds of articles published every year regarding Single Use Systems, the vast majority of these have some commercial basis and typically represent one supplier's or organization's viewpoint and experiences. The PDA Technical Report is a consensus document and the concepts and points of interest have been vetted and discussed among the task force members, which consists of Suppliers, Regulators and End Users. The PDA Technical Report is very comprehensive, presenting strategies that tie together Technical, Quality, Business and Implementation factors for Single Use Systems, in a coherent fashion rather than addressing one or two of these aspects as is seen in many existing articles.

PhM: The focus of the TR is on implementation—from this standpoint, what are end users still finding the most challenging? What's hindering implementation?

R.R.: One area that is frequently overlooked when considering SUS is a well thought-out implementation plan. In order to achieve improvement over traditional multi-use systems and have a successful implementation, an organization must evaluate how SUS fit into their existing quality systems, material logistics, and work flows. Each organization has to evaluate if a particular SUS application will be effective individually. Several factors come into play which might make SUS successful for one organization and not another. The organization's business model, existing facilities, need for flexibility, stage of development, experience, and number of runs per year all become factors which impact a successful implementation. Overall the biggest challenge facing end users is fear of the unknown, stemming from an inadequate understanding of regulatory expectations for Single Use Systems as well as the Single Use Technology itself, which publication of this Technical Report will help resolve.

FUNNY PHARM

"This bridge will have to be a lot longer once we start manufacturing these products in China."
– Walter Bradford

Funny Pharm comics, drawn by professional cartoonist Jerry King, appear twice a month on PharmaManufacturing.com. Readers submit suggested captions. Above is a recent cartoon and winning caption.

PhM: You're encouraging "transparent partnerships" between solution providers and end users. It sounds obvious and easy, but what makes it difficult in practice?

R.R.: SUS can eliminate equipment assembly, cleaning and sterilization and much of the value from Single Use Systems comes from this "ready to use" status. However, to be successful end users must ensure that these value-added activities were done effectively and that can only happen by developing quality systems which can monitor and control SUS quality throughout the SUS Supply chain. Only a partnership with a SUS supplier can ensure that quality is as good as, or better than, what is achieved with traditional systems. A purchase order doesn't make a partnership! SUS suppliers provide equipment that includes the outsourced value-added activities that make a SUS ready to use and these value-added activities are important for the success of both organizations. A winning control strategy for SUS has elements in both the supplier's and end user's quality systems. Because of this, strong communication is essential.

PhM: The task force was comprised of end users, suppliers, regulators, and other experts. Can you give an example of one part of the report that clearly illustrates the input from these diverse groups? What sections or topics were the most contentious and hard to hammer out?

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R.R.: Early on it became clear we should not call a SUS supplier a vendor. Vendors sell things that don't require a long-term commitment to be successful. The task force came to the realization that to be successful suppliers and end users had to be able to share information to build successful control strategies. Developing a relationship focused on success requires good communication and understanding expectations, so the task force focused on way to improve these areas between a supplier and end user. We all learned a great deal from the different perspectives that drive SUS success and the technical report is a much better document because of these long discussions.

PhM: Extractables and leachables are always an issue—what will the technical report present on the topic that's new or uniquely useful?

R.R.: Extractables and leachables can be a make or break issue for SUS implementation and this is one area where the SUS supplier can provide a great deal of information and value. E and L profiles are dependent on the consistency of the materials utilized in your process and collecting this information from suppliers is a logical starting point, but the end user must understand any specific product and process risks. Plastic resin suppliers are a potential source of variability. The SUS supplier can build control strategies to address this issue underscoring the essential need for a strong relationship with your SUS supplier.

PhM: Finally, a general question: The quality of single-use systems is always under scrutiny. Where are we now in terms of the quality of single-use components and systems?

R.R.: The general feeling among the task force is that SUS's can be very reliable and may be used successfully to make either clinical or commercial material, but only when an organization has the necessary controls and quality systems in place. The industry's experience with traditional multi-use systems helps set baseline expectations for SUS in terms of reliability, but to truly be successful an organization may need to develop control strategies specific for SUS and not just apply methods used with traditional multi use systems. As an example, a pressure hold is often used with traditional systems to verify integrity and before a tank or bioreactor is charged with processing fluids. This pressure hold strategy will not work, however, for a SUS bioreactor since the vessel walls are flexible and typically cannot withstand significant pressures. SUS bioreactors can, however, accomplish the same integrity goals as is verified in a traditional pressure hold test, but it will be accomplished with different control strategies than those used with traditional stainless steel bioreactors. In the case of a SUS Bioreactor, this might actually begin with bag and component pressure testing performed during assembly when the system was in a state where proper measurements could be obtained. The end user's Quality systems must ensure that control strategies for SUS comply with global regulations and cGMP requirements. In 2012 the SUS supplier will have a more integral role in executing these strategies.

PHARMA REPLAY

"It's been trashed. It's come to represent a stark and sterling example of corporate hypocrisy."
– Allen Jones, the "Risperdal whistleblower," on Johnson & Johnson's famed Credo.

"He works for a company that creates cancer in people at a Six Sigma level. Why is it that our industry can only cure it at Two Sigma?"
– Consultant Ali Afnan, poking fun at the drug industry, at the expense of his friend Gawayne Mahboubian-Jones of Philip Morris.

"Breakthrough technologies deserve a breakthrough in the way the FDA evaluates them."
– Former FDA commissioner Andrew von Eschenbach, imploring FDA to better foster innovation.

"The easiest way to lose a civil service job at the FDA is to push the approval of something that is later found out to have a problem."
– Carl Weissman, CEO of a biotech capital firm, questioning whether the Agency can truly support innovation.

"Doctors don't have the bandwidth anymore. The patients are now the primary drivers of diagnosis."
– A tweet from patient advocate Wendy White (aka @sirenwendy) during a recent conference.

"I was pressurised to read this statement."
– The head of the Pakistani Pharmaceutical Manufacturers Association, responding to a crisis in which a contaminated heart drug led to the deaths of more than 100 patients.

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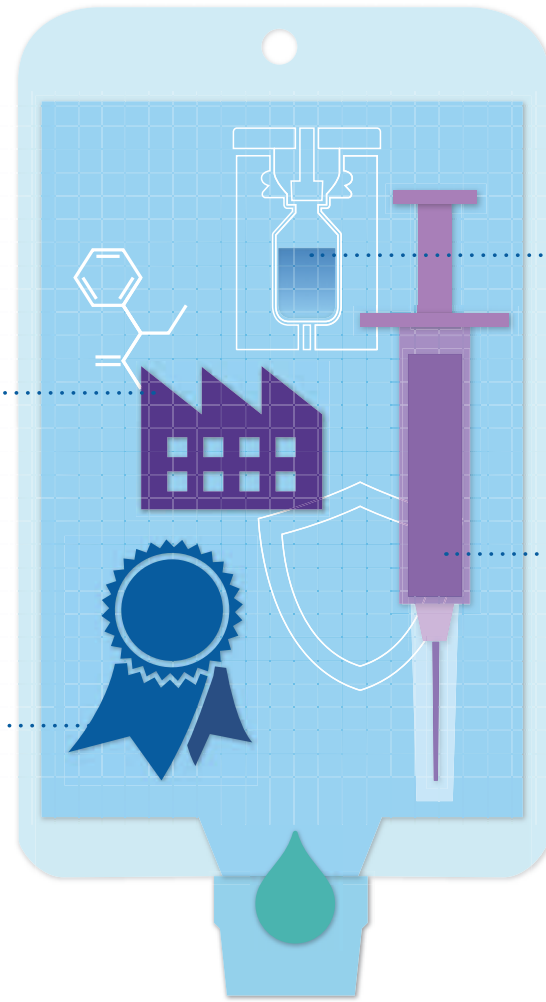

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Bi-Parting Doors Gain in Cleanroom Applications

BY JON SCHUMACHER, RITE-HITE DOORS

PHARMACEUTICAL MANUFACTURERS have always used bi-parting cleanroom doors, yet there were perceptions that the doors took up too much space, compared with fabric rollup or "upward acting" doors. Designs have evolved to make them more compact, while maintaining speed and efficiency.

Any industrial door used in a drug manufacturing plant is designed to let users maintain a specified level of cleanliness and positive air space pressure. Most facilities incorporate multiple pressure steps within the building's structure. The steps typically range from 0.02 to 0.05 w.g. between rooms, although they can reach, or even exceed, 0.20 w.g. Generally, a pressure differential of 0.1 w.g. or less is maintained between rooms. A properly designed door helps ensure the facility's makeup fans can satisfy the required amount of makeup air needed to maintain pressure.

Fabric rollup doors have gained use in cases where bi-part doors won't fit. These doors require very little wall space because their curtain collects in a head assembly at the top of the door when it's opened. By comparison, a rigid-panel door that opens from the center requires considerable wall space on each side of the door in order to function. For example, a rigid panel door spanning a six-foot wide opening requires approximately three feet of wall space on each side.

However, new bi-parting doors have been designed to use much less wall space, while operating safety and at high speeds (video clip: http://bit.ly/jaonyW). Newer designs reflect the following changes:

Fabric bi-parting doors that conserve space. A significant change in bi-parting doors involves the use of a fabric curtain in place of stainless steel or fiberglass panels. The curtain opens from the center and collects in the side frames on opposite sides of the door when it's opened. The rolled-up curtain takes up approximately one foot of wall space on each side of the door, allowing bi-parting doors to fit where they couldn't before, including at openings close to perpendicular corridor walls.

Seals and stabilizer struts enhance environmental control. Mechanisms, such as stabilizer struts, that resist air pressure on the door's fabric curtain, are incorporated

into bi-parting doors to maintain a tight seal on all four sides of the door opening. Some doors also use multiple layers of seals within the side frames. A tight fabric curtain, combined with speed and extra sealing capability, addresses the need to maintain pressurization. Some doors of this type have been rated to withstand pressures up to 0.20 w.g. The end result is less air movement between cleanrooms and other areas.

Drive systems for advanced productivity. Advances in various door technologies, including drive systems, allow fabric bi-parting doors to consistently and safely operate at high speeds. Some bi-parting doors operate up to 120 inches per second. By comparison, older rigid-panel doors typically operate at approximately 30 inches per second. A high-speed bi-parting door that opens from the center also means the fabric curtain has half the travel time of a roll-up door. The result is almost immediate access to the opposite side of the door opening, which results in increased productivity. Additionally, a bi-parting door provides full-height access when compared with some roll-up doors. A door that opens and closes quickly also reduces the potential for air transference between rooms. Primary design goals include:

Cleanliness and ease of cleaning. Bi-parting doors engineered for pharmaceutical applications incorporate a variety of features that prevent contamination. Examples include non-porous fabric curtains, stainless steel headers and side frames, and sloped headers to minimize dust and debris collection. The materials used in advanced doors can also withstand repeated cleaning in keeping with cGMP initiatives.

Maximum uptime. Advanced bi-parting doors minimize the potential for door impact, resulting in increased uptime when compared with slower-moving rigid-panel doors. The flexible curtain on some doors can also withstand incidental impacts without damage, while the movement to fewer moving parts has reduced routine maintenance requirements.

Safety. An advanced bi-parting door that opens quickly from the center can provide near-instantaneous, top-to-bottom visibility to the opposite side of the opening for enhanced safety. Some curtains also incorporate large windows for high visibility when the unit is closed. Manual override systems also allow the doors to be opened in the event of a power outage.

PRODUCT SPOTLIGHT

Track and Trace Gains Prominence in the War on Fake Drugs

BY FRANZ LUDWIG, BOSCH PACKAGING TECHNOLOGY

COUNTERFEIT PHARMACEUTICALS are a major ongoing threat to patients and pharmaceutical manufacturers alike. Although the extent of counterfeiting remains unknown, it estimated that one percent of pharmaceuticals in developed nations, and 10-50 percent of the medicines in the developing world, are fake. They are responsible for an estimated 2,000 deaths daily worldwide and represent a grey industry anticipated to be worth up to $205 billion touching Europe, America, Japan and emerging markets.

The problem is worsening. According to a directive from the European Union, the number of counterfeit medicines seized at its outer border has tripled between 2006 and 2009 to reach approximately 7.5 million items. Now, counterfeiters are branching beyond lifestyle-enhancing drugs to falsify costly life-saving drugs. Last month saw counterfeit versions of Roche's cancer drug, Avastin, reach the market.

Over the past few decades, various factors have contributed to the growth in counterfeit drugs, including globalization, the economic crisis, and the rise of sham websites on the Internet. Over half the medicines purchased on the Internet have been found to be counterfeit. However, counterfeit products are increasingly reaching the legal supply chain via wholesalers.

Helping to harmonize efforts are the EU Serialization initiative, which will be introduced in 2014 followed by the new FDA/California Serialization standard in 2015. Additionally, the World Health Organization (WHO) has established the IMPACT (International Medical Products Anti-Counterfeiting Taskforce) initiative, involving a range of stakeholders in collaborative efforts to protect consumers from buying and using counterfeit products. Further, international institutions such as Interpol, the World Customs Organization (WCO) and The European Directorate for the Quality of Medicines (EDQM) are working closely with governments and companies to create a global security system and strengthen regulations.

Any brand protection strategy involves a combination of anti-tampering, serialization and authentication technologies. A growing number of commercial products are available in each of these categories. In serialization, track and trace is gaining increased use.

Among the commercial options available is Bosch Packaging Technology's platform, which uses a Carton Printing System (CPS) module consisting of a printer and camera that automatically prints on each product. To enable tracing of individual products, it prints a unique serial number and expiration date on each package including a batch number and global trade item number (GTIN). The system encodes the data into a machine-readable 2D data matrix code. Printed tracking data is automatically checked for accuracy by the camera, which reads and verifies each printed digit

with the Optical Character Recognition and Verification (OCR/OCV) tool. Within milliseconds, this tool cross-checks the human-readable text with the 2D data matrix code. All camera-read data are stored in a central database for tracking and tracing.

Manufacturers can benefit from track and trace systems as it provides them with documented proof of what has been produced at the item level and allows tracking and tracing of the product after it exits the factory. Also, the central database can be modified to provide access to regulatory agency staff.

Mr. Ludwig, After Sales Product Manager at Bosch Packaging Technology, can be reached at franz.ludwig@bosch.com.

COMPLIANCE QUIZ

Welcome to Compliance Quiz. (Find each month's full quiz, and more details on answers, on PharmaManufacturing.com.) This month's quiz focuses on USP. For answers, see below, right.

1. _____ is the term The Federal Food, Drug, and Cosmetic Act uses to refer to the United States Pharmacopeia (USP) and the National Formulary (NF).

a. The giant red tome
b. Food Chemicals Codex (FCC)
c. Official Compendium
d. Theatrum Chemicum

2. As written standards that describe substances, chemicals, drugs or excipients, USP Monographs published in any USP compendium must contain:

a. A definition and package, storage, and labeling requirements
b. Status of approval by FDA under the FD&C Act, New drug application (NDA)], the Public Health Service Act (PHS Act) and/or a Biologics License Application (BLA)
c. Information on tests needed to ensure the substance is of the appropriate strength, quality, and purity
d. A and C

3. When proposing a new USP Monograph or a revision of an existing one, the tests included in your proposal should include:

a. A stability-indicating assay procedure
b. Stability-indicating impurity procedures
c. Either a stability-indicating assay procedure or a non-stability-indicating assay procedure, with accompanying stability-indicating impurity procedures.

4. USP <797> stipulates that personnel must wear shoe covers, gowns, gloves, hair covers and masks with the following requirements:

a. A non-shedding exterior gown (either disposable or launderable) with frontal coverage to the wrists and neck that is worn for a single shift (to be changed if contaminated during that shift) with powder-free gloves that have been tested with 70% isopropyl disinfectant.
b. An anti-static gown, a NIOSH-approved disposable particulate mask (or European Standard EN143 P3 mask), latex-free gloves that have been tested with 70% isopropyl disinfectant.
c. A non-shedding exterior gown (either disposable or launderable) that provides full coverage front and back with powder-free gloves that have been tested with 90% isopropyl disinfectant.

5. USP requires training in hand hygiene and garbing in compounding sterile preparations (CSP). Competency evaluations must be performed initially and how often thereafter?

a. Low and Medium risk levels CSP: Semi-Annually
High Risk level CSP: Monthly
b. Low and Medium risk levels CSP: Semi-Annually
High Risk level CSP: Bi-Monthly
c. Low and Medium risk levels CSP: Annually
High Risk level CSP: Semi-Annually
d. Low and Medium risk levels CSP: Semi-Annually
High Risk level CSP: Annually

Answers
1.C 2.D 3.C 4.A 5.C

Towards a Better Prefilled Syringe

West and Vetter look to meet the needs of parenteral manufacturers and regulators demanding safer syringe options.

BY PAUL THOMAS, SENIOR EDITOR

THE PARENTERAL drug market has long used 1-mL long glass prefilled syringes. While these syringes have experienced success, they have been prone to, for example, breakage or production inconsistencies. Increased regulatory scrutiny of glass syringes, vials, and cartridges, and the way in which they are filled and processed, has led drug manufacturers to search for alternatives.

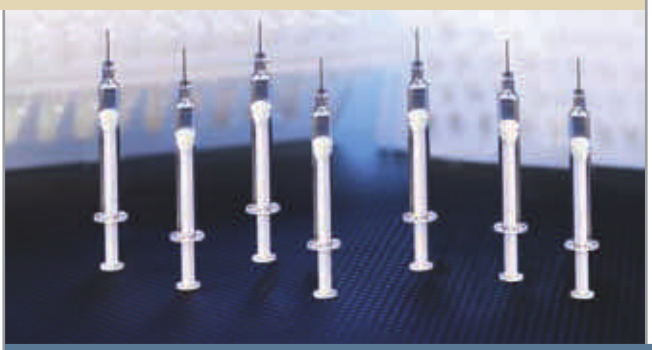
A few years ago, syringes of Crystal Zenith, a proprietary cyclic olefin polymer from Daikyo Seiko, were introduced. The polymer syringes are said to be not only more resistant to breakage, but are known to have improved manufacturing consistency.

Recently, West Pharmaceutical Services and Vetter Pharma partnered to offer 1-mL Crystal Zenith syringes to their clients. Drug manufacturers have the option to conduct the syringe filling within their facility, or to outsource to Vetter. To find out more, we presented questions to West and Vetter. Responses were provided by Graham Reynolds, West's VP for Marketing & Innovation; Mike Schaefers, West's VP for Marketing in Europe; and Vetter Managing Director Thomas Otto.

PhM: What do drug manufacturers need to know about the CZ syringes? Are there new manufacturing issues or validation challenges to consider?

Schaefers: The Crystal Zenith polymer offers many advantages, including glass-like transparency, which permits visual inspection of the manufactured components and of the parenteral products that are delivered to the end user. In addition, the material is highly break-resistant and forms an excellent moisture barrier. Packaging systems based on Daikyo Crystal Zenith have been used for many years on marketed drug products. The 1mL long insert needle syringe system features new enhancements such as automated cleanroom manufacturing, 100% vision inspection (including the needle), and an insert molding process for the needle that eliminates the need for adhesive or tungsten.

Reynolds: We feel the syringe is ideally suited for biopharmaceutical drug delivery. It is sterile, silicone-oil-free and the plunger is laminated with Flurotec film, which helps to lower protein adsorption and serves as a barrier to leachable substances while enabling effective functionality without the need for silicone oil lubrication. The material's tight dimensional tolerance and consistency of syringe functionality can help to make a delivery system's operation predictable.



REGULATORY FACTORS WILL CONTINUE TO HAVE AN IMPACT ON THE DEVELOPMENT **OF DRUG DELIVERY SYSTEMS.**

PhM: When will commercial-scale filling be available? Do you expect manufacturers of commercialized products to look to switch syringes?

Reynolds: Syringe manufacturing capacity is in place today to support customer stability trials and initial activities, which will be required prior to full-scale commercial launch of a drug. West has sufficient capacity to meet these requirements, as well as initial scale-up, and has plans to introduce more capacity within our Scottsdale, Arizona, facility in the near future. Infrastructure is in place, and additional manufacturing cells will be added to ensure customer needs are met. Vetter has installed capacity to meet initial customer needs for technical trials, stability fills and early-phase clinical fills.

PhM: The solution promises "automated cleanroom inspection and 100% vision inspection." Tell us a about the technology behind this.

Schaefers: West applies 100% vision inspection of the syringe at various stages, including inspection of the needle

OUTSOURCING NEWS AND NOTES

DSM Pharmaceutical Products contracted with India's Indoco Remedies for commercial cooperation on eight API's.

Merck will partner with **Supera Farma Laboratorios**. Merck will own 51%, and expects to market 30 of the Brazilian company's products.

Milton Boyer has been appointed president of injectable drug CMO **Oso BioPharmaceuticals**, moving up from VP of development and sales.

Bosch Packaging Technology has acquired **Eisai Co.**'s machinery business, which specializes in pharmaceutical inspection machinery.

NanoGuardian signed an agreement with a "Top 10" global pharma company to supply its On-Dose NanoEncryption technology.

Thermo Fisher Scientific recently released iPhone and iPad optimized versions of its Chromatography Columns and Consumables catalog and HPLC technical guide. They are available as apps from iTunes.

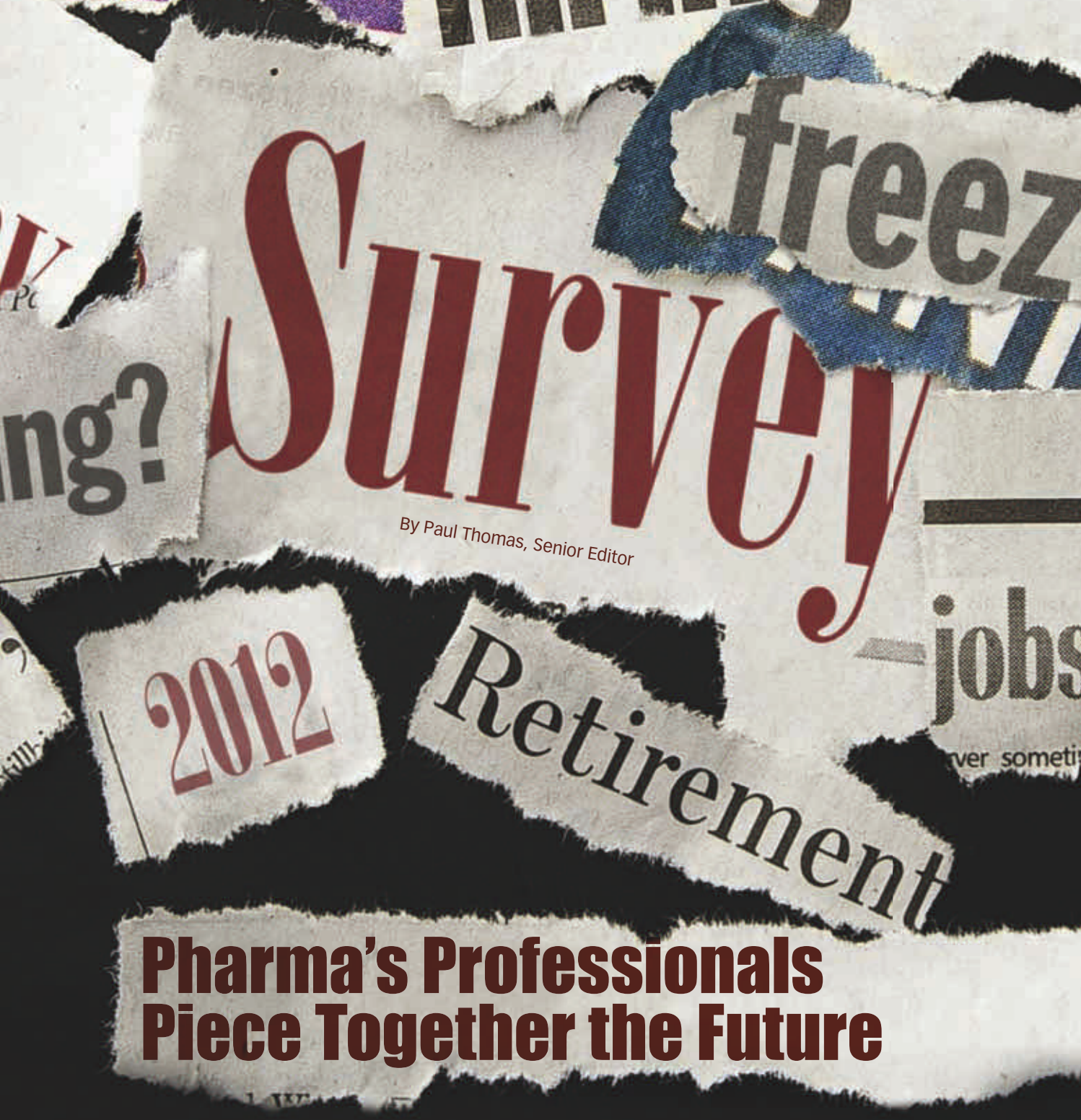
to ensure integrity. Robotic handling in a classified cleanroom, with minimal operator intervention, contributes to a product of extremely high quality and low particulate levels.

Otto: Vetter will apply the same high standards and systems as used for their filling of glass syringes. In its European facilities, the company has adapted a cleanroom especially for filling the Daikyo Crystal Zenith 1mL long insert needle syringe. Using RABS technology to minimize contamination risk, the line is operating with two filling needles. Meeting cGMP specifications, it has a capacity of up to 3,000 units per hour. All syringes are 100% visual inspected following the filling process.

PhM: How does the prefillable syringe market look for 2012?

Reynolds: Drug companies are working closely with drug delivery device manufacturers at an early stage to ensure that there is efficient development of an overall system to enable cost-effective drug delivery. The FDA is placing extra scrutiny on the area of combination products, such as auto-injector systems that use a prefillable syringe, and there is uncertainty about how this may impact drug development. Clearly, regulatory factors will continue to have a key impact on the development of delivery systems.

Schaefers: The prefilled syringe market, estimated at around 2.5 billion units, is likely to continue to grow close to 10% per year. Significant growth will continue for therapies to treat chronic conditions such as autoimmune diseases. Novel systems to enable effective treatment of chronic conditions such as high cholesterol will also grow. In addition, understanding the importance of the drug container as it relates to the integration into the overall drug delivery system will continue to be a key factor.



Pharma's Professionals Piece Together the Future

By Paul Thomas, Senior Editor

AFTER WEATHERING a brutal economy in 2009 and a wave of layoffs in 2010 and 2011, it appeared that the drug industry, from a jobs perspective, was headed towards a promising 2012. Yet recent events—AstraZeneca announcing it will terminate some 7,300 more employees worldwide, for example—have dented optimism. When asked what made him happiest about his job, one AZ employee who answered our survey this year lamented, "Nothing. I'm now redundant after 25 years of service."

Make no mistake, things are still tough out there. The pharmaceutical industry is being buffeted by any number of "cross-currents," making sweeping predictions dicey, says John Challenger, CEO of the recruiting firm Challenger, Gray & Christmas. "Pharma continues to go through restructuring," Challenger says. "Patents are expiring. The new U.S. healthcare law effects are still being seen. And there is still general uncertainty in the economy. This is leading to a new spate of layoffs."

In other words, says Challenger, pharma's great paradigm shift, transition period, or shaking out—call it what you will—will take a few more years. "We have plenty more to go before things get back to an equilibrium."

And yet in spots, there are jobs, even plenty of them. "Boomtown" is what Megan Driscoll, head of Pharmalogics Recruiting, is seeing. Driscoll's firm focuses exclusively on recruiting biopharma employees, with three-quarters of the business geared towards downstream manufacturing and Quality positions.

"We've seen unprecedented growth in our sector," she says. "I'm dumbfounded at how incredibly fast it has come back."

"There is wind in the sails of biopharma," Challenger agrees. One of the cross-currents he refers to is a sudden wealth of venture capital for small to mid-size firms. Many can't hire fast enough, or can't find the right hires for their needs. Another factor, says Challenger: "FDA is opening up the pipeline a bit" and approving more new drugs.

INSIDE THE NUMBERS

That's certainly good news compared to the doom and gloom (and more doom and gloom) of the past few years. Particularly in North America, manufacturing is on the rebound, and the economy has stabilized.

Our eighth annual Job Satisfaction and Salary Survey reflects a turnaround. One of the staples of our questionnaire is, "Are you concerned about job security?" After creeping towards the 70% "yes" mark for several consecutive years, that number has once again dropped, to 63.8% (Figure 3)—not exactly rosy but nonetheless a pendulum swing in a different direction.

Other statistics are worthy of note. Your overall level of job satisfaction is slightly higher than last year (Figure 1). Fewer of you are anticipating potential plant closings, a good sign (Figure 4).

The most sweeping shift in our data is from an emphasis on external economic concerns to cost-cutting, restructuring, and other internal matters (Figure 4). As Figure 5 shows, nearly 50% of you dealt with a reorganization or the introduction of a new team in the past year. Disruption in your work lives is commonplace.

That same chart shows that roughly 50% of you have taken on an increased workload due to staff cuts. If there's a silver lining, it's that this percentage was 10% higher last year. The statistics in Figures 6 and 7 roughly correspond to what you told us in 2011—burnout continues to be a significant issue, for you individually, but also for your colleagues and site productivity.

Another silver lining: Hiring and salary freezes have dipped over the past year, and fewer of you are expecting layoffs than last year (Figure 8). (For more data and analysis from this year's survey, see PharmaManufacturing.com.)

> Our eighth annual survey says the big picture is brighter, though not clearer.

A TALE FROM PHARMA'S FRONT

So while many of the pieces of data in our survey in and of themselves are hardly cause for champagne, when compared to the past few years they offer some relief and encouragement. The future is brightening, though the present is still a bit painful.

The experience of one long-time industry professional, who wishes to remain anonymous, illustrates the kind of cross-currents of which John Challenger speaks. When the economic crisis hit a few years ago, "Mike" was asked to move from his long-time manufacturing operations position with a large biopharma company into a new role—the company valued and wanted to keep him, and he valued staying employed though the new position did not draw from his core skills. A few years later, the company has embarked on an all-out leaning of its business and operations, predicated on cost-cutting across the board. The circumstances find Mike fearing for his job.

The company is doing the right thing, he admits. It has to stay competitive. "I'm just not sure how long my job is going to be here," he says.

To be safe, Mike is keeping in touch with acquaintances and former colleagues. He's using LinkedIn, and has gotten a lot of attention from recruiters there, but not for positions in his sweet spot, manufacturing operations. "All of the inquiries I get from recruiters are related to my

What is your overall level of job satisfaction?

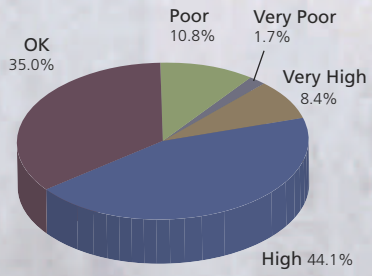


Figure 1.

What is most important to you for job satisfaction?

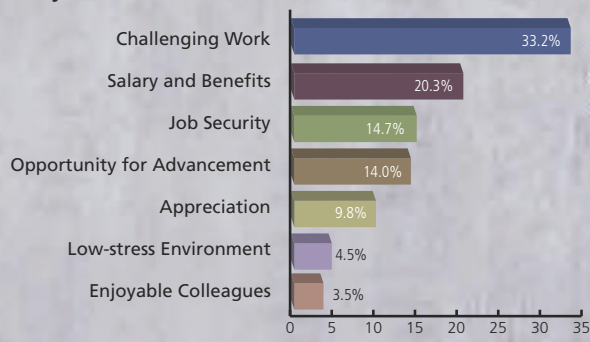


Figure 2.

Are you concerned about job security?

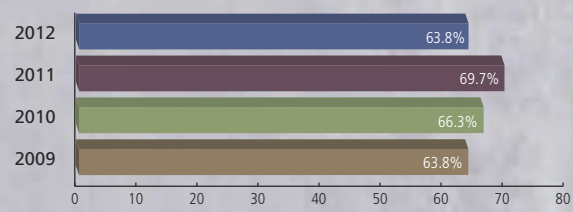


Figure 3.

current work. If I'm going to make a change, it's going to be back in operations."

"It's been great for the recruiters," Mike jokes. "I've been giving them a lot of leads for other people!" He adds: "It's okay. The help and cooperation I've been giving to [recruiters] will eventually pay dividends for me."

While Mike understands his company's rationale for leaning itself, he deplores the fact that management at his facility is short-sighted. "We have a leadership team that is not open to hearing different ideas from what they believe," he says. "I've been basically told by my boss to keep my mouth shut. So that's what I do."

For Mike, something's got to give soon for the good of his career and well-being. He knows he could find work if he would just relocate, but for now it's not an option. "I put my family first," he says. "I'd just like to get my kids through school."

JOBS FOR HIRE?

From his perch overseeing traditional pharma R&D and manufacturing, Derek Lowe, who runs the popular *In the Pipeline* blog, is a cynic. "The big companies still appear to be laying off, and the pain doesn't seem to be anywhere near over at the ones with the biggest patent expiration problems" such as AstraZeneca and Lilly, he says. "Smaller companies aren't very cash-rich, to put it mildly, so they won't be able to soak up the excess completely. But I hope that the startup environment is getting a bit better; that's my only ray of sunshine these days."

There has been a notable increase in new people joining the life sciences workforce in North Carolina, says Doug Drabble, director of the state's BioNetwork, which teams with community colleges and manufacturers to train workers. "If someone is willing to relocate somewhere else in the state, we can usually put them in touch with five or six companies that are hiring."

The openings are coming from manufacturers and other companies that are expanding and newly locating to the area. In addition, says Drabble, workers—middle managers, supervisors, floor operators, and maintenance professionals—are retiring. "You are seeing an attrition out of those groups," he says. A good amount of what Drabble calls backfilling is taking place—employees at higher positions retiring, resulting in a cascade of internal

What makes you **happiest** about your current position?

- A great team of colleagues and managers—everyone is motivated, encouraging and understanding.
- Ability to wear many hats and be involved in multiple projects
- Challenging work (just too much for one person)
- I'm still getting a paycheck, though not sure for how long
- I leave it in six weeks to move into a new industry
- Not much lately—getting ready for retirement
- Respect for my work
- The ethics and spirit of the people I work alongside
- The variety of work and the challenges that come up every day. No two days are ever the same in my position.
- Job satisfaction from knowing that my contributions make a difference to the public in terms of quality and cost of medications.
- My company asks a lot of its employees, but treats us very well and rewards those who excel.

What makes you **unhappiest** about your current position?

- Everybody is in the same boat—we are all miserable.
- Constant stress level of not knowing if you're going to be employed from one year to the next.
- Doing the same work for less pay
- Not doing what I truly love
- Securing health benefits at my age
- The mediocre performance of some of my colleagues
- Way too lean—I am wearing too many hats.
- I am paying dearly for the failure of others.
- Senior management are accountants with concern for their spreadsheets and no appreciation for customers, market dynamics, or what we must do to maintain competitive differentiation.
- Recognition and salary—I have not had a promotion in 10 years.
- Raises last year were given to those who "exceeded expectations"—this caused lackluster goal planning for this year.

If you are concerned, what is the greatest threat to your job security?

	External financial pressure on my company due to the current economic crisis	Continued internal cost-cutting measures	Possible plant closing.	The trend toward outsourcing	The diminished relevance of my skills due to changing technologies and industry focuses.	Personal issues with coworkers or supervisors.
2012	29.9%	39.8%	8.3%	7.9%	6.6%	7.5%
2011	47.1%	21.3%	14.2%	8.0%	3.1%	6.2%
2010	30.3%	31.6%	13.9%	7.4%	4.3%	12.6%
2009	39.6%	32.6%	11.7%	7.8%	2.2%	6.1%

Figure 4.

promotions, leaving mostly entry-level positions open.

The jobs that Driscoll of Pharmalogics is seeing right now are primarily in late-stage development. Positions hard to fill include those ranging from analytical development, formulation, and clinical development to regulatory and "anything in Quality."

All major biotech hubs are heating up, she says. "We have lots of openings in California, and are expecting more openings in the next few months on the East Coast, from New England to the mid-Atlantic."

Manufacturing is not robust, but it's not dead either, she says. "But that cycle will change as products get approved." Thus, while development and clinical jobs are hot now, manufacturing jobs will follow, and eventually drug discovery and early-phase research will make a comeback.

"Companies are strapped for cash. They need to make the most of the drugs they've already discovered, and there's not a lot of revenue being put back into research."

Isn't this a recipe for disaster? "Yes, pipelines will

What are the biggest changes that you've had to face in the past year? (Check all that apply.)

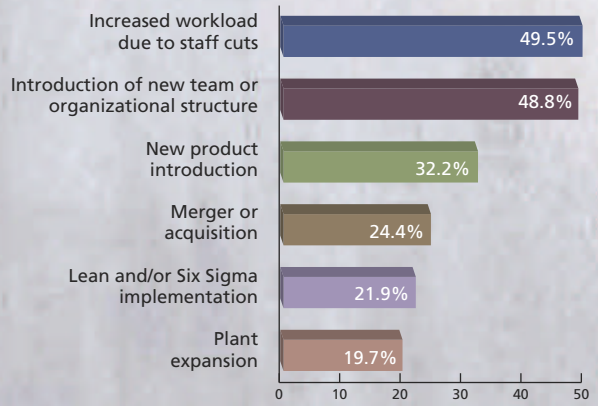


Figure 5.

Do you feel overly stressed or burned out at work?

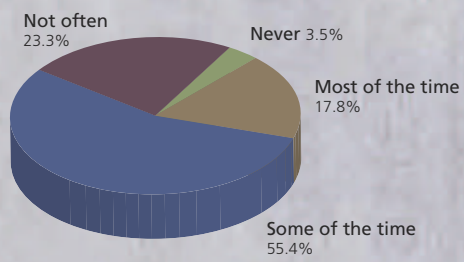


Figure 6.

Is burnout a problem among those you work with?

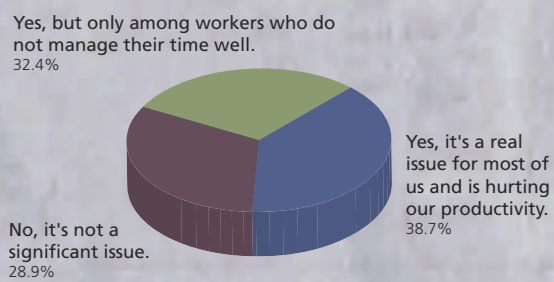


Figure 7.

be dry," she says. "But better firms will successfully acquire new drug candidates."

Lowe isn't so sure. "It's what the investors expect by now: the hardest cost-cutting possible." The problem is, he says, "you don't know you've cut too deep until you see blood."

GOING, GOING, GONE?

Challenger, Gray & Christmas estimated that some 300,000 jobs were lost within the pharmaceutical industry between 2,000 and 2010 [1]. Challenger himself doesn't believe that kind of fat-trimming will be duplicated any time soon. He also notes that layoffs do not necessarily mean overall job loss. "I do think there are places for people to go," Challenger says. "Big companies are laying off and rolling out [employees], but people do go to work for smaller, more nimble companies that are finding niches." Challenger adds that approximately 30% to 40% of those workers whose skills are transferable do indeed move to other industrial sectors when they are laid off.

Most downsized workers have found work with contract research and manufacturing organizations, says Alan Edwards, VP and product leader for Kelly Services' Science business. "The life sciences workforce is transforming to one where individuals are in charge of their own career working for a company within the pharma supply chain as a contingent worker or 'free agent'. Many organizations are embracing this trend as part of their overall workforce strategy."

Still, manufacturers struggle to find competent employees in certain skill areas. Some experts point to a "skills gap" that perplexes the industry. "There's been a lot of talk about this," Challenger says, "especially in what you might call semi-skilled positions" such as bench technicians and line operators. These jobs are going overseas due to wage pressures (i.e., it's still much cheaper in places like India and China), or due to the fact that manufacturers in the U.S. are not finding enough qualified technical staff.

For the first time ever in our survey, we asked you a few questions about the suitability of your, and your colleagues', skills to the work that you do, and whether this is affecting productivity. Interestingly, only a small number of you felt that you were grossly mismatched to your position

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Tonia Becker, Publisher, tbecker@putman.net
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Michele V. Wagner, Senior Digital Editor, mvaccarello@putman.net
Jack Jones, Director Audience Care & Development, jjones@putman.net

How has the economy affected your company recently? (Check all that apply.)

	Hiring Freezes	Fewer Promotions and Raises	Layoffs	Salary Freezes	More Outsourcing
2012	37.6%	56.3%	40.9%	19.4%	24.7%
2011	49.8%	62.6%	52.7%	29.2%	33.8%
2010	52.5%	57.9%	45.8%	34.4%	24.1%
2009	50.0%	42.8%	37.3%	22.2%	19.3%
2008	47.2%%	34.7%	39.6%	13.8%	29.4%

Figure 8.

(Figure 12). Approximately one-quarter of you, however, felt that there is a significant enough skills gap within your organization that limits productivity (Figure 13).

Here's a chilling account from one survey participant: "Bench chemists and managers are being used to make up the shortfall in operators when work does come in. We are currently staffed at 50% capacity."

A few more anecdotes:

- "I try to provide training for our employees, but with expenses so tight it is hard to accomplish."
- "We are suffering from promoting scientists without considering their managerial or decision-making skills."
- "We are experiencing a brain-drain. There are many new people without enough experience for the roles they were hired for."

MIND THE GAP

Like it or not, a skills gap is something that most every high-tech industry should expect to deal with going forward, says Lynda Gratton of the London School of Business [2]. Technologies will advance, eliminating semi-skilled positions in particular. Demographics are playing a role, as Baby Boomers will retire in record numbers over the coming decade, taking with them the "deep tacit knowledge that has come from a lifetime of experience and which they have often failed to bequest to those members of Gen X who follow them."

Finally, "the knowledge and skills that high-value jobs demand has shifted to engineering, IT and the sciences," she writes. "This is good news for countries like Germany and India, where these disciplines are considered a good professional choice—but bad news for the UK and the USA, where fewer students take these options."

The life sciences industry's skills gap is actually smaller than that in other industries, says Edwards of Kelly Services. The bigger issue is "an unknown hiring gap between the candidate's expectations of the position and the employer's job criteria. Millennial recruits desire to be mobile and work from home and Baby Boomers are staying in the job market longer. Both types of candidates want to work for innovative companies and have meaningful assignments."

Employers need to change their recruiting practices and source the work where the talent is located, he says. This is called "modular deployment." Utilizing contingent workers is another way for companies to get the talent they need—the number of contingent workers is growing at a rate 25 times that of full-time workers, says Edwards.

In the Pipeline's Lowe thinks manufacturers can use the supposed skills gap as an excuse. "If drug companies really are saying such things, it may just be window dressing, to make people less upset about all the outsourcing going on," he says. "I think a more honest assessment would be for them to say, 'We can't find people with the skills we need who will work for what we want to (or have to) pay them.'"

The opinion is supported by some manufacturing experts. "Some of the complaints about skill shortages boil down to the fact that employers can't get candidates to accept jobs at the wages offered," says one. "That's an affordability problem, not a skill shortage" [3].

Manufacturers have to work a little harder, Megan Driscoll says. They need to offer more money, good relocation plans and other perks, as well as "lower their standards and be more flexible about hires."

"Good companies find the candidates that have the right skills," she says. "They pay for them."

Vertex Pharmaceuticals is one example. "They have always been able to 'flex' a job specification and salary around a person," Driscoll says. "Their success has hinged one-hundred percent on their ability to attract top talent. They can see past things that candidates might lack in technical skills."

"It's about finding a fire and a passion in someone" even if they don't meet all the exact prerequisites for a job. "Many companies are very rigid and they miss 20

to 30 percent of candidates who would bring incredible skills to their organization."

Major manufacturers are taking this to heart, says Drabble. "Companies are not looking for a perfect fit" in candidates, he says. "They want a fundamental fit."

As an example, the new Merck vaccine facility opening this year in Durham will require some 800 new hires. "They're looking for fundamental skills sets and then training these people internally," Drabble says. "They're not expecting individuals to have, for example, aseptic [processing] training, but they're providing it the day the workers start."

The smaller the company is, the more stringent and inflexible they tend to be, he adds. "You have to be our expert in this area," they might tell an applicant. It is incumbent upon the manufacturer to keep an open mind, says Drabble.

FUNDAMENTAL FAILURE

Easier said than done. Many young professionals lack fundamentals that companies now feel are "must haves" rather than "nice to haves." Foremost among them are simple people skills, Drabble says. "It's more of a social skill gap than an industrial skill gap."

Drabble implores students and young professionals to brush up on their people skills. He also recommends they look for work in other industries in order to gain experience: "They should identify analogous industries that they could work in that provide the opportunity to do a lateral transfer from one industry to another."

Many of you report what might be called a fundamentals gap. "We have a fairly significant turnover among our manufacturing personnel in spite of these jobs paying well for our area of the country," one survey participant writes. "The issue seems to be lack of quality basic education. Many applicants who do not have some type of training beyond high school are unable to perform their jobs satisfactorily due to poor reading comprehension and/or poor basic math skills. Our floor jobs normally require some level of technical competence which is getting more difficult to find, particularly in individuals under age 30."

What is your annual gross salary

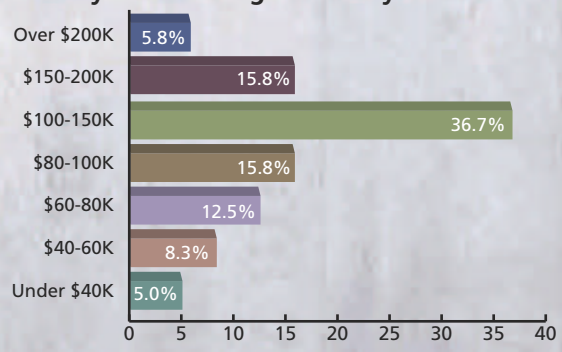

Figure 9.

How long has it been since your last salary increase?

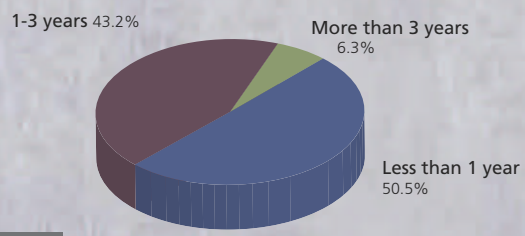

Figure 10.

Do you receive timely and meaningful feedback on your job performance each year?

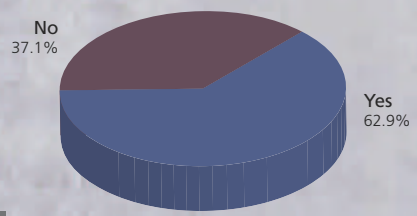

Figure 11.

How would you rate the suitability of your skills to your current position?

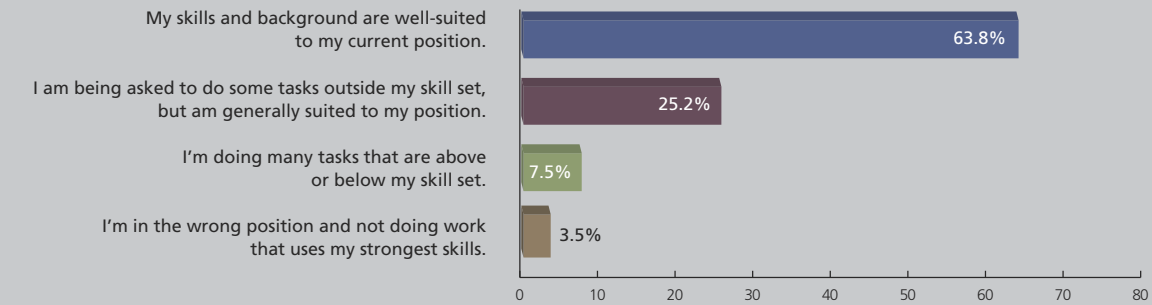

Figure 12.

Do you see a skills "gap" or mismatch within your organization?

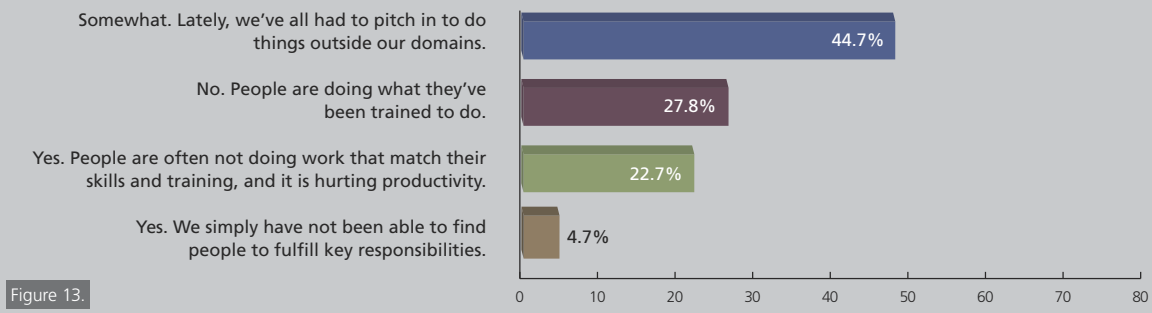

Figure 13.

BACK TO THE U.S.?

Struggling to find qualified candidates is a more enviable problem for pharma than is a dearth of jobs. In light of President Obama's "insourcing" campaign, pharma experts are pondering whether there may already be a "back to the U.S." movement afoot. Manufacturers continue to look overseas, says Challenger, but "some have faced quality issues that were worse than expected, and this is leading them back home."

"Right now, it's going in both directions," he says—simultaneous and active outsourcing and insourcing.

"Projects are coming back to the U.S.," Drabble says. In one case, a drug maker was burned by regulatory and environmental issues abroad and is bringing its operations back to the Carolina region. Going overseas "looked nice to begin with," he says, "but became a royal pain."

Insourcing is real, says Lowe, "but again, the numbers are not going to add up. Some companies seem to have found that they've over-outsourced, and that the problems (time zones, communications, oversight) have outweighed the benefits of spending less money. But the number of jobs coming back will not, I think, come anywhere near making up the number that have been lost."

And some jobs are just "flat-out vanishing" altogether, he believes. "It's not a zero-sum game."

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Raman's New Reach

BY AGNES SHANLEY

Allied with other imaging techniques, Raman spectroscopy is being used for more QC, process control, and QbD efforts

EXPERTS OFTEN repeat the fact that no single analytical technology should dominate any pharmaceutical quality control toolkit (p. 50). Each method, from the ubiquitous near-infrared (NIR) spectroscopy on, has its strengths.

However, what was clear from a tour of technology exhibits at the 26th International Forum for Process Analysis and Control (IFPAC 2012) in late January (Box), is the fact that Raman is developing more of a presence in pharma QC applications.

Raman has become a more popular screening technology, especially as portable miniaturized systems have entered the marketplace, and since quantitative results can be generated in some applications. Raman allows for remote in-situ measurements, and can take readings of material within containers. It can also help users discern polymorphs, and crystalline vs. hydrated forms of the same material.

As applications grow in anticounterfeiting and raw material quality verification, Raman is also seeing increased use in process monitoring and control applications. Pharmaceutical manufacturers, including BMS and Vertex, are also using Raman in drug development, in efforts to define the Design Space and optimize critical quality attributes and process parameters.

For traditional Raman spectroscopy, the National Institute of Standards and Technology (NIST) is working on calibration and validation standards that would make it easier to compare spectra from different vendors' instruments. FDA has also been involved in work designed to make Raman spectral libraries more useful and openly accessible.

Today, three-dimensional visualization techniques are incorporating Raman spectroscopy, allowing users to image surface areas in greater detail. In confocal Raman imaging, for instance, a Raman device is combined with microscopy to allow analysis at the micron level, for example, to analyze trace levels of API. Filters optimize the level of light reaching the detector, allowing image contrast to be closely adjusted. Thousands of individual spectra are combined to form one highly detailed image.

Spatially Offset Raman, meanwhile, offers analysis at depths that conventional Raman spectrometers, using backscattering light collectors, cannot reach. Based on technology developed at Rutherford Appleton Laboratory, and commercialized by Cobalt Light Systems, it allows materials to be analyzed, even in opaque containers.

Raman is also being combined with other methods, including light-induced fluorescence (LIF) and machine vision. At Pittcon 2012, Raman's combination with machine vision was the topic of a presentation by Mustard Tree Instruments. In May, the Royal Society of Chemistry will hold a symposium on pharmaceutical applications of novel Raman platforms. (For more information, visit http://www.rsc.org/ConferencesAndEvents/conference/alldetails.cfm?evid=109595.)

Here is a brief summary of some of the imaging platforms incorporating Raman that are available for quality control, monitoring and other applications.

Bruker Optics offers a number of hybrid systems combining confocal Raman and FTIR, as well as Raman with atomic force microscopy and photoluminescense.

B&W Tek recently added BWIQ, a chemometric software package, to its i-Raman platform, which features CleanLaze technology for improved laser stabilization and line width. The device now offers an 830-nm excitation wavelength option in addition to the 785nm and 532nm configurations. BWIQ combines traditional chemometric methods such as Partial Least Squares Regression (PLSR) and Principal Component Analysis (PCA) with new methods, such as B&W Tek's adaptive iteratively reweighted Penalized Least Squares (airPLS) algorithm. The company also introduced the NanoRam handheld instrument designed for in-plant QC applications, enabling qualitative and quantitative analysis, and the ability to analyze both organic and inorganic compounds over a wide spectral range.

ChemImage offers the Falcon II Raman imaging system, using wide-field Raman for spectroscopy and chemical imaging. The platform can help detail morphology, concentration and other parameters

Cobalt Light Systems' TRS100 rapid analysis system is designed to analyze capsules, tablets, powders and other dosage forms, in tact in opaque containers. Included is a chemometric package, ContentQC, which helps with trending analysis.

Horiba Scientific offers confocal Raman including ARAMIS and XploRA for polymorphic analyses and applications involving coatings, among others. Its product line includes transmission Raman for content uniformity, Raman probes for blend uniformity, and Raman microscopy for composition analysis

Kaiser Optical Systems offers the Raman Workstation, which combines transmission Raman spectroscopy and Raman microscopy. Its phAT probes and RamanRXN systems offer solutions designed to move from lab to pilot plant to manufacturing facility.

ALSO SEEN AT IFPAC 2012

Custom Sensors and Technology (Fenton, Mo.): The company exhibited its Protox line of UV visible and fluorescence transmitters as well as its light-induced fluorescence (LIF) sensors designed for pharmaceutical process analytical technology (PAT) applications. The sensors can be combined with NIR, Raman and other forms of spectroscopy.

Hamilton Company (Reno, Nev.): On display were its pH dissolved oxygen and conductivity sensors at IFPAC, including its VISIFERM optical dissolved oxygen probe, as well as its ARC sensors which are designed to measure more reliably and to communicate directly with process control systems.

Stratophase Ltd., a spinoff from the University of Southampton U.K.'s Optoelectronics Research Center, related the news that it is refocusing commercial plans for its sensor technology, to focus on the development of real-time biopharmaceutical applications monitoring glucose during processing. The company has trial installations and is developing strategic partnerships with partners in the industry.

Mustard Tree Instruments offers Lab2Line solutions. Its VTT 1000, for example, incorporates Raman, machine vision and RGB detection. The company recently introduced a YouTube channel devoted to Raman spectroscopy and other relevant imaging solutions (www.YouTube.com/MustardTreeTV).

Perkin-Elmer Life Sciences' relevant product lines includes its Raman Station, Raman Flex, Raman Micro 3000, and Raman Identicheck portable systems.

Real-Time Analyzers offers a range of Raman analyzers for process and laboratory use. Its industrial Raman Analyzers can be used for applications ranging from raw material identification to polymorph analysis and tablet uniformity studies.

Rigaku Raman Technologies specializes in x-ray diffractometers and Raman spectrometers, including its First Guard and Xantus portable products.

Thermo Scientific's portable TruScan and TruScan RM are designed pharmaceutical QC and screening.

Witec offers confocal Raman technologies. Its CRM 200, for instance, can identify different polymorphs of a crystalline solid, normally undetectable via traditional imaging techniques. This technology allows users to map samples, noninvasively, at deeper levels than possible with traditional Raman.

9th ANNUAL

IMACS

INTERNATIONAL MEETING ON AUTOMATED COMPLIANCE SYSTEMS

May 8 & 9, 2012

Boston, MA (USA)

The ninth annual IMACS conference is the only technical and management conference dedicated to automating compliance-based processes for cGMP operations. This conference is designed to outline implemented solutions for laboratory-based operations in the pharmaceutical, biotechnology, medical device, CRO, CMO and generic fields. The conference fosters a stimulating information exchange on best practices and lean operating initiatives between senior analytical lab managers, IT groups and QC/QA GMP electronic notebook users with implementation details and performance metrics in automating quality systems for regulated environments.

IMACS 2012 will be held in conjunction with the Accelrys user group meeting. All IMACS attendees can participate in the full agenda. All papers and panel sessions are delivered by experienced pharmaceutical industry experts on subjects such as:

- Operational excellence impacts of automated compliance technologies on your QC, development, laboratory and plant manufacturing operations (linking critical quality attributes to critical process parameters)
- Implementation approaches for best practice technology harmonization on a local and global basis
- Supporting new product lifecycle management for development and launch activities (e.g., formulations, stability, process optimization, methods development, and tech transfer to commercial operation)
- Integration of R&D ELNs and GMP electronic notebooks with analytical instruments, LIMS, CDS, MES, ERP systems, and analytics software for QbD and advanced reporting

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BioManufacturers Doing More Supplier Auditing

Quality management is part of an increased focus on productivity and performance.

By Eric Langer, BioPlan Associates, Inc.

AUDITING OF suppliers is a universal practice among biomanufacturers. As the industry matures, however, we are seeing an increase in the amount and types of auditing being done, as a result of the industry's increased focus on productivity and performance. In the *8th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production* [1], we found that almost half of biomanufacturers are auditing more of their suppliers and secondary suppliers (with nearly all presumably already auditing key vendors).

We studied the quality management techniques being used by global biomanufacturers to assure quality of supply. Today's evolving biopharma environment requires that biologics developers pay increasing attention to quality management issues to avoid production problems, capacity bottlenecks, and failures. An integral facet of this oversight is the supply chain: End-users are seeing more importance in supply chain management, and are increasingly attempting to take control through managing, assessing and protecting their supply of materials.

Our annual survey, with responses from 352 global biomanufacturers, asked respondents to identify what, in the past 12 months, their organization had done to assure consistent quality in raw materials and ingredient supply. Not far behind "audited more of our suppliers," which was cited by 49% of respondents, was "audited our suppliers more frequently," at 45% of respondents.

These numbers are not entirely unexpected—supply chain management and oversight are becoming more essential, particularly as the industry continues to adopt single-use/disposable bioprocessing equipment. Here, bioprocessing equipment is repeatedly purchased, used and disposed of, rather than being permanently installed and recycled. These repeated purchases place more stress and importance on the supply chain. Vendors and equipment suppliers (and, in turn, their materials, parts and component suppliers), must be in full compliance with regulatory and related documentation requirements. (See Figure 1.)

In addition to these data, our study shows that biomanufacturers:

- Specifically identified secondary suppliers (e.g. *those who supply our suppliers*)
- Implemented more dual-sourcing
- Held more frequent meetings between quality staff and manufacturing staff
- Manufactured some ingredients in-house

CMO TRENDS

We also compared biomanufacturers' responses to those of contract manufacturing organizations, and found that CMOs, by nearly 10 percentage points, are more actively auditing their suppliers and secondary vendors (47% for biologics developers vs. 56% for CMOs). They are

What has your organization done to assure consistent quality in raw material and ingredient supply?

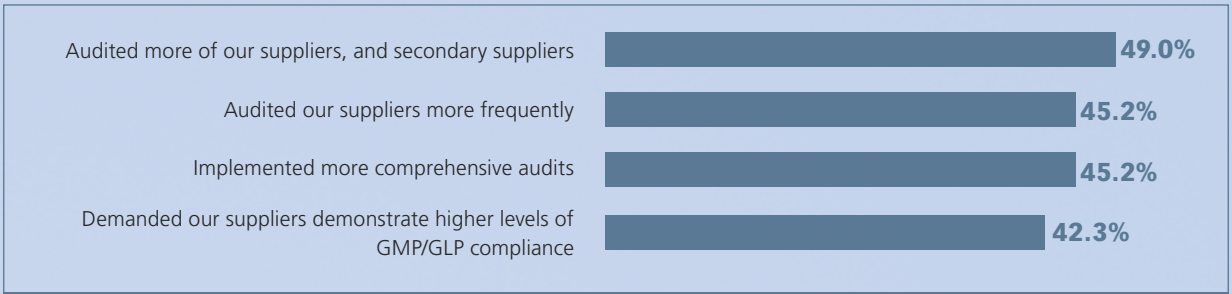

Figure 1: Selected Responses—Industry Trends in Global Quality Supply Management

also auditing suppliers more frequently (50% of CMOs vs. 43% for biologics developers), and they are far more likely to test individual ingredients (44% for CMOs vs. 16%).

Biomanufacturers, however, are more active in demanding that suppliers demonstrate higher levels of GMP (43.7% vs. 31.3% for CMOs). They are also more apt to develop new, more rigorous tests for incoming materials (34.5% for developers vs. 18.8% for CMOs). Communication tools are clearly preferred by biomanufacturers, with double the amount of biomanufacturers holding more frequent meetings or calls between quality staff compared to CMOs (25.3% vs. 12.5%).

VENDORS BLAMED FOR QUALITY PROBLEMS

In addition, we evaluated seven key areas where respondents felt vendors have created quality problems. This year, making the top of the list of quality problems resulting from vendors, was vendors making promises they cannot keep (noted by 49.1% of respondents), poor product quality followed a close second, with poor service quality, inexperience with regulatory requirements, and inadequate certificates of analysis, record keeping or others (Figure 2).

Where vendors, particularly sales reps, make promises they cannot keep and/or provide defective or inadequate products, it can be presumed that their customers will seek out other vendors with more documented up-front product claims and better follow-through and quality products. To some extent, vendors not meeting their promises may be due to vendor-customer communication problems and customers taking in only the positive information supporting their purchase decisions. It is interesting to note that, when looking at the data compared to 2010, more respondents pointed to vendors making promises they could not keep, but less complained of poor product and service quality. Even though these latter issues appear to be on the decline, they continue to be key issues in need of attention.

To mitigate product quality issues, biomanufacturers need to develop better relationships with suppliers.

SURVEY METHODOLOGY

The 2011 eighth Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production in the series of annual evaluations by BioPlan Associates, Inc. yields a composite view and trend analysis from 352 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations (CMOs) in 31 countries. The methodology also encompassed an additional 186 direct suppliers of materials, services and equipment to this industry. This year's survey covers such issues as: new product needs, facility budget changes, current capacity, future capacity constraints, expansions, use of disposables, trends and budgets in disposables, trends in downstream purification, quality management and control, hiring issues, and employment. The quantitative trend analysis provides details and comparisons of production by biotherapeutic developers and CMOs. It also evaluates trends over time, and assesses differences in the world's major markets in the U.S. and Europe.

In which of the following areas have vendors created quality problems for you?

Figure 2: Quality problems traced to vendors

WEB RESOURCES

REFERENCES FOR FINDING A CONTRACT PARTNER

Need to find a good CMO, CRO, or other contract partner? The following are some places to start, courtesy of brand and marketing agency That's Nice.

Company	URL
Nice Insight	http://niceinsight.com/
MedTrack	http://www.medtrack.com/research/default.asp
PharmaSource	http://www.pharmsource.com/
CMO CRO, a subsidiary of PharmaCircle	http://www.cmocro.com/
Evaluate Pharma	http://www.evaluatepharma.com/default.aspx
BioPharma Insight	http://www.biopharminsight.com/
CMO Locator, by Kymanox	http://www.cmolocator.com/
Go Balto	http://www.gobalto.com/directory
Find a Pharma Manufacturer	http://www.findapharma.com/
Select CRO	http://www.selectcro.com/
High Tech Business Decisions	http://hightechdecisions.com/index.html

Probably the greatest issue for industry with vendors is the unanticipated change that was not communicated to the manufacturer. Many times the vendor will not realize that a change they are making will result in a problem for the manufacturer until after the fact. This problem is a critical reason why clear quality agreements should be in place. More frequent audits, to be certain that suppliers understand what industry expects (and *vice versa*), will also contribute to better long-term relationships. According to our study, these audits are indeed becoming more regular, and it will be interesting to see if this contributes to a continued downward trend of product quality complaints through 2012.

The data also show a definite trend in the *reduction* of vendors' inexperience with industry regulatory requirements, from 46.3% in 2008 to 30.8% in 2010 and 28.1% this year. This suggests that both industry vendors and buyers are becoming more experienced with regulatory requirements, and suggests that it is learning from mistakes. It also may reflect the increased regulatory enforcement or perception in increased enforcement, and the necessity of understanding requirements.

IS COST-CUTTING AFFECTING QUALITY STANDARDS?

Surprisingly, we found that only one in six (17.5%) respondents agreed or strongly agreed that manufacturing quality has suffered as a result of cost-cutting. As the current economic stress is causing many vendors to focus on cost-cutting, conventional wisdom suggests this would manifest itself in increased quality problems and resulting concern from customers regarding both poor product and service quality. Our survey indicates this may not be the case (Figure 3).

We compared the responses from U.S. and Western European biomanufacturers, and found that a higher

percentage of U.S. biomanufacturers feel that cost-cutting is affecting their ability to focus on quality manufacturing—19.8% of U.S. companies vs. only 10.5% that "agree" that cost-cutting is creating a quality pinch.

In comparing the responses from global CMOs and biomanufacturers, we found that a much higher percentage of CMOs feel that cost-cutting is affecting their ability to focus on quality manufacturing. This is possibly due to the fact that CMOs may perceive themselves as vendors. In a high-cost, labor-intensive service, cost-cutting invariably will affect quality. Clients of CMOs may need to put more emphasis on vigilance in investigating and confirming CMO standards, SOPS, documentation and quality-related practices and policies. This may include investigations regarding changes in corporate policy and cutbacks likely affecting quality and performance.

Although perceptions of decreased quality standards are much lower among commercial product manufacturers, it is important that the industry pay attention to CMO concerns. In particular, as vendors are forced to be cost-competitive just to survive, the potential exists for more stress and limitations on their ability to proactively deal with quality issues.

"Over the past 12 months, as a result of cost cutting, I believe that my facility has reduced its overall focus on quality operations compared with our earlier quality standards."

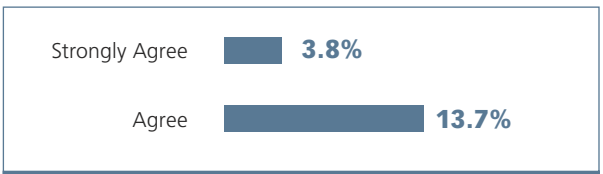

Figure 3: Quality Focus

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About the Author

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Cleanroom Couture

A look at what's new for the cleanroom set, from garments to cabinets. By Paul Thomas, Senior Editor

ASEPTIC PROCESSING experts will tell you that people are dirty. Any human interaction into a process introduces a greater potential for contamination. In most situations, of course, that's just not feasible, and so manufacturers continue to improve aseptic methods and cleanroom standards.

Just as the use of disposable equipment is one way they're doing so, they're also increasingly looking to disposable gowns and other apparel. As with manufacturing processes, gowning procedures can involve degrees of variability, and transitioning to disposable gowns is one way to reduce this risk, says Damon Larkin, senior professional and category manager in the scientific business at **Kimberly-Clark Professional**.

"Most sterile facilities will opt for disposable garments due to potential contamination concerns related to reusable garments returned from laundering facilities," Larkin says. "Disposables eliminate the need for repeat washing, packing and sterilization, all of which are variables that can impact contamination control."

In an effort to be clean and green, Kimberly-Clark recently formed a partnership with **TerraCycle**, an "upcycling" company. TerraCycle collects used garments, converts and resells them as either bulk plastics or consumer products. A barcode system allows Kimberly-Clark to track waste reduction and report results back to clients.

Moving from traditional to disposable apparel involves an orchestrated transition, says Larkin, with various parties involved. "It's important to create an implementation plan that establishes who will be involved and assigns specific responsibilities," he says. The facility's safety team and safety officers must approve use of the product and ensure it meets EPA or OSHA regulations, while changes to processes are also concerns for regulatory personnel, as they may impact the company's FDA license.

Next, Quality will play a key role in testing and qualifying the new product, says Larkin. QA must review procedures and process records, test the product to ensure sterility, and approve the final selection based on its data. Meanwhile, QC must inspect all incoming sterile products.

"Most pharmaceutical companies will conduct a new garment validation process for three to nine months," explains Larkin. During this time the new garments would be worn in a controlled area, though not

necessarily in the actual cleanroom in which the garment is designed to be worn. In many companies, he says, "a new sterile gown will also need to undergo testing on three lots before it is validated and approved. In some cases, a change to the standards of practice for that environment will also be required."

Training workers to don the apparel is the final step, Larkin says. In some companies, cleanroom workers receive training in the new procedures as part of their annual aseptic donning qualification. In order to pass, employees need to demonstrate the donning technique at least three times in a consecutive acceptable manner.

Now that we're all dressed up, let's have a look at other new cleanroom products hitting the runways this spring:

Palbam Class, which specializes in cleanroom furniture design and manufacturing, has introduced a new range of 304L stainless steel, electropolished cabinets. Cleanroom cabinets have notoriously been difficult to electropolish, says sales and marketing manager Paul Fenn. Palbam's design has divided the cabinets into individual parts, making them easier to electropolish and to ship flat-packed, he says. The cabinets are available on either cleanroom casters or leveler legs.

Grieve has introduced an electrically-heated 500°F Class 100 cleanroom cabinet oven, used for drying water from stainless steel and Teflon filter assemblies. The oven's dimensions are 24" x 36" x 27". It has four-inch insulated walls and a Type 304, 2B finish stainless steel interior with continuously welded seams. The exterior is finished in white epoxy paint and has a brushed finish stainless steel door cover and control panel face. Safety equipment is included for handling flammable solvents, including explosion venting door hardware. Controls include a digital programming temperature controller and SCR power controller.

ABB Robotics has just introduced an ISO 5 (Class 100) Cleanroom version of the IRB 120, its smallest ever 6-axis robot. The component materials of the original IRB 120 prone to generating particulates have been modified to eliminate the potential for contamination of the manufacturing area and the parts being processed, the company says.

ISO 5 cleanroom robots are suited for various pharma material handling and assembly applications. The IRB 120 features a four-layer paint with varnish clearcoat for easy, cloth cleaning, as well as unpainted mounting holes and stainless mechanical stops, and special glue-seals. In certain conditions it can meet more stringent, ISO 4 (Class 10) requirements. More and more, says Joe Campbell, VP of ABB Robots and Applications, manufacturers need a "fast and compact robot that meets stringent anti-contamination requirements."

Nilfisk has expanded its line of combustible dust vacuums with the CFM 118/50EXP. It's designed to collect dry dust and debris that can accumulate on floors and overhead areas in Class I, Group D, and Class II, Groups E, F, and G environments. The vacuum is completely grounded, composed of non-sparking 304 stainless steel, and equipped with conductive hose and accessories to eliminate percussion arcing and static charge, the company says.

The FDA recently cleared **Vioguard**'s first product, a self-sanitizing computer keyboard. The keyboard uses UV light to automatically clean the surfaces

on shared workstations. On a predetermined basis, the keyboard retracts into its own "clean, light-tight enclosure." It is then flooded with UV light. Users can then wave their hand in front of a motion sensor to open the enclosure and access the sanitized keyboard.

Vioguard claims that the ultraviolet light generated by the keyboard's two 25-watt germicidal fluorescent lamps killed a minimum of 99.99% of harmful bacteria and viruses, including E. coli, MRSA, and other pathogens. The company is gearing the product towards hospitals and clinics, though it has obvious potential for certain lab and cleanroom environments.

Meissner now offers a stainless steel FlexCessory stand to support its FlexFill single-use biocontainers. The stand "provides the luxury of one-handed liquid transfers," the company says. The stand interfaces with the FlexFill inside a laminar flow hood to facilitate aseptic fluid transfer. Excess fluids can be stored in the biocontainer and on the stand for future use.

It's not brand new, but the Clean Air Trakker, a cleanroom fogger by **Clean Air Solutions**, continues to gain traction, says Jim Campbell, company president. The Trakker uses mega-sonic sound energy and water to produce a fog that enables cleanroom managers to verify fume containment, trace migration paths, and show unidirectional flow, he says. It is made from electropolished 316L stainless steel and packaged in a cleanroom case.

Time Away

"It is worth having dreams," and worth fulfilling them.

BY PAUL THOMAS, SENIOR EDITOR

THERE ARE times in each of our lives when work gets to be too much. We hear a whisper inside our heads: Just quit. Leave. Take time off. Do something big. Travel. Live life now, before it's too late.

We hear the whisper yet easily dismiss it: Not now. I can't afford it. I have obligations.

Anna Kroczak heard the whisper, too. When her department at Novartis Consumer Health in Nyon, Switzerland, went through a restructuring early last year, she decided it was time for a change and left her job. An experienced project manager and expert in pharmaceutical manufacturing, Anna would have been attractive to other companies, even in a down economy. But instead of hitting the job market, she first hit the road—setting off on a round-the-world trip with her husband, Alek, and 10-year-old son, Marcin (photo).

Tokyo, Kyoto, Bali, Singapore, Australia, New Zealand, Hawaii, San Francisco, New York, and more. Now back home, Anna wouldn't trade her experience for anything. Even as workers at Novartis and other manufacturers in the EU—including in Anna's native Poland—face layoffs and uncertainty, she feels more confident than ever to get started on the rest of her career.

"I am sure there will be employers, headhunters or HR people who will not like my choice, who might call it ignorance or lack of seriousness," Anna says. "But I just need one employer who can see and understand the positive sides of such a decision and all the benefits I have taken from it—for myself and for everybody around me, including my future employer."

We might not have the ways and means to travel the world. But that doesn't mean we can't learn something from Anna. At my request, she has written down some of her thoughts about the importance of her time away:

Back from Sabbatical—How Will My Career Go Forward?

If you had asked me one year ago whether I would like to go on a Round the World trip, I would have told you it was impossible. Our jobs, our careers, our son's school . . . all the obligations we had.

But we wanted it so much—to travel all together as a family and not to wait for it until we were retired. We managed to get our sabbaticals from work, we agreed on the itinerary, prepared the budget, bought the Round-the-World ticket, read some travel books and off we went.

This trip was, for our family, a source of incredible power and energy. It has increased our self-awareness, given us the chance to discover and rediscover each other, to understand who we are and what we want from life.

The value of problems is different now; there is less stress and much more joy and happiness.

During the trip we completely disconnected from anything that was part of our everyday life before. We started noticing the beauty and simplicity of life, the amazing views and the incredible landscapes. I want to remember this now that I am back to reality. I want to make sure that I enjoy the simplicity of life even when I am back in my complicated world.

Our son has grown up and we have suddenly had time to notice it. He has never spent that much quality time together with his parents. We were hiking, swimming, sailing, windsurfing, diving, walking on long wild beaches; we have seen animals and plants we have never seen before. But we were also visiting museums and temples, learning and discussing history, geography and culture. The learning for him and for us was enormous.

We have fulfilled dreams which were ending up on our New Year's resolutions list for years now.

Looking for a job is a very positive experience for me now. I know what I want from life. I have come back reassured on what values and principles are important for me and why. I realize what my strengths are, what my experience is, what my value in the job market is.

Will this experience help me in my career going forward? I have no doubts it will. But I will be able to prove it only some time from now when my job search, which I am just starting, proves successful.

Three-Step Quality Network Transformation

Large-scale benchmarking and local intervention allowed one manufacturer to diagnose network performance in three months.

BY NICOLAS ESMAÏL, LORENZO POSITANO AND VANYA TELPIS, MCKINSEY & CO.

PRESSURE ON pharmaceutical quality functions is increasing, from all sides. Regulators have bigger budgets and a more aggressive approach to inspection and enforcement. The direct financial impact of quality issues can run into the tens or hundreds of millions of dollars, but pharma companies can't afford to tackle these issues by throwing huge amounts of money at problems. Faced with a shortage of high-value new products, spiraling R&D expenditure and aggressive competition from low-cost market entrants, they must learn to do much more with much less, calling for a step-change in efficiency from quality assurance functions.

But even unearthing the key issues and opportunities for performance improvement can be difficult across a global network of plants. When the FDA demanded that they shut down one plant and issued warning letters about several others, managers at one global pharmaceutical manufacturer knew they had to define innovative ways to uncover the root cause of their quality issues. High-level benchmarking could give an overview of the performance of different plants, but would do little to indicate where the company should take action to improve performance. While individual quality processes are relatively simple, the overall effectiveness of a quality system relies on complex interactions between hundreds of separate actions, and a considerable amount of human judgment. The failure in a single process or a single interface between processes can have profound consequences.

Detailed investigations of every individual plant, on the other hand, would identify action points but would take too long. Instead, the company adopted a hybrid approach, combining the breadth of global benchmarking and the application of modern risk management tools with the depth of focused diagnostic assessments in selected sites.

FIRST STEP: TAKING THE GLOBAL HIGH-LEVEL VIEW

The first step was building a high-level picture of the fitness of the company's quality function, using benchmarks to compare its current performance to that of industry peers, and to identify the variation of performance between its own plants.

Out of 13 key quality activities investigated, the company measured the effectiveness of quality activities by examining the recurrence rates of issues, indicating a failure to get to the root cause of issues. It studied efficiency by looking at the number of worker-days devoted to each quality issue.

Some plants had such inefficient processes that a single quality deviation would absorb considerable resources, while others devoted very little to each problem, suggesting a tendency to go for fast fixes instead of attempting root cause analyses.

OPERATORS TOOK RESPONSIBILITY FOR THEIR OWN CELLS RATHER THAN RELYING ON **EXTERNAL PROCESS QUALITY CHECKS.**

Beyond the specific benchmarks, this effort also revealed some important basic issues. Another important aspect of the high-level view is the risk evaluation—understanding the relationship between current performance and potential future quality risks.

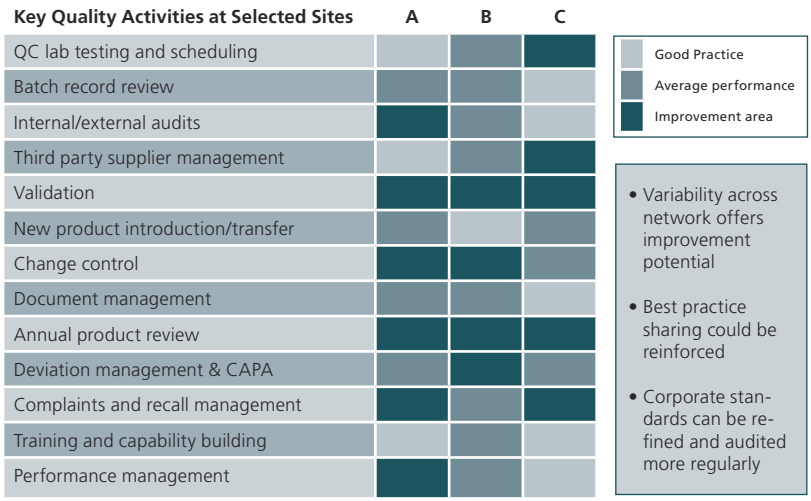
SECOND STEP: FOCUSED ASSESSMENT OF SELECTED SITES

For deeper analysis, the managers selected three sites which stood out from the others, either due to a particularly high value at risk, strategic importance, or because they were recognized as having exceptionally good quality performance. It dispatched an evaluation team to investigate those sites. The 15-strong team included senior quality managers from all of the company sites worldwide, together with specialists from the local and central quality functions to provide assistance collecting and analyzing data.

Because the members of the evaluation team had the results of the benchmarking and risk analyses, they could focus their time and attention on the processes in the plants that gave the most cause for concern, or on those that seemed to perform much better than those elsewhere (Figure).

At each plant, the team worked with staff on the ground to map the processes, identify the root causes of issues, streamline and standardize. Critically, because

COMPARISON OF MAJOR QUALITY ACTIVITIES TO DEVELOP COMMON STANDARDS



the team included quality personnel from many other plants, they could share their own experience of tackling similar problems elsewhere, and when the team discovered something new, they could see immediately if the issue was specific to the plant in question or more generally applicable.

In many cases, the teams identified situations where current procedures both increased costs and risk and reduced quality. For example, as many as four different people could be responsible for checking the settings on a particular machine after tooling changeovers. Not only did waiting for four people to complete the checks add cost and delay, but no individual felt truly responsible for the state of the machines, so incorrect settings were relatively common.

Where an established solution to an issue was already in use elsewhere, the team would encourage the local plant to adopt that approach. Where no such solution existed, the team brainstormed with local staff to find one. They then established pilot projects to evaluate the effectiveness of their proposals.

In the changeover case above, for example, best performing plants relied on a single operator to complete machine checks, ensuring quality with tool designs that made changes more error proof, and a plant culture that encouraged operators to take responsibility for the output of their cells, instead of relying on external process quality checks.

The team didn't just focus on problems however. It also looked at areas of the plants that benchmarking suggested were performing particularly well. Again, team members were able to see very quickly whether local good practice might have wider application. One plant, for example, had managed to embed an impressive continuous improvement culture: shop floor teams were constantly identifying opportunities to improve quality and productivity in their cells, and used a formal process to ensure ideas were tested and implemented.

THIRD STEP: SUSTAINING THE CHANGE

The evaluation team's work had put in place the foundations of a fundamental improvement in the company's quality performance. Comprehensive quality scorecards and metrics were developed from top-to-bottom across the organization, including supply chain and third parties. The company also put in place a two-year quality transformation roadmap

When the company repeated its benchmarking and risk heat mapping exercise for a second time 12 months later, it found overall risk levels had dropped by 20 percent and efficiency improved by about 25 percent.

Beyond this initial impact, however, the benchmarking and diagnostic effort had a profound effect on the culture of the company. Teams understood the value of experience sharing through workshops and shop floor visits. They recognized the power of finding and replicating solutions to quality problems developed elsewhere in the network, and the importance of mechanisms that would allow them to do so.

Quality costs and metrics are more transparent, included in each scorecard and discussed during all performance reviews across the organization. Finally, quality teams placed a new emphasis on operator mindsets, training and coaching: while formal procedures provided an important safeguard,

As this manufacturer learned, building a quality culture and enhancing problem solving skills not only improves quality but it can also have a huge impact on productivity by reducing downtime and rework.

About the Authors

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Profitability and the Cost of Poor Quality

Now that emerging pharma markets are tightening their grip on quality, are U.S. manufacturers losing theirs?

BY BIKASH CHATTERJEE, PRESIDENT, PHARMATECH ASSOCIATES, INC.

AS MAJOR blockbuster drugs come off patent, the scramble among generics to capture these new markets is just beginning. We can expect the U.S. market to experience continued change and consolidation with cost-cutting remaining the top priority. We can also expect emerging market drug powerhouses to try and gain market share as these blockbusters come off patent. Pressure to be competitive in these new market opportunities is creating a sort of perfect storm.

When we first started discussing the impact of emerging markets in pharma, we focused on whether offshore manufacturers could make the leap in quality to be able to compete in U.S. and Europe.

The maturation of these markets has answered that question to some extent, although there is still uncertainty as to how completely these operations can meet FDA standards. Now I have to ask whether U.S. manufacturers would drop their quality commitment to the same level as these overseas manufacturers in the quest for profitability and business competitiveness.

2012 promises to continue 2011's trend of high-profile pharmaceutical operations failing the most basic elements of the GMPs. The McNeil and Genzyme consent decrees continue as these organizations move to reestablish their reputations. The recent voluntary recall by Novartis for mixed tablets and a breakdown in their complaint-handling system reveals an organization that has lost its way in terms of quality. Are these events the result of a more aggressive FDA attempting to demonstrate it is still relevant? Much has been made of the discussions to scale back the agency, to reduce its budget and rely on industry self-policing and regional enforcement. Such recall events speak volumes to the contrary.

Perhaps the most disturbing regulatory action has been the recent consent decree issued by the U.S. Department of Justice to Ranbaxy regarding data integrity. The consent decree signed between the Indian generics manufacturer and the DOJ serves as a warning shot for companies supplying to the U.S. market that FDA findings of falsified information in applications or cGMP records will have substantial consequences.

The decree includes provisions requiring Ranbaxy to thoroughly investigate—with independent expert oversight—the integrity of its submissions and manufacturing operations. Before the FDA will review applications from the implicated Indian facilities, Ranbaxy will have to identify how the problems occurred and remove the employees responsible, put in place the systems, procedures and hiring practices needed to prevent recurrence, forfeit 180-day exclusivity for some pending applications and withdraw any applications containing untrue statements or misleading omissions. In addition, the company will have to pay stringent fines for applications found to contain untrue statements [1].

USING KEY METRICS SUCH AS COPQ CAN CRYSTALLIZE THE TRUE RISK OF **DOING A JOB POORLY.**

Is Ranbaxy's behavior purely a case of negligence or are there other contributing factors to what has become a very disturbing trend in our industry?

Consolidation creates chaos before it creates order. Shareholder focus from Merger and Acquisition is always on the payback period. As companies sort through organizational redundancies and merge disparate cultures, the likelihood that quality issues will arise is significant. What can be done to stop the slide in quality?

I think the answer has been in front of us for many years but we have refused to embrace it. The basic principles of business dictate that we need to make a quality product as efficiently as possible so we can sell it for a fair margin.

Granted, Congress and government want to squeeze that margin in the name of Public Pricing Protection, but I don't think this protection means that we want bad drugs at a good price! Today the World Health Organization says counterfeit drugs kill approximately 2,000 people a day and that one out of four drugs sold in the developing countries is counterfeit. It is an industry that is expected to grow to over $205 billion dollars this year [2]. Equating counterfeit drugs with poor quality systems may be a stretch, but the underlying risk to the public is not that different. At a recent industry event, FDA's Richard Friedman, Associate Director of the Office of Product Quality, described an urgent need for pharma

to modernize the way it controls manufacturing processes and assesses quality risks.

This doesn't mean we need to spend more money or add more people. We need to change our thinking in terms of how we ensure quality. We have spent years talking about Six Sigma, lean manufacturing, Quality by Design and the application of risk management tools but only in the context of applying the tools, not in the underlying principles behind them. One metric that has struggled to get a foothold in our industry has been the concept of Cost-of-Poor-Quality (COPQ).

COPQ qualifies what the true cost is in infrastructure, resources and loss of market share from a quality event. At one client that makes over-the-counter (OTC) drugs we calculated that the COPQ for their top three drugs alone was over $100 million. Accepting the concept that process understanding as a surrogate for inspection and testing must be mandatory to be competitive is still foreign to many in our industry.

As generic drugs make up 78 percent of the prescriptions in the U.S. today—and that figure only looks to increase—it is extraordinary to imagine the development data for many of these products consists of a single characterization lot, and testing a small-scale bioequivalency lot before moving to commercial manufacturing. There is little or no opportunity to gain any understanding of what drives process stability and product performance before moving to the commercial operation. In many cases it takes an FDA warning letter to get management's attention that things must change.

I believe as an industry we can be very competitive with the emerging markets if we apply the principles of ICH Q8, 9, and 10 and operational excellence as a foundation for our approach to product development and quality. Differentiating ourselves on quality and measuring key metrics such as COPQ can crystalize the true risk of doing a job poorly. Regardless, we must stem this tide of complacency and restore the concept of integrity to our quality and operating philosophy if we hope to compete in the world market.

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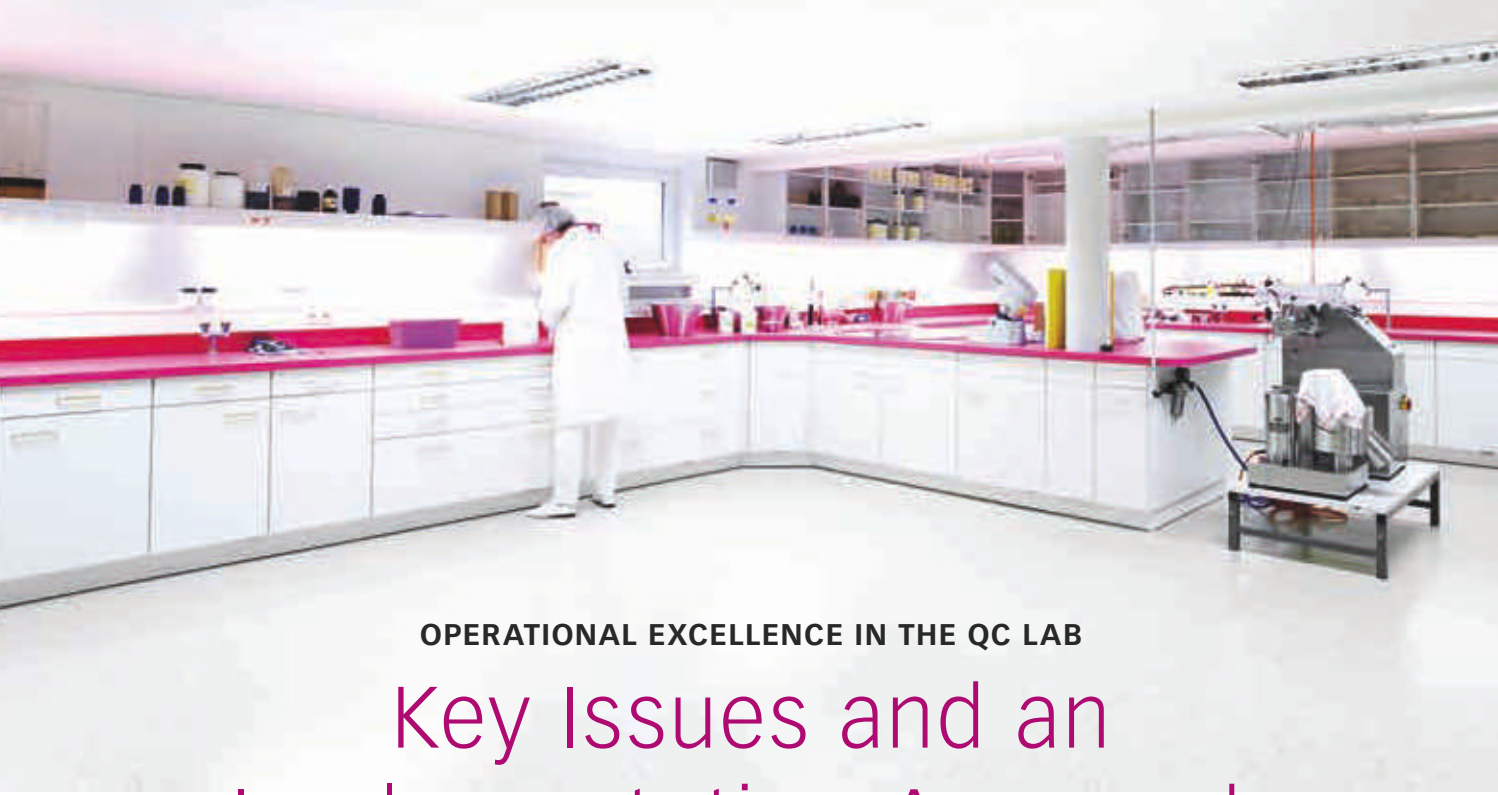

OPERATIONAL EXCELLENCE IN THE QC LAB

Key Issues and an Implementation Approach

The temptation to revert to old habits will be tested, but must be avoided.

By Fred Greulich, Maxiom Group

LABORATORY ENVIRONMENTS are one of the next frontiers for the application of Operational Excellence (OE). OE applied in Quality Control labs makes a great deal of sense, allowing organizations to focus on testing that delivers quick, cost-effective results, enable better quality results, provide safer workplaces, and reduce workplace frustration.

Implementing OE principles is also considered by many to be the best way to improve lab efficiency and reduce cost since the principles and techniques have been well proven in many other areas of business, including within the life sciences.

There are, however, a number of unique factors that make OE implementation in life sciences QC labs somewhat different than in manufacturing or other business areas.

For example, there is typically more workload volatility and variability along with less process reliability and predictability (as opposed to manufacturing) and often longer task cycle times. Additionally, in QC labs there is a more frequent need to deal with the abnormal, such as managing out-of-spec results, and there tends to be a mix of routine and non-routine testing along with "non-test" tasks and projects.

As a result, when working with clients to apply OE in QC lab environments, we are often confronted with a "current state" that exhibits some or all of the following behaviors and characteristics. These frequently become the issues around which the work of achieving lab excellence is organized:

- Inefficient labor deployment—resources dedicated by test or task, "weekly bucket" scheduling, or simply mapping available work to the available people;
- Queues and high volumes of Work in Process (WIP);
- Poor processes and significant effort applied to controlling, tracking and prioritizing samples;
- Ineffective "fast track" systems or situations where a significant portion of work is "fast tracked";
- Lab analyst roles that are not optimized or balanced;
- Lack of defined sequences, batch sizes or standard work;
- Minimal performance management—some focus on individual test accuracy and cycle time, very little attention paid to productivity and efficiency;
- Lack of lab tech cross-skilling and overall poor tech training protocols;
- Long lead times and low productivity;
- Software systems (e.g., LIMS) implemented on top of flawed processes.

Figure 1. Developing Flow and Eliminating Waste

Addressing these factors requires the tailoring of various OE tools and methods, but the basic principles and approach logic remains the same. In QC labs we tend to focus concurrently on developing flow and eliminating waste, utilizing a four step path (Figure 1):

In Step 1, **Identify Value**, it is important to understand, from the customer's perspective, the key lab outputs and success measures. This is frequently done through structured one-on-one or small group stakeholder interviews and is sometimes supplemented by a survey, if broader organizational input is desired.

In Step 2, **Map the Value Stream**, a cross-functional client team develops a map of the entire value stream and subsequently analyzes it in order to identify areas of waste/inefficiency. This step typically includes some team education regarding how to develop the value stream map as well as how to identify the various areas of waste—wasted motion, defects, overproduction, transportation, waiting, inventory, and over processing. Note that in most cases some or all of the behaviors and characteristics outlined previously emerge as key issue areas.

Developing approaches and work plans to address identified opportunities also begins in this step. Often we recommend beginning implementation by improving lab workplace organization and increasing use of visual management systems, typically utilizing the 5S methodology. Starting here helps in seeing how work moves through the lab, while visual management boards help facilitate schedule and issue management.

Step 3, **Level the Load and Drive Flow**, is critical in QC lab environments and focuses on providing, as much as possible, a level and predictable workload into the lab. In most labs, this issue of fluctuation in overall and individual lab analyst workloads is by far the largest area of waste. Key to this step is identifying a leveling strategy which defines the method to be used for leveling the demand.

In labs, as in other places, a strong link exists between leveling and flow . . . work cannot flow through a lab unless the workload is level, at least on a near-term basis, and fluctuating workloads usually cannot be leveled unless flow is employed.

The simplest and often best leveling strategy is to develop a system to test samples as quickly as possible at a leveled rate of demand. This is done by determining a repeating cycle of testing that allows the samples to move through all required tests quickly. Adopting this strategy reduces the throughput time and allows for holding of samples in a leveling queue at the front end of the process. While in this queue, samples can be sequenced based on customer need. However, when samples enter the lab in the leveled workload, they are run, without exception, in first-in, first-out (FIFO) order.

In Step 4, **Define Standard Work**, once testing sequences have been identified and other areas of waste and inefficiency have been addressed, standard work needs to be developed, documented, implemented and sustained. This will ensure testing and other lab tasks are completed in the same manner, in the same order, and at the same time in order to be reproducible and predictable and to meet the required demand.

REAL LIFE

While it's straightforward to understand each step outlined above, real life implementation can be a bit tricky. Design of new "operationally excellent" lab processes is only the first hurdle. A single step move from the old processes to the new one is frequently not possible or, at the very least, not practical. Since manufacturing and other customers must continue to be served, operating under a dual system might be advisable for a period, with gradual phase-out of the old system at the appropriate time.

As with most changes, the temptation to revert to old habits will be tested, but must be avoided. Strong and active leadership is required, as well as frequent communication about the benefits of change.

The move toward applying operational excellence in QC labs is not a one-time project; it is a journey. As with all OE efforts, continuous improvement opportunities for the new processes should be explored and performance managed using appropriate performance indicators.

About the Author

Fred Greulich is VP of Operational Excellence at Maxiom Group. He has a B.S. with distinction in Civil Engineering from Worcester Polytechnic Institute. Mr. Greulich can be reached at fgreulich@maxiomgroup.com.

A Rap on the Head

Wishing won't move pharma from a tribal to a diverse, cross-functional culture.

BY ALI AFNAN, PH.D., PRINCIPAL, STEP CHANGE PHARMA, INC.

THOSE WHO read this column should know what my guiding principles are. The way I express them may anger some friends, or win over some enemies. But, like everyone working in this industry today, I do care deeply about the quality of pharmaceuticals on the market. Collectively, we have vast knowledge of our processes.

Recently, though, I was asked a very simple and very timely question. Considering recent events, it was not much of a surprise, yet I had no idea how to respond, or whom to turn to for a reasonable explanation.

The question was, "Why has the number of pharmaceutical product recalls increased recently?"

How would you answer it?

Now, I refuse to believe that any pharmaceutical manufacturer would intentionally make adulterated or sub-quality product. I do not believe that any company's quality system has been modified so drastically to cause this increase in product recalls. I don't believe that manufacturing processes have changed, intentionally or even accidentally, or that manufacturing professionals have stopped following procedures on a grand scale. FDA has not changed the way it operates. So what is different?

Visionaries from within the industry continue to warn us of what will happen if we do not change the way we approach drug development and manufacturing. What is preventing necessary change?

Pharma is suffering from acute homeostasis, which, in turn, has resulted in state of equilibrium, in which tension or the drive for change has been reduced or totally eliminated. The silo mentality that continues to exist within this industry is both a sign, and a driver, of this equilibrium, and has led to an almost adversarial relationship among key functions that need to work in concert: R&D, manufacturing and quality control.

Consider some of the change projects that your own companies may have initiated recently. They are all designed to foster change, but in reality, how many really aim to return the system to equilibrium? How many embrace true cross-functionality, and open, universal access to information and resources?

If any of you have watched the classic Disney children's film, *The Lion King*, you may recall the scene in which the wise baboon Rafiki raps the lion, Simba, on the head, noting that one can either run away, or learn, from the pain of the past. What will pharma learn from this painful period of acute drug shortages, QC problems and product recalls? Will all this pain, cost and negative publicity be enough to bring about change?

Surely just wishing for a different system is not enough. Hard work is needed, both systematically and tactically, but it will require a unified effort, rather than a random set of projects or actions. What is required is nothing less than a fundamental change of culture from tribal and siloed, to open and universal.

PHARMA'S SILOS REFLECT, AND DRIVE, A CULTURE THAT IS LOCKED **INTO EQUILIBRIUM.**

Change agents will be needed, and they'll require support from senior and middle management through the rank and file workforce. Alliances need to be forged, maintained and nourished through open and honest interaction and the development of a collective vision.

This culture must embrace diversity of thought. Different functions must recognize, as Deming did, that work processes cross boundaries of multiple sub-systems.

Identifying the change that we desire is a vital necessity. Recognizing the forces resistant to this change, and those supporting it, is also vital.

Having achieved these goals, everything we do must aim to weaken negative forces and strengthen those that support change. There are those who may feel that the forces resisting change are too strong to overcome, whether they come from within their own organizations or from regulators. They subscribe to a static culture.

Change has already been documented in other industries, spurred by thinkers such as Deming and Juran. Such change is not beyond pharma's reach.

Do you think that our industry is in desperate need of revitalization? Do you believe that you could be a change agent, or do you at least believe that change is possible?

Are you willing to take action within your organization, or even, simply to engage in a dialogue on this forum? If so, please write me at aafnan@stepchangepharma.com.

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AUCTION

EQUIPMENT & CUSTOM SERVICES

No Analytical Method's a One-Trick Pony

Sometimes, analytical methods, including NIR, just aren't enough.

BY EMIL W. CIURCZAK, CONTRIBUTING EDITOR

RECENTLY, I uttered words no one ever thought I would say: "Just using near-infrared (NIR) may not be enough." I was attending a session at this year's IFPAC meeting, and the speaker was showing how his company used several NIR instruments to monitor/control an extruder for continuously manufacturing a "ribbon" of polymer/API that was chopped, lubricated, and pressed into tablets. The NIR instruments measured the excipients and API as they blended, melted, mixed, and extruded.

The one point that was ignored was where a vacuum pump pulled off volatiles. From experience with this type of extruded polymer/API mix, I suggested another option. Depending on the dwell time at that stage, the temperature, and level of vacuum, a number of things happen. The desired result is that unwanted volatiles, often monomers from the polymer used, are removed, making the product safer. Another effect is that the porosity of the granulation changes. Usually, the higher the vacuum and temperature, more gases are exhausted, causing the granulation to have smaller and fewer pores.

This can affect the dissolution rate. Since most polymer extrusions are used for continuous/sustained/controlled release tablets, the porosity could be a CQA (Critical Quality Attribute) for a number of products. One control approach might be a vision device, which can correlate the release properties of the product with visual appearance, and parameters can be set.

Another application of NIR (mentioned quite often at the meeting) was for the release of tablets. I have seen transmission NIR used on tablets removed from the process line and reflection NIR used on-line; either give more than sufficient results.

One measurement that has become quite popular is to use NIR (or Raman) and an MVA (multi-variate analysis) such as partial least squares (PLS) to either predict the release at a specific time or the time at which a specific percentage is released. Usually, such an approach is quite fine. The resultant equation uses a few factors and can be tested quite easily. There are situations where the correlation between the physical parameters (as seen in spectral differences, mostly peak shifts) needs a rather large number of factors to produce satisfactory statistics. I have seen 13 PLS factors needed to generate an equation. Keep in mind that companies seldom do follow-up or on-going IVIVC (*in-vivo* *in-vitro* correlation) studies to show that dissolution is more than an indicator of "something" happening to the product over time. This tenuous blood level correlation becomes even more tenuous by further correlating dissolution to a NIR spectrum, using a 13- or 14-factor equation!

If a process is to be controlled in anything near real-time, the test used needs to be fairly rapid. Obviously, performing a classic dissolution test on a time-delayed would take far too long to be of use to the production staff. There is a possible solution, however: a number of instrument manufacturers' dissolution test instruments that are capable of rapid, nearly continuous readings (through fiber optics). This potentially generates a massive number of data points for a predictive equation.

IF PREDICTED NUMBERS ARE NOT STATISTICALLY "GOOD" ENOUGH, YOU NEED **MORE DATA OR A STRONGER EQUATION.**

How? Perform "classic" dissolutions on a number of (passing) production lots, using this equipment. The number will depend on the reproducibility of the product; the better the lot-to-lot agreement, the fewer lots will be needed. The analyses should be run at the maximum data acquisition rate, generating a digitalized release curve. Gather the data and arrange it, depending on the software you plan on using.

Basically, you fit a polynomial equation to the actual data (possibly ignoring the initiation period of a minute or two) and generate an equation. Using this equation, perform the first 10-15 minutes of the dissolution of a different set of tablets and, using the equation, predict the percent released at the required time points. If the predicted numbers are not statistically "good" enough, you either need more data or a stronger equation.

When you are able to generate a (statistically) satisfactory equation, then you will have a dissolution prediction test that will generate numbers fast enough to be considered a process control tool. Yes, it is based on math, just like the NIR method, but the math is based on actual dissolution data, not spectra. That makes me feel more comfortable about using it as a control tool.

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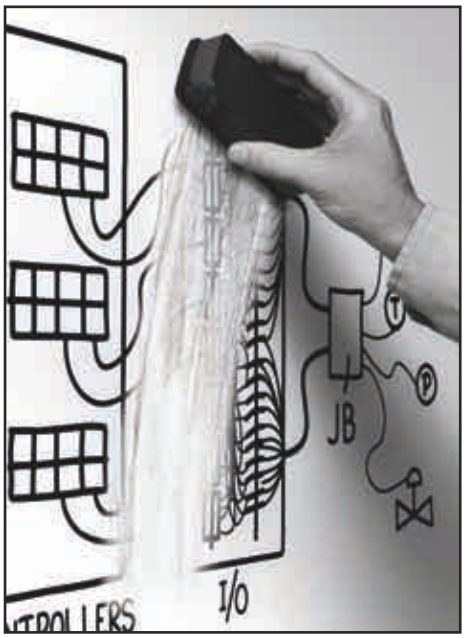

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