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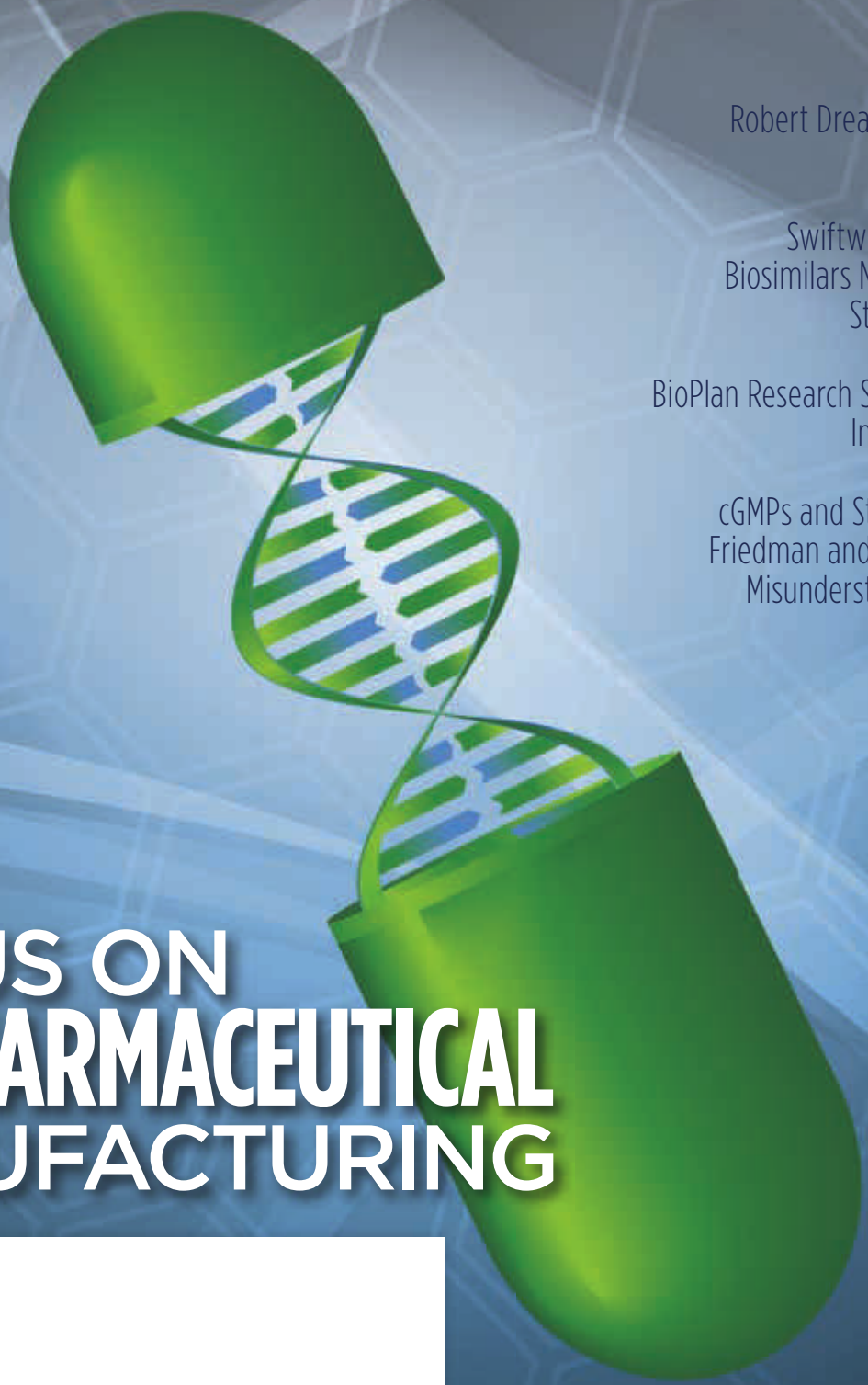

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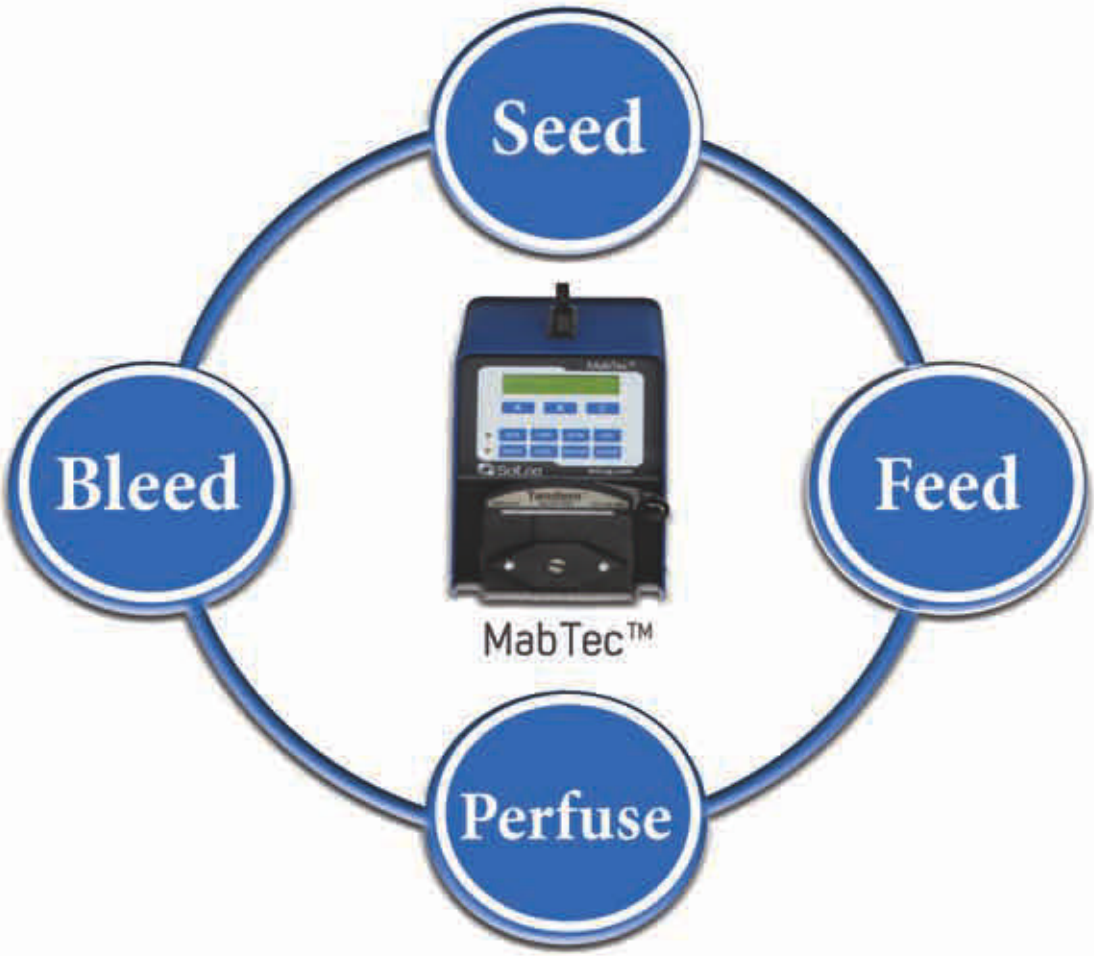

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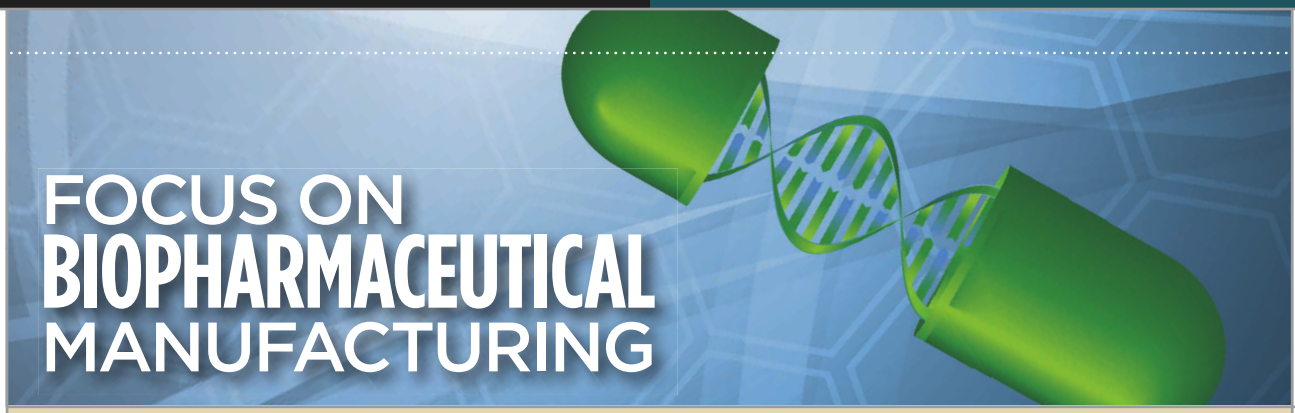

FOCUS ON BIOPHARMACEUTICAL MANUFACTURING

Features

Departments

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Inspiration and Innovation

The yin is just as important as the yang; sometimes, even more so.

MOST OF you reading these pages are men. That's what our surveys tell us. Many of you, and even our women readers, may feel the tiniest bit uncomfortable or even roll your eyes at discussions of women in business. After all, professional women have made great advances in the past few decades. It's easy to forget that, not too long ago, women were a distinct minority in professional circles, ignored or left out of the boys club and, mercifully, the risqué joke-telling, or, worse, bar or strip club invitations at business events. Those were the days when maternity leave, no matter how brief and unsatisfying, could mean the beginning of slow career death.

Since then, the workplace has become a lot more human. However, the business world still prefers the traditional competitive male spirit. In the process, it often neglects other qualities essential for success, which are so often associated with women: nurturing and consensus building, for instance.

The most outstanding people in any business, male or female, manage to combine the yin and the yang, and balance the "male" need for visible achievement with the "female" need to inspire, engage and care for others.

Consider Mary Crowley, whose mission remains at the heart of so many innovations that are driving biopharmaceutical development forward. Her grandson, David Shanahan, now President of the Mary Crowley Cancer Research Centers, spoke about her at the PDA Annual Meeting in April.

Another example, operating on a smaller stage, is Julie Cappelletti-Lange, co-owner of our company, Putman Media. Beautiful and full of life, she passed away last month at the age of 50, from a rare condition that results from an adverse reaction to an antibiotic. The publishing world is diminished by her absence.

Both were single mothers, a role that few seek. During the Great Depression, Ms. Crowley made the bold decision to leave her improvident husband and move from Missouri to Texas, where the oil business was growing. Harnessing male *chutzpah* and female endurance, she studied, worked and raised two children alone, eventually starting an interior design firm that became a multimillion dollar business.

Crowley had been diagnosed with cancer in the late 1960s and hospitalized. She recovered, but the cancer came back in the 1980s. Noting that therapies and treatments had advanced so little in over 20 years, Crowley decided to fund research into innovative cures. Today, as Shanahan reported, the center that bears her name touches the lives of over 4,000 patients. For 20 years, it has been at the forefront of personalized medicine and biopharmaceutical R&D, and over 300 clinical trials of vaccines and other therapies.

What makes it tick are flexible, scalable manufacturing technologies, developed by Gradalis, a company that Shanahan founded. Work done with the Crowley Center has been instrumental in shaping the flexible biopharmaceutical plant as we now know it.

GREAT PEOPLE IN ANY FIELD NOT ONLY PEFORM WELL, BUT INSPIRE OTHERS.

In magazine publishing, Julie Lange ran many of Putman's operations, while raising children alone. Trained in psychology, she showed a level of empathy that few possess. During tough economic times, when our much larger competitors were doing this, she refused to cut travel budgets, reasoning that editors needed to get out there, learn and report. She even adopted a family from the inner city, and, without patronizing, made them part of her extended family. Julie made each employee feel that way too. Any innovations that Putman magazines might have made in print or on the Web were, in some way, inspired by her.

So when anyone hints that empathy and nurturing are best left to the female of the species, and out of the workplace, consider those who transcend limits and stereotypes. It's the combination of yin and yang that moves the world forward. Who knows what it might inspire in your organization?

AGNES SHANLEY, EDITOR IN CHIEF
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Memories of Our Masthead

A tribute to Julie Cappelletti-Lange

MICHELE VACCARELLO WAGNER, SENIOR EDITOR, DIGITAL MEDIA

MY MONTHLY column sits adjacent to our masthead (left), which contains the names of the people who help put this magazine together. You most likely skip right over it month after month. (It's okay to admit—I do as well.)

A *masthead*, of course, is also a nautical term—the top of a ship's mast, which rises above the sails, rigging, booms, deck and everything else. In layman's terms, it guides the rest of the ship. I ask you to take a quick look towards the bottom of our masthead. You'll see the name of Julie Cappelletti-Lange, whose name has been there every month since our very first issue in 2003. Julie was the Part-Owner, Vice President and head of Human Resources of Putman Media for more than 28 years. In late April, she passed away, very tragically and unexpectedly, after a week-long battle with Stevens-Johnson syndrome, a one-in-a-million disease triggered by an adverse reaction to a common antibiotic. Taking a drug to make her feel better ended up taking her life. She had just turned 50 years old.

I wish a magazine masthead could list so much more. I wish it could tell you that she was the heart and soul of the Putman Media family. I wish it could say that she was a strong, intelligent businesswoman who helped create the company's brands and inspire the people behind them. I wish it could tell you that she was kind, witty and a great storyteller and that her bright energy always kept everyone around her in good spirits. I wish it could tell you she was a single mother of four who raised her children to be strong and assertive, but also compassionate and humane. And I wish it could tell you that, in addition to all her business and family responsibilities, she spent her remaining time doing endless charity work around the community, and even opening her home at holidays for those without a place to call home.

Julie was truly the masthead of our own company ship, to use a cliche. She was the one who kept everything and everyone afloat, kept the oars in motion but also knew when one of us needed help. Maybe there is an individual in your own company that sounds like Julie, and I hope that he/she knows how much they're appreciated.

Recently, a team of FDA researchers, led by Michael Norcross in CDER's Office of Pharmaceutical Sciences, have made progress in learning how to identify and understand drug-related autoimmune reactions. "We hope that, in the future, health care professionals will be able to identify people who are at high risk of developing serious reactions to various drugs, and offer them alternative treatments," said CDER director Janet Woodcock.

FDA and the drug industry do so much good, but also have such an important mission in regard to patient well-being and safety. It is too late for Julie, but it is my truly great hope that research like this can help save the lives of others who might otherwise experience adverse, and even life-threatening, reactions to medication.

In the meantime, we here at Putman Media will all keep sailing strongly on in the memory of our dear friend and colleague, Julie Cappelletti-Lange.

FDA: Progress in Reducing Drug Shortages

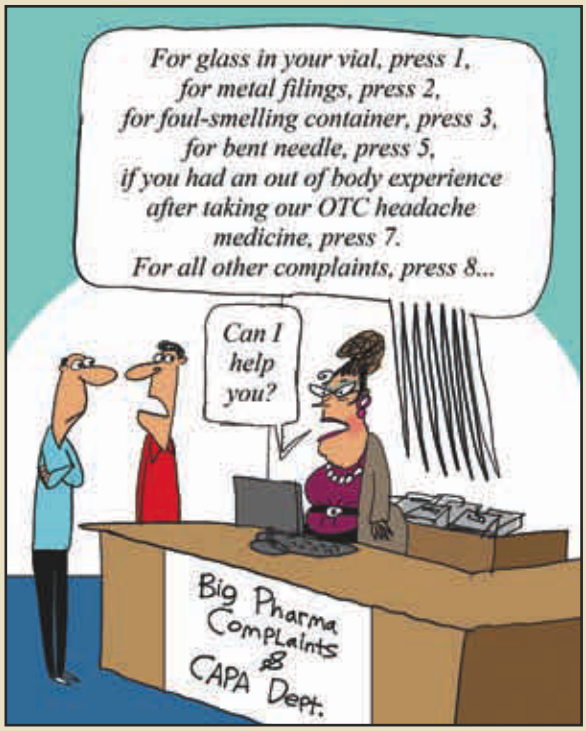
Despite improvements, counterfeiters continue to exploit existing shortages.

BY AGNES SHANLEY, EDITOR IN CHIEF

LAST MONTH on FDA's blog, *FDA Voice*, Commissioner Margaret Hamburg summarized progress that the Agency and industry have made in the six months since President Obama issued an Executive Order empowering FDA to take proactive steps to help prevent drug shortages and develop alternative suppliers.

"Since reaching out to industry," she wrote, "there has been a six-fold increase in early notifications from manufacturers." As a result, she said, FDA has been able to prevent 128 drug shortages, and to reduce the average number of shortages—42 new drugs this year compared with 90 new shortages at this point last year.

FUNNY PHARM



"The only reason I came here is because the '7' on my phone is broken."

— Bill Russo

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.

Hamburg noted progress in addressing critical cancer drug shortages. Currently, she said, supplies of methotrexate, used to treat childhood leukemia and osteosarcoma, are currently meeting all demand, and FDA does not expect any further supply issues. She attributed this to closer work and communication with its supplier, Teva. Doxil, used to treat ovarian and some other cancers, is also in adequate supply, Hamburg said, since FDA mandated importation of equivalent product from India.

FDA has also been working more closely with suppliers of anesthetics—for example, with Hospira, which, Dr. Hamburg said, notified the Agency in advance of expected shortages of propofol, allowing FDA to work with other manufacturers to ensure increased supplies.

Moreover, the Agency is working with Congress, Hamburg said, on bipartisan legislation to require and expand early notification of drug supply problems that could cause shortages. Drug manufacturers "have a responsibility to manufacture quality drugs and to have a process to ensure supply continuity of critical drugs," she said.

"Today's six-month check-up demonstrates what government and industry can accomplish when we work together," she added. "While there's no simple solution, we are making progress. And we'll remain vigilant—doing all we can and using every resource available—to make sure patients have access to the critical medicines they need, when they need them." The letter is posted on PharmaManufacturing.com.

Despite progress, last month came more evidence that counterfeiters are actively exploiting shortages. FDA reported that a counterfeit version of Teva's ADHD and narcolepsy treatment, Adderall, was being sold online. The drug has been in short supply due to shortages of its APIs. Where the real drug contains four APIs, the fake version, based on tests that FDA ran, contained tramadol and acetaminophen. The tablets were also white, rather than orange, and contained a number of packaging and spelling errors, including "NDS" rather than "NDC."

Last month, too, FDA sent letters to eight physicians in Illinois warning them of potential counterfeit cancer treatments purchased from Richards Pharma and Quality Specialty Products, suppliers in the U.K. Included was Avastin. Nearly 100 physicians throughout the U.S. have received similar letters from FDA.

GMP Failures (Perspectives from MHRA)

THE U.K. regulatory agency, MHRA, recently released its report on "worst practices" in GMP based on plant inspections and other enforcement efforts between April, 2011 and March 2012. (To download the document, visit PharmaManufacturing.com.) This report cited, in order of importance, inadequacies in the following areas:

1. Deviation or "anomaly" investigation
2. Change control (in Quality Management Systems)
3. CAPA
4. Complaints and recall responses
5. Quality management systems
6. Supplier and contractor audits
7. Contamination
8. Documentation of procedures
9. Documentation of manufacturing
10. Process validation

Also highlighted in the report were inadequate staff training, deficiencies in design and maintenance of facilities and equipment, failure to prevent contamination, to adequately supervise suppliers, and to respond adequately to prior inspection findings.

— Agnes Shanley

COMPLIANCE QUIZ

Welcome to Compliance Quiz, which focuses this month on cold chain management. Answers are below, right. (Find a full quiz and answer details on PharmaManufacturing.com.)

1. Under Title 21, Part 211, Subpart H – Holding and Distribution, Sec. 211.150 Distribution procedures, Warehousing procedures must include:

a) A procedure whereby the oldest approved stock of a drug product is distributed first. Deviation from this requirement is permitted if such deviation is temporary and appropriate.
b) A system by which the distribution of each lot of drug product can be readily determined to facilitate its recall if necessary.
c) both

2. According to the World Health Organization's "Good distribution practices for pharmaceutical products" Annex 5, WHO Technical Report Series 957, 2010: "All [temperature] monitoring records should be kept for at least . . . "

a) . . . the shelf-life of the stored pharmaceutical product.
b) . . . the shelf-life of the stored pharmaceutical product plus one year, or as required by national legislation.
c) . . . the shelf-life of the stored pharmaceutical product, or as required by national legislation.
d) . . . the time span required by national legislation.

3. According to the Code of Federal Regulations Title 21, Part 205, section 205.50, inventories and records on prescription drugs must be kept for review and photocopying:

a) 3 years after the date of their creation
b) 5 years after the date of their creation
c) 7 years after the date of their creation

4. PDA's Technical Report 39 outlines the Transport Process in five areas. Which of the following is NOT one of them?

a) Ambient Temperature Variance
b) Modes of Transportation
c) Transit Duration
d) Route
e) Time Temperature Recording Method
f) Material Handling

Answers 1.C 2.C 3.A 4.E

FDA Modifies Biopharma Sterility Test Requirements

FDA HAS published in the Federal Register new rules amending sterility test requirements for biological products. Changes were designed to offer greater flexibility, the Agency wrote, and increase the use of modern

PHARMA REPLAY

"Our findings contradict recent criticisms of the speed of review by the FDA."
– A new report says FDA processes drug approvals much faster than Canadian and EU counterparts.

"Every case is a huge maelstrom of hope, begging, corporate self-interest, slow bureaucratic due process, media spotlighting and public frustration."
– Bioethics professor Art Caplan on chronically ill patients and their desire for drug companies' experimental and risky treatments.

"Biopharmaceutical companies are good for sales, and biotech companies for innovation, but neither is good for manufacturing,"
– Samsung BioLogics president Tae-Han Kim, suggesting his company is better equipped for the task.

"By chasing wholesalers and manufacturers, the DEA is simply going after the wrong actors."
– Writer/blogger Adam Fein on the Drug Enforcement Agency's tough stance toward Cardinal Health and other manufacturers and distributors. Rather, patients, physicians, and pharmacies are to blame, he says.

"Kudos on your positive results, now go back and fix the stuff they missed."
– A member of the FDA Inspections LinkedIn group, responding to another who boasted, "We passed our FDA inspection with zero observations!" The commenter added: "Zero observations does not equal perfect performance. It means your inspectors didn't look at everything."

methods to assure product safety. The new requirements also recognize recent advances in technology, including adenosine triphosphate bioluminescence, chemoluminescence and CO_2 head space methods. Among other things, the new rules replace sample size specifications with the requirement that samples be appropriate for the situation. It eliminates specified test methods and culture media formulations and modifies guidelines for repeat sterility tests and requires them only once per lot. For more, see Pharma-Manufacturing.com.

–Agnes Shanley

Compliance Winners and Sinners

Each month for the rest of this year, we'll highlight companies winning and sinning in regards to compliance. These reports will lead up to our Special Report on FDA Compliance, coming in November/December:

Sinners:

Hospira: In April, the company voluntarily recalled one lot of morphine sulfate injection, after a customer reported two syringes containing up to twice the required amount of active pharmaceutical ingredient. Opioid pain medications such as morphine can lead to life-threatening results if overdosed.

Vertex and Its IT Vendor: Stock prices tumbled by 10% in late May, when the company revealed that relative improvements had been presented in its FDA documentation as absolute improvements, due to "misinterpretation" of statistics between Vertex and its unnamed statistical software vendor.

Winner:

Abbott Labs: FDA recently terminated the consent decree that Abbott Labs had been operating under since 1999, for failures primarily in its diagnostics division. After 12 years, FDA has finally determined that Abbott has changed its ways. "Many consent decrees that FDA enters with firms allow the firms, under defined circumstances, to seek court termination of the decrees following extended periods of compliance. That is the case with this one," an FDA spokeswoman told the *Pharmalot* blog.

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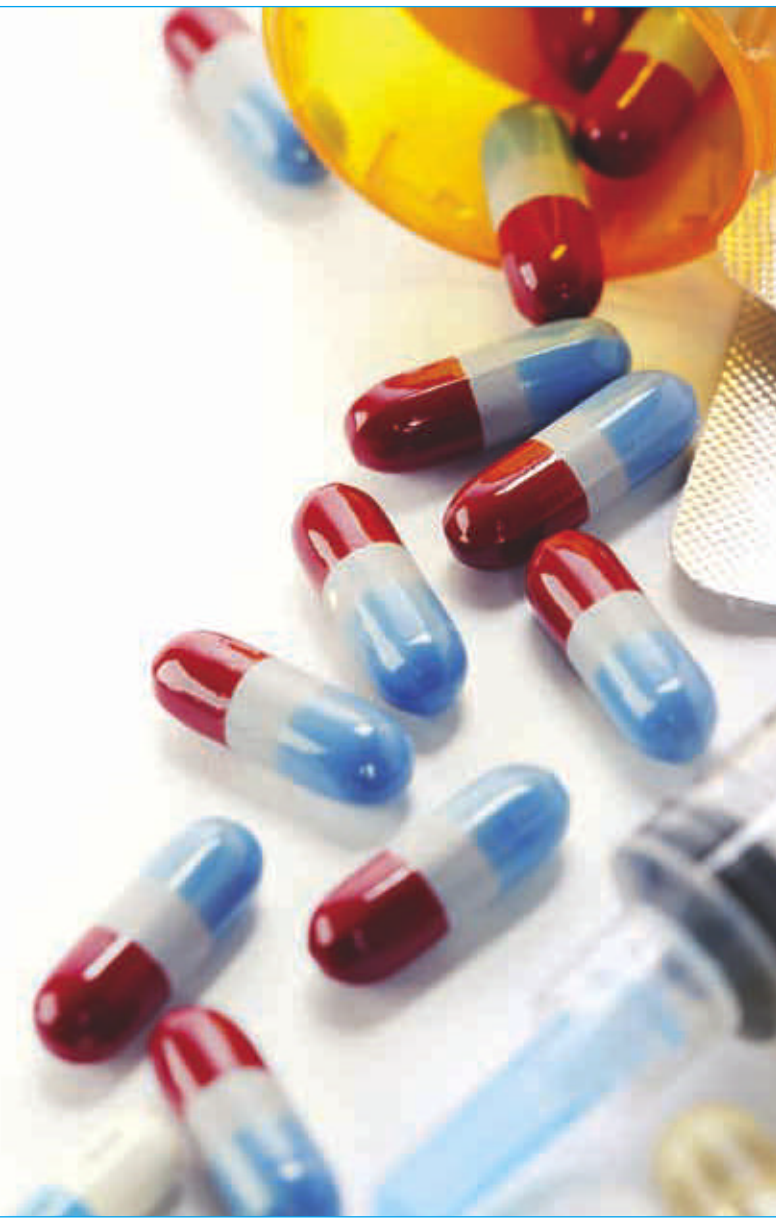

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"Viega ProPress® allowed us to pre-run all the pipe parallel to the existing lines while production still ran. We were able to do the final cut-ins during lunches, so they had very little downtime."

Tommy Stiles,
A.W. Stiles Contractors,
McMinnville, TN

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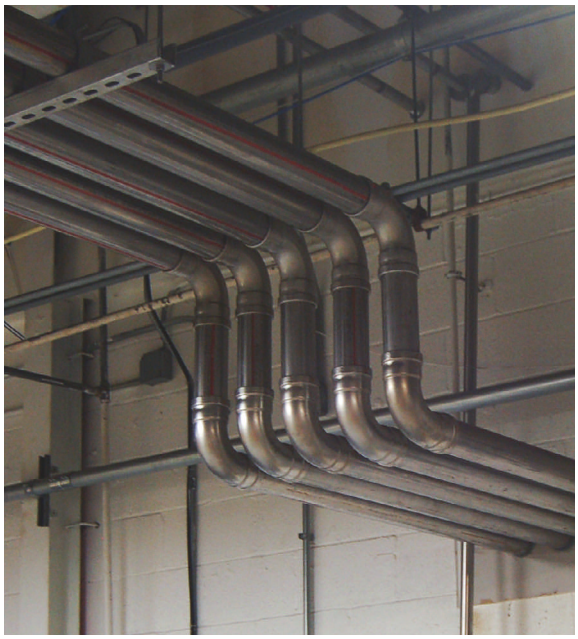
Viega ProPress® for stainless saves labor, enhances safety for Bio-Pharm applications

For bio-pharmaceutical piping applications, Viega ProPress for stainless steel offers substantial savings in man-hours when compared to welding and grooving. The system also provides a safer, cleaner, higher-quality installation.



> *"The Viega ProPress system allowed us to pre-run all the pipe, except for the connections at each end, parallel to the existing lines while production still ran. Viega can be installed so fast—we were able to do the final cut-ins during lunches, so they had very little downtime."*

A.W. Stiles Contractors recently installed Viega ProPress for stainless steel at a facility that manufactures personal care products such as mouthwashes, shampoos and baby powder. The upgrade involved switching from PVC piping to stainless steel for the peroxide lines.

Prior to the new installation, whenever a different percentage of alcohol was used in the product, the lines had to be flushed. That resulted in about $20,000 a month in waste materials. With the upgrade, not only was the flushing no longer necessary, but the problem of melting PVC lines was also eliminated.

According to Tommy Stiles, it would have cost $200,000 to weld all of the stainless piping. That amount didn't include the lost production from downtime. The project ended up costing only $60,000 with A.W. Stiles using Viega ProPress for stainless. The adaptability of the system allowed the contractor to integrate the new piping with the existing pumps and other equipment in the customer's system.

"Downtime was not an option," Stiles said. "The Viega ProPress system allowed us to pre-run all of the pipe parallel to the existing lines, except for the connections at each end. And, we did it while production still ran. The system can be installed so fast, we were able to do the final cut-ins during lunches, so they had very little downtime.

"Pressing was five times faster than if we had welded all of the joints," Stiles estimated. "Of all the joints we installed, not one leaked. That's almost unheard of with other joining methods. In some environments, welding is not allowed—especially with the alcohols and other flammable materials running through the lines."

To learn more about Viega ProPress for stainless in Bio-Pharm applications, visit TheTorchIsPast.com or call 866.766.7805.

Pharma Manufacturing on the Move

Global supply needs are dictating facility locations and CMO selection.

BY BILL CONNELL, VICE PRESIDENT, SUPPLY CHAIN, MAXIOM GROUP

GLOBAL DEMAND for qualified pharma and biopharma CMOs continues to increase, driven in part by a growing patient population. The past 20 years has seen the rise of many emerging nations whose populations require more and better drug products.

Another factor behind the rise of contract manufacturing has been changes in the structure and needs of drug companies of all sizes. Smaller companies with promising molecules in development don't have the facilities for large-scale commercial production. They need CMOs for API and drug product manufacturing as well as packaging as they move from clinical to commercial operations. They seek support for their entire supply chain, including the licenses and approvals required from numerous regulatory agencies so that the product can be sold in many global markets.

Many have learned hard lessons. One U.S.-based company received EU approval for its product and selected a German CMO to manufacture and package it for seven individual markets. A year later, it decided to launch a branded generic version in the U.S. but ran into delays in obtaining FDA approval of the German facility. Obviously, the company would have been better served by working with a CMO with both EMA and FDA regulatory licenses from the start.

This article will look at some of the major factors driving the demand for and availability of global CMO facilities, from the perspective of large manufacturers. (For more on small- and mid-size manufacturers, see a longer version of this article on PharmaManufacturing.com.) These companies continue to shrink their number of worldwide API, manufacturing and packaging facilities for various key reasons:

1. *Internal initiatives for global plant rationalization to shrink the number of plants,* reducing their overall asset base, global footprint, and manufacturing redundancy.
2. *Mergers and acquisitions*, which are driving product consolidations and creating production redundancies in the combined manufacturing networks and supply chains, leading to asset divestitures and facility closings. In many cases, these plants are sold to CMOs to continue manufacturing existing products.
3. *The drive to expand business opportunities in growing and emerging markets*, which requires developing regional partnerships which can include a need for "local content"—in regards to manufacturing, packaging, labeling or all three. This "local content" can provide lower costs, better market access, and reduced regulatory requirements.
4. *The need to implement global API, manufacturing and packaging strategies from a truly global perspective* versus the more traditional "regional" strategy. Traditionally, large pharma companies have built their supply networks with duplicate product and manufacturing capabilities in the world's major regions. This strategy is being replaced by one that identifies global centers of manufacturing excellence by type and dosage form. Many times only one or two locations are required to manufacture a certain product or dosage form for worldwide distribution.
5. *The global shift from traditional oral solid dose to biologics* is a trend that will continue for the foreseeable future and is contributing to large global pharma companies having excess capacity for oral solid dose manufacturing and packaging while lacking capacity on the biologics side.
6. *The change in strategy towards more horizontally integrated companies.* Vertical integration was an important strategy years ago when there were limited options for qualified CMOs and packagers. This has changed now that CMOs and plants are plentiful in most global regions.
7. *Product life cycle management issues related to the overall portfolio*, where older established products are in sales decline or nearing patent expiration causing the originating manufacturer to:
   i. Reduce the infrastructure needed to produce and support these products
   ii. Sell the products to other manufacturers, including start-ups who need CMOs to produce and package
   iii. Shut down API, manufacturing and packaging operations after product divestiture

The selection of which CMO to partner with, and where facilities should be located, continues to become more complex. CMOs that present the lowest risk and that are most in tune with the global shifts and trends described above will ultimately be chosen.

Biopharma's Flexible Imperative

Business forces, bioterror and pandemic risks demand new approaches

By Robert F. Dream, Principal, HDR Company, LLC

RECENTLY, A number of different trends have converged to demand a new type of biopharmaceutical facility, one that emphasizes flexibility and agility. Drawing this new blueprint are:

- business needs to minimize timelines and financial risks;
- "biotech on demand," and the ability to shore up local manufacturing capacity, quickly, to meet market needs;
- national security needs for systems that can easily and rapidly respond to biological attacks;
- urgent national health needs to protect the public from large-scale, fast moving epidemics and pandemics.

Today's biopharmaceutical manufacturing facilities are smaller and more flexible, efficient and cost-effective than those of the 1990's, and they are able to adapt quickly to market changes.

The goal isn't technology in and of itself, but greater product and process knowhow for speed to market. With modular systems, we can now place an entire small-scale clinical production line inside an 18' x 42' x 13' (W x L x H) environment.

Based on defense and health department standards, vaccine manufacturing facilities have been blazing new trails. Traditionally, it has taken between 14 and 20 years to move from pathogen identification to vaccine safety and efficacy trials. The new goal, set by the U.S. Defense Department's DARPA (Defense Advanced Research Projects Agency), and repeated in specs set by BARDA, is to cover the same ground in less than 22 weeks.

The lifeblood of this flexible, multiproduct and multitechnology future will be the Mobile Bioprocessing Unit (MBU), which has already been built for manufacturing small, clinical-scale quantities of some therapies. (Figures 1-4 illustrate the National Center for Therapeutics Manufacturing, housed at Texas A&M University in College Station, Texas.) The key feature of these mobile units is that they are self-contained, with inherent air handling and other critical equipment and controls built in and standard.

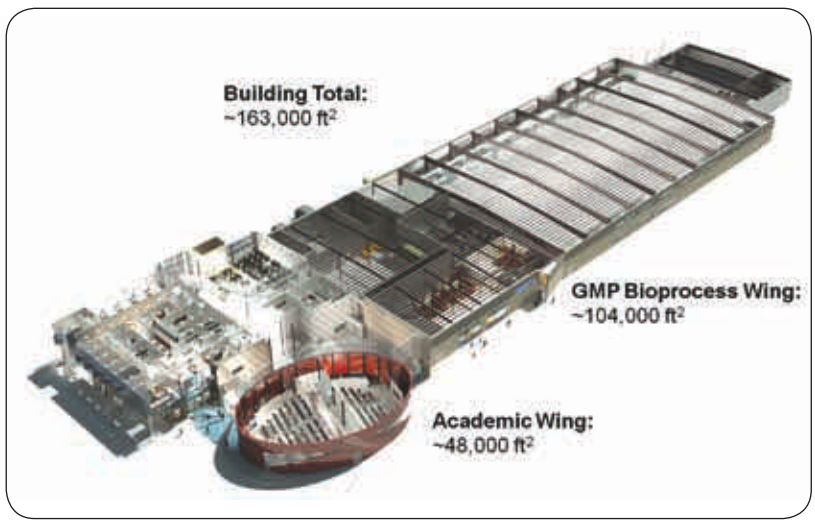


Figure 1. National Center for Therapeutics Manufacturing, designed and built based on Flexible Manufacturing Criteria

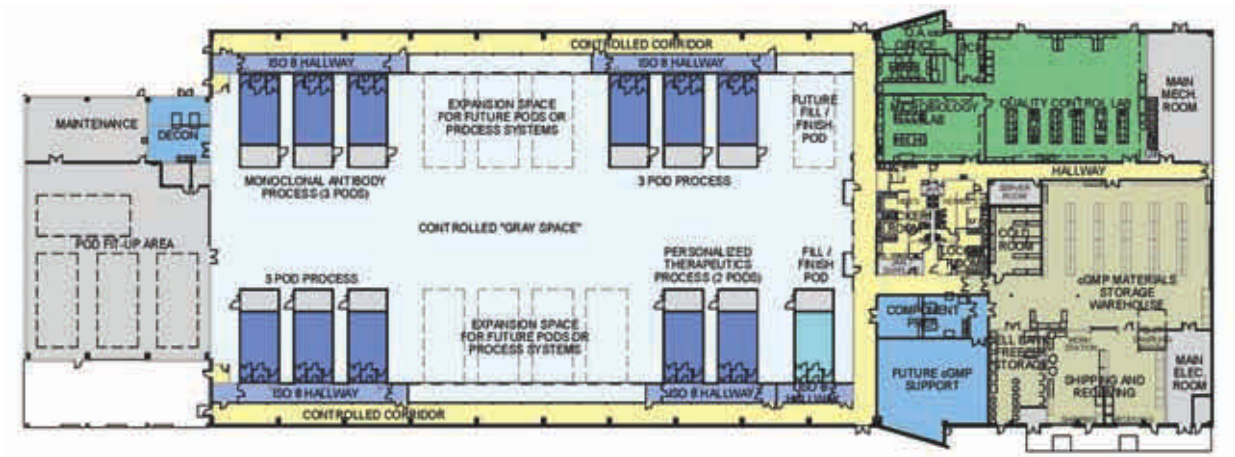


Figure 2. Manufacturing Wing of the NCTM

Each MBU is used for a single, biologically distinct technology (bacteria, mammalian cells, plants, etc.), thereby eliminating any cross-contamination issues with regulatory agencies. When they are not being used, MBUs are designed to be moved to cleaning and refurbishing areas, and ready to connect when needed. The goal is to:

- Enable low-cost, rapid production of proteins/products, all of which are correctly folded and biologically active, as well as cGMP-qualified master virus banks and cell lines;
- Draw on extensive clinical use and regulatory history;
- Scale MBU's to large volumes and high cell densities;
- Feature FDA-qualified cell lines and virus banks;
- Produce cGMP clinical materials affordably and to provide manufacturing and treatment capacity on a moment's notice.

The Strategic National Stockpile facility for flu vaccine, for instance, calls for 8 to 10 modular process trains for surge production, and allows surge capability to 10 times baseline capacity within 24 hours.

Key features of these facilities will be stockpile pods containing complete process lines, and a life-cycle management program, with scheduled rotation through production.

In addition, DARPA is considering construction of adjacent facilities to integrate and validate "clinic ready" emerging technology platforms. These facilities will be closely integrated with other operations, including animal model development and validation, biomarker evaluation, imaging, GLP pre-clinical studies and animal rule efficacy, and human Phase 1 clinical trials.

VACCINES, BIOTHERAPEUTICS AND PERSONALIZED MEDICINE DEMAND AGILITY

Business demands are also demanding new facility designs and technologies. By 2016, five of the top ten biopharmaceuticals

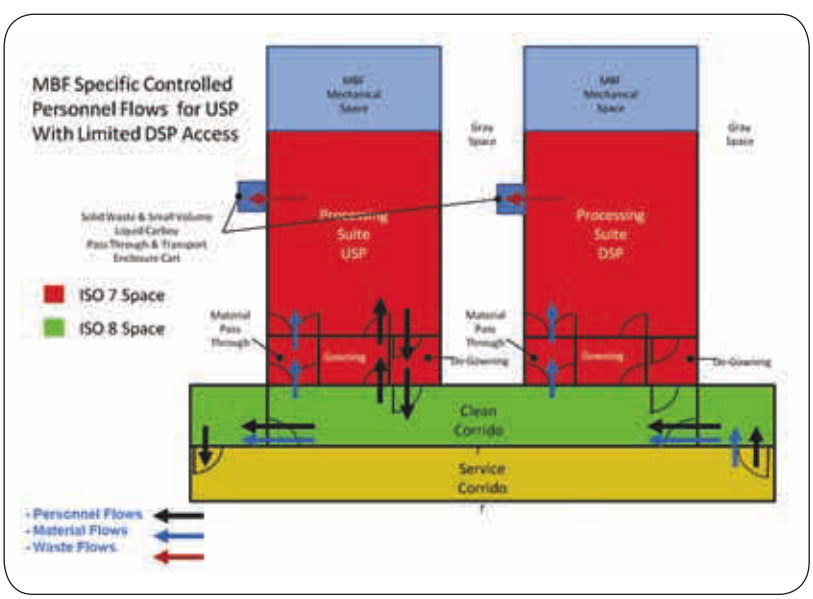


Figure 3. Depiction of a manufacturing suite in the NCTM

Figure 4. Inside the NCTM

are expected to be monoclonal antibodies (MAb's). Follow-on (biosimilar) versions of these will most likely become available in the coming years due to patent expiry and the introduction of legislation for biosimilars. Personalized therapies will further drive the fractionation of the biopharmaceuticals market, thus increasing the need for smaller batch sizes and campaign-based production schemes.

Business realities, combined with demographic and market forces, will accentuate the national imperative for flexible and more cost-effective manufacturing. Compared with other biopharmaceutical products, monoclonal antibodies are large proteins that require relatively high doses—and traditionally necessitate high-volume manufacturing process equipments/systems and facilities. Many biopharmaceutical facilities are still designed as traditional fixed equipment/systems and facilities, with fixed piping and vessel layout and large bioreactor volumes. Such facilities require a significant financial investment along with high total installation costs.

Recent increases in cell culture yields/titer have led to significantly reduced bioreactor volume requirements, which again have opened the door for single-use manufacturing technologies such as pre-sterilized assemblies of single-use bags, tubing and filters that are only used once and then disposed of. With a financial investment reduction and simplified installation, single-use technology could be more appealing than other fixed technologies.

Combining single-use technology and high-yield processes could further reduce the price tag for comparable facilities by 50 percent. This combination is being pursued in a number of biopharmaceutical facilities today—the full effect is truly a paradigm shift.

Additionally, single-use technology runs a much lower risk of batch-to-batch contamination, which is of particular importance in multipurpose facilities. A facility based on single-use technology is easy to reconfigure and can therefore be ready for a new product in a matter of days. This flexibility translates to reduced development timelines and thus accelerated time-to-market peak.

In an increasingly fractionated market, the need for speed to secure market shares is more important than initial minimal cost of manufacturing. And with remarkably increased cell titer, the cost contribution from the manufacturing facility is limited compared with development costs.

With single-use technology, it becomes possible to optimize facility installations based on anticipated product life cycle stages. For instance, to start with, the strategy could be to use just one single-use bioreactor to get material for clinical trials and then upgrade the

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Figure 5. A downstream processing suite developed as part of Project GreenVAX at NCTM. GreenVAX uses tobacco rather than egg-based vaccine technology.

facility with additional bioreactors later in anticipation of market supply production while clinical trials are taking place. As the next pipeline product must be developed, the facility can change the lifecycle stage back to clinical production and the extra bioreactors moved to a market supply expansion facility. Such a strategy becomes possible because single-use technology is so decoupled from the facility building itself.

As an interesting side effect, environmental impact studies show that single-use technology is up to 50% less energy intensive than fixed reusable manufacturing. It may appear counterintuitive, but the emissions from disposing single-use material are more than offset by elimination of the cleaning and sterilization processes required for reusable technology, basically because heating up many tons of water and metal is extremely energy intensive. Full implementation of high-yield processes and single-use technology results in facilities with a markedly reduced carbon footprint per kilogram of product compared to the fixed facilities of the 1990s. Usually 60% of piping in a fixed facility is installed to perform CIP/SIP.

The need for local biopharma manufacturing capacity is increasing in the fast-growing emerging markets as the customer base expands and national initiatives manage the markets. The trend is being amplified by blockbuster patent expiry and the implementation of regulatory legislation for accelerated pathways for biosimilars. For biopharmaceuticals, emerging markets are not about low-cost manufacturing hubs, but about being on location to get access to the local market. Consequently, many big pharmaceutical companies as well as local manufacturers are investing in new facilities in these countries. A blueprint facility concept that can be established as interesting markets develop will become an important strategic asset for biopharmaceutical players with global aspirations.

In reality, the important issue is not stainless steel or single-use technology, but rather how technologies could be combined to provide the most productive and cost-effective process in a fast and predictable way. Choosing one or the other technology concept or a hybrid of the two depends on both strategic considerations and feasibility studies of each individual case.

Clearly, biopharmaceutical manufacturing's paradigm is changing from stainless steel to hybrid combinations of single-use and stainless steel, and complete single-use facilities. Manufacturers are already exploring opportunities, aggressively, and we can expect this trend to continue.

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Manufacturing Strategies for Biosimilars

Regulators have paved the way for low-cost biologics, but it's up to manufacturers to select the right technologies and define quality.

By Tom Fritz, Christine Lightcap, Ph.D., and Kundini Shah, M.S., Swiftwater Group

AMIDST BIOLOGICS patent expirations and the push for personalized (yet low-cost) medicines, the age of biosimilars is upon us. The European Union has paved the way with its biosimilar approval pathway, while FDA passed the Biologics Price Competition and Innovation Act (BPCIA) in 2010. The Act codified into law the 351(k) abbreviated regulatory pathway for biosimilars approval, and formally opened the door for biosimilars product approval in the U.S. However, the law provided no advice regarding what requirements the FDA would need for approval, so in early 2012, the Agency issued draft guidances describing CMC considerations in demonstrating biosimilarity to a reference protein product (U.S.-approved or foreign innovator biologic) [1].

Like their reference products, biosimilars are complex, difficult to characterize, typically have more than one biological effect, and frequently generate immune responses. Because of this, the guidance necessarily lacks a list of specific steps for developing biosimilars, leaving developers to integrate quality attributes on a case-by-case basis using the totality of evidence approach. Although approval of a biosimilar will rely on current data of the reference product, the guidance paves the way for producing biosimilar proteins through the use of alternative expression systems and novel manufacturing technologies. To do this, however, developers must ensure they use the principles of Integrated Drug Development to incorporate robust quality considerations in their development programs.

This article provides a review of the essentials of developing and manufacturing biosimilars today. We review current animal-, yeast-, and plant-based expression systems, predominant manufacturing technologies, and key quality considerations for developers and manufacturers of biosimilars—all with an eye toward the integration of these elements.

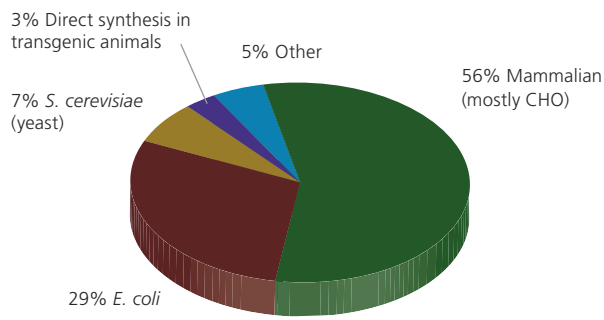

Figure 1. Expression Systems Used for Manufacture of Approved Drugs

ALTERNATE EXPRESSION SYSTEMS

For more than two decades, most biologics have been manufactured in well-known, well-characterized, FDA-approved cell lines that were developed by the innovator manufacturers. Figure 1 shows global product approvals from January 2006 to June 2010 by distribution of these cell lines [2].

Historically, CHO cells have shown the highest expression rates and are easily cultured and sustained. Bacterial and yeast cell lines like *E. coli* and *S. cerevisiae* require minimal growth media conditions and are fast growing, making them economical. However, these traditional cell lines are inherently prone to host cell protein contamination and adventitious agents such as endotoxins. Developers often opt to use traditional cell lines because they have established upstream and downstream purification processes, historical literature data is available for reference, and regulatory agencies are familiar with the expression systems. For biosimilars developers, however, these cell lines provide less opportunity for innovation, fewer intellectual property advantages, and minimal patent protection.

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ANIMAL- OR YEAST-BASED ALTERNATIVE EXPRESSION SYSTEMS

FDA has approved novel products using animal or yeast-based alternative expression systems (Table 1).

- YF-Vax was developed in Avian Leukosis Virus (ALV)-free chicken embryos. Chicken embryos have historically been used for protein expression and experimentation, and are economical and easily accessible. Most importantly, chicken embryos lack an immune system, making them ideal candidates for production.
- Due to their susceptibility to a wide range of viruses, VERO cells, a kidney epithelial line isolated from the African Green Monkey, have served as a popular expression system for vaccines, such as RotaTeq, Rotarix, ACAM2000, and Ixiaro.
- HEK293 cells (Human Embryonic Kidney cells) have also been used in the manufacture of an approved drug, Xigris. (*Note:* Xigris was withdrawn from the market in 2011 due to lack of efficacy, not due to any manufacturing deficiencies.) Similar to CHO cells, HEK293 cell lines are easy to culture, have higher rates of expression for proteins of interest, and are easily scaleable.
- The baculovirus insect cell line, used to produce Ceravix for the treatment of HPV, produces large quantities of proteins in cultured insect cells or insect larvae and these proteins are easily purified with tags or using affinity chromatography techniques.
- In 2009, Kalbitor produced from *P. pastoris* (a yeast) was also approved. These yeast cells can grow to high densities compared to the more common yeast *S. cerevisiae*. *S. cerevisae* is also known to release ethanol during the fermentation process, which can deter cell growth and protein production.
- In 2011, Benlysta was approved for the treatment of lupus and was expressed in the mouse myeloma cell line NS0. The NS0 cell line cannot produce endogenous antibodies, making it an attractive platform for protein production. However, as seen with CHO cells, NS0 cells have the potential to generate glycosylated proteins, which are known to produce immunogenic effects.

PLANT-BASED ALTERNATIVE EXPRESSION SYSTEMS

FDA has also been open to plant-based expression systems (i.e., plant cell cultures and whole plants). (See Table 2.) These systems have gained increasing popularity due to attractive protein yields; simpler methods of expression, cultivation, and manufacturing; and economical developmental requirements when compared to mammalian cell lines. One of the most enticing benefits to using a plant-based production system is the decreased likelihood of clinical immunogenic responses, since plants do not contain mammalian pathogens or endotoxins. However, when working with plant-based expression systems, extensive DNA or protein characterization is required, unlike with mammalian cell lines. These systems also show greater potential for aflatoxin contamination.

FDA approved the first plant-based recombinant therapeutic protein, Elelyso, in 2012. Protalix developed Elelyso using ProCellEx (ProCellRx Platform Overview), a proprietary carrot cell expression system in combination with a closed novel bioreactor system using disposable plastic bags. The 12-month delay in approval was due to a lack of efficacy data, not FDA's concerns about the novel cell line.

Although not discussed here, companies are pursuing expression systems outside even these novel

Drug Name	Indication	Stage of Development	Sponsor	Cell Line
Xigris (withdrawn in 2011)	Sepsis	Approved 2001	Eli Lilly & Company	HEK293 cells
RotaTeq	Rotavirus gastroenteritis	Approved 2006	Merck Sharp and Dohme Corp.	VERO cells
ACAM2000	Small Pox	Approved 2007	Sanofi Pasteur	VERO cells
Rotarix	Rotavirus gastroenteritis	Approved 2008	GlaxoSmithKline	VERO cells
YF-Vax	Yellow Fever	Approved 2008	Sanofi Pasteur	ALV-Free Chicken Embryos
Kalbitor	Hereditary angioedema (HAE)	Approved 2009	Dyax Corp.	*P. pastoris* cells
Ixiaro	Japanese Encephalitis	Approved 2009	Intercell Biomedical	VERO cells
Ceravix	Human Papillomavirus (HPV)	Approved 2011	GlaxoSmithKline	Baculovirus Insect cell
Benlysta	Lupus	Approved 2011	Human Genome Sciences	NS0 cells

Table 1. Recent FDA-Approved Products Using Animal/Yeast Alternative Expression Systems

Drug Name	Indication	Stage of Development	Sponsor	Cell Line
Elelyso	Gaucher disease	Approved 2012	Protalix Therapeutics	Carrot
Locteron	Hepatitus C Virus (HCV)	Phase 2	Biolex Therapeutics	Lemna (duckweed)
H5N1	Influenza	Phase 2/3	Medicago Inc.	Tobacco
Lactoferrin	Antibiotic Associated Diarrhea	Phase 3	Ventria Bioscience	Rice

Table 2. Biologic Products Using Plant-based Alternative Expression Systems

systems, including ciliates, alternative yeast and bacterial species, and cell-free expression systems. One day these expression systems may have the same degree of success as animal and plant-based systems.

SELECTED MANUFACTURING TECHNOLOGIES

Several innovative manufacturing technologies are available for both high throughput screening of recombinant protein variants as well as rapid protein production. Principles of synthetic biology and industrial engineering are used to enhance product expression and development.

HIGH THROUGHPUT SCREENING

These principles form the basis of Intrexon Corporation's proprietary UltraVector Platform which offers a dynamic library of modular components to customize, test, and optimize various protein candidates in a cell line of interest based on host cell performance. Combined with its Laser-Enabled Analysis and Processing (LEAP), developers have the option to rapidly identify and select high-secreting, genetically modified mammalian cell lines producing the protein of interest.

PRODUCTION TECHNOLOGY

The need to get to the market quickly will lead companies to explore flexible, cost-effective manufacturing tools such as single-use technology (SUT). SUTs have reduced cleaning validation requirements between product changeovers and batch-to-batch processing. Single-use portable bioreactors, for example, are available at various capacities, providing linear scaleability throughout the manufacturing process for biosimilars using alternate cell lines.

According to technology provider Xcellerex, the SUT platform allows production lines to start up within 15-18 months, and manufacturers benefit from a decrease in total capital cost by 50-75% and operating cost by 20%. This presents biosimilars developers with the ability to accelerate upstream manufacturing processes and dedicate the upfront cost savings towards commercial production needs.

PURIFICATION PROCESSING

While high-producing alternative cell lines and less complex upstream manufacturing techniques offer some advantages, downstream purification processing can be

Attribute	Assay
Identity	DNA Sequencing
	Enzyme-linked immunosorbent assay (ELISA)
	Mass Spectrometry - Peptide Mapping
Identity and Purity	Mass Spectrometry - Intact Molecular Mass
	Western Blot
	High Pressure Liquid Chromatography (HPLC) such as reverse phase (RP), size exclusion (SEC), and ion-exchange (IEC)
Purity	SDS-PAGE
Functionality	Binding Capacity
	In vitro and *in vivo* biopotency

Table 3. Protein Assays for Product Characterization

a significant bottleneck to CMC development. For some development programs, downstream purification accounts for 80% of the total manufacturing cost [2]. Streamlining purification and reducing the number of steps required in the purification process are two commonly used techniques. However, more emphasis is being placed on optimizing purification systems. For example, 3M Purification's Zeta Plus line of single-use, depth-filtration systems can remove cells and selected contaminants and host cell proteins from cell culture media at the primary recovery step using charge-modified depth filters. This system can also be applied to mammalian cell harvest or bacteria, yeast, and insect cell lysates clarification. The specialty media has been shown to reduce host cell proteins, protein aggregates, and endotoxins. This not only provides time and cost efficiency but reduces protein yield loss observed during multiple purification steps.

QUALITY CONSIDERATIONS FOR BIOSIMILAR DEVELOPMENT

If using a different expression system, it is impossible to generate a biosimilar which is identical to the reference product. However, it is possible to develop *highly similar* products with no clinically meaningful differences by remembering that "the process is the product." Upstream production and downstream processing techniques can yield protein fluctuations and impurity profiles that vary among expression systems.

When using alternate cell lines, the FDA expects developers to provide sufficient justification that the construct encodes the same primary amino acid sequence as the reference product, with data supporting that minor modifications do not affect safety, purity, or potency of the product. Comprehensive cell line development and characterization data shared early in the development process with the FDA will enable the developers to collect sufficient safety and efficacy data.

Products that are highly similar to reference products can be developed by implementing consistent and complete product characterization testing per International Conference on Harmonization (ICH) quality guidelines. This includes identity testing and structure confirmation during all stages of protein folding (primary through quaternary). A purity assessment accounting for all host cell-related protein availability, and those impurities associated with the protein itself, such as truncated

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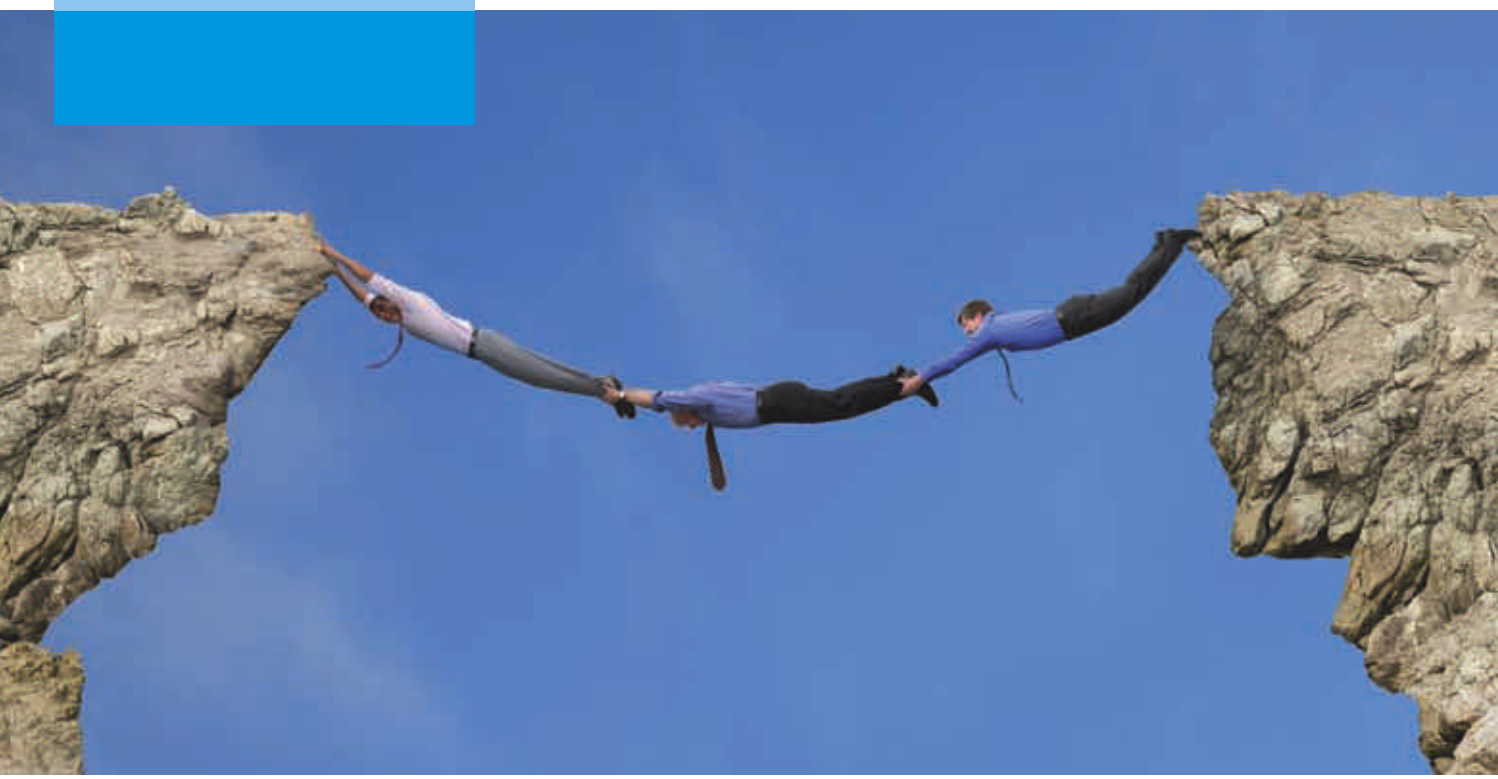

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forms, aggregates, or modifications (e.g., glycosylation) should be completed. These impurities could have an effect on protein quality, potency, and the amount of safety and efficacy data required during development. Protein function should also be assessed. Table 3 lists recommended assays for product characterization, which will vary based on the type of protein and production process.

Once fully characterized, a master cell bank (or seed bank when working with plant expression systems) is generated based on the quality traits desired. This banking system is designed to ensure consistent production of a highly similar protein product. A stability protocol using many of the assays used to characterize the original protein should be in place to control for changes during storage and shelf-life of the product. Agency reviewers expect that the stability protocol assesses phenotypic traits, such as protein production and titre, as well as genotypic stability. DNA sequencing and segregation analysis can be used to monitor potential changes to the protein construct on a DNA level, prior to the expression of the protein itself.

A developer must keep in mind that, although a full protein characterization may initially support a highly similar protein product, the expression system can introduce new, and specific, product- and process-related impurities and substances. This is especially true if the reference product was made using a different system.

Not all impurities are detrimental to development. Levels should be based on ICH-guided drug substance and drug product impurity specifications and knowledge gained from the production process and batch history analysis. FDA requires a functionality and potency assessment. In many cases, as long as the safety and efficacy of the protein drug is maintained, the additional substances are not a concern. If the specific impurities are shown to impact functionality, further upstream and downstream process optimization may be required. This can impact the product development plan from a safety and efficacy perspective as well.

AN INTEGRATED APPROACH

CMC challenges related to upstream scale-up and downstream purification strategies and the growing cost of product development have contributed to a shift in innovation and evaluation of product candidates in alternative systems and other technologies. Developers are considering new ways to expand product pipelines and will move to integrate those systems that provide them with a competitive advantage. The 351(k) pathway for biosimilars development will compel manufacturers to build quality into the process in the early stages, use a risk-based approach to proving comparability and characterization of their product, and to work together with key subject matter experts and the FDA to create a successful development program.

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DEVELOPMENT DELIVERY SUPPLY

Biomanufacturing Shows Signs of Maturity

Manufacturers are reporting fewer batch failures, adopting PAT and other quality initiatives, and stepping up supply chain quality control.

By Eric Langer, BioPlan Associates, Inc.

IN BIOPHARMACEUTICAL manufacturing today, quality management is critical for steering clear of production problems, capacity bottlenecks, and operation failures. The good news is that manufacturers appear to be doing a better job over the past 10 years.

In our "9th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production" [1], we evaluated, along with more than 80 other biomanufacturing trends, the frequency of batch failures among global biomanufacturers. We weighted information shared by 302 respondents to estimate the batch failure rate for the industry. Based on the responses, batch failures occur on average every 60.3 weeks per facility. This is a significant improvement over last year's average of 54.5 weeks, and shows a continuing trend over the past five years (Figure 1). Indeed, in 2008, we found batch failures to occur every 40.6 weeks. This means that in five years, the batch failure rate has improved by 49%.

Delving further into the responses, we find some interesting patterns in play. For example, the proportion of respondents who said that the last batch failure at their facility occurred either two years or more ago stands at 36.5% this year, up significantly from 29.9% last year, 25.8% in 2010, and 26.7% in 2009. On a similarly encouraging note, the proportion experiencing a failure in the past one to three months dropped to 14.1% this year, after being steadily around the 20% mark for the past few years (18.5% last year, 21.1% in 2010, and 21.6% in 2011.)

Year	Avg. Weeks/Failure/Facility
2012	60.3
2011	54.5
2010	50.9
2009	51.1
2008	40.6

Figure 1. Batch Failure Rates per Facility, 2008-2012

Tempering the good news, though, is our finding that the proportion of respondents experiencing batch failures very recently (within the last week or last month) is markedly up. This year, more than 1 in 10 (10.6%) reported a failure either within the last month (8.2%) or the last week (2.4%). This is a step above the 7-8% who have indicated this in past studies.

Taken together, though, the news on the whole is encouraging. The continuing reduction in frequency of batch failures is a good sign, and represents a maturation in performance, likely even within smaller organizations. Some of this improvement is directly related to training of operations staff, which, according to the study, received significant budget increases this year.

Although the specific causes contributing to this improvement are not fully defined, companies are clearly managing their manufacturing more effectively, most likely by: improving their process design; resolving supply chain issues; using increased process monitoring and process analytical technology (PAT); gaining experience in preventing contamination; and otherwise learning from prior contamination episodes. Also, it is possible that "natural selection" is at work, with those companies experiencing more process failures also tending to have other problems contributing to failures.

PAT ADOPTION ON THE RISE

One potential reason for the decline in batch failure frequency is the industry's increased adoption of PAT. In many respects PAT is nothing new and involves no new specific requirements beyond those needed to support cGMP approval. PAT, Quality by Design (QbD) and other

SURVEY METHODOLOGY

The 2012 Ninth 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 302 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations (CMOs) in 29 countries. The methodology also included 185 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.

process measurement-based quality programs are efforts to better quantify, model and otherwise understand manufacturing processes.

Our study shows that continued improvements in sensors, probes and analytical equipment are facilitating process quantification and PAT. Thus, as bioprocessing becomes increasingly monitored by improved and new chemical, physical and microbiological detection methods and assays, including single-use sensors/probes, the resulting data will increasingly support and be used for mathematical modeling and risk analysis. Besides this technological progress promoting increased use of PAT or comparable quality programs, industry adoption will also likely increase as PAT is recognized as an effective method to increase productivity by reducing waste, improving yields, increasing automation and facilitating other cost-saving measures.

Our survey data supports this view. When we asked respondents about the quality initiatives they have implemented, just 21.3% cited PAT, the lowest of the 12 initiatives we identified, and far behind others such as QbD and risk analysis. This may not be surprising, given that adoption of PAT is voluntary. However, when we factor in respondents' plans for the next 12 months, the story changes. Indeed, 29.3% of respondents plan to use PAT in the next year, the highest proportion of any of the initiatives, and up from 16.1% who responded that way last year. This puts PAT adoption on par with process modeling (52% using or planning) and knowledge management (50.6%), and ahead of other initiatives such as multivariate data analysis, factorial testing of critical process parameters, and stage gate and in-line product reviews.

Increased use of PAT may also be owing to the lessening burden presented by various hurdles to implementation. When we asked respondents about the most significant hurdles in implementing PAT, we found that, in general, most factors are on a multi-year decline. For example, the most common factor identified as significant or very significant, "time required to implement," was cited this year by just under three-quarters of respondents, down from 79.5% in 2009.

REGULATORY REQUIREMENTS MORE OF A VENDOR PROBLEM

Regulatory issues remain a concern for PAT adoption, and they're also a key problem when looking at quality control in supply chain management. With PAT adoption increasing, and the frequency of batch failures decreasing, we examined what quality problems can be traced to vendors. In keeping with the positive findings from above, we find that overall, vendor problems are declining.

In fact, the only area in which significantly more respondents this year saw a problem was in vendors' inexperience with industry's regulatory requirements. This year, this problem was noted by 31.3% of our respondents, up from 28.1% last year, and halting a 4-year downward trend. This may reflect an increased view of the importance of regulatory factors and the perception and need to understand requirements.

Vendors are taking note of this issue, too. When we asked 185 suppliers to tell us the areas in which they perceive their clients are demanding additional support, 30.5% indicated better regulatory compliance, ranking this area higher than others such as lower prices (29.3%), better quality product offerings and better IP protection.

On the whole, though, most of the other quality issues traced to vendors by biomanufacturers have declined in importance. This year, as they did last year, respondents indicated that the key problem from vendors involves making promises they cannot keep (41.3%). (See Figure 2.) Even so, the proportion citing this has fallen relatively significantly from last year, when it stood at 49.1%. Other problems that have seen significant drops include poor quality of products (just 27.5% this year, as compared to 45.6% last year and a 5-year high of 53.8% in 2010), and poor quality of service (26.3% this year compared to 34.2% last year and a 5-year high of 45.8% in 2009).

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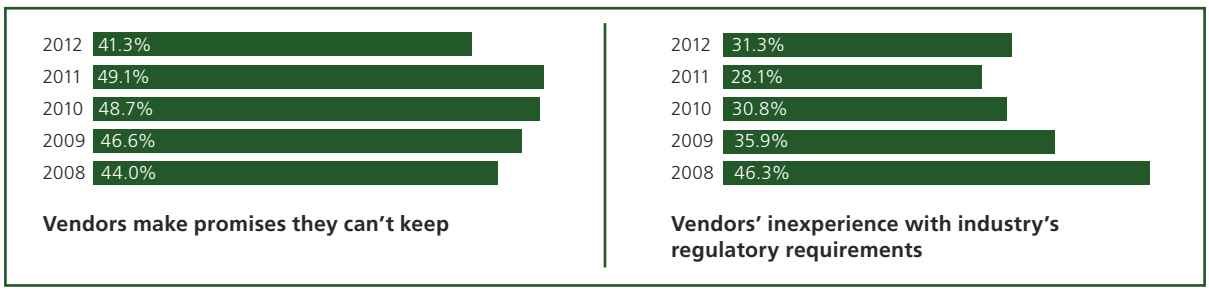

Figure 2. Selected Quality Problems Traced to Vendors, 2008-2012

GLOBAL QUALITY SUPPLY MANAGEMENT

The declining significance of problems traced to vendors might be a reflection of increased auditing that manufacturers are undertaking in the supply chain. We separately asked respondents to identify what, in the past 12 months, their organization has done to assure consistent quality in raw materials and ingredient supply. We found that a majority (51.4%) audited their suppliers more frequently, a relatively significant jump from 45.2% last year who were more frequently auditing suppliers. The proportion of respondents implementing more dual-sourcing also increased, from 39.4% last year to 45.9% this year.

Some factors dropped on a year-over-year basis. For example, the proportion of respondents who said that they audited secondary suppliers (those supplying their suppliers) fell from 49% to 40.5%, while this year only 36.5% implemented more comprehensive audits, down from 45.2% last year.

Even so, on a number of counts, we found that biomanufacturers are adopting more comprehensive quality supply management: More have developed new, more rigorous tests for incoming raw materials and supplies, while almost one-quarter have increased the volume of testing of incoming raw materials and supplies.

Comparing responses from biotherapeutic developers and CMOs yields some interesting divergences. CMOs, at a rate dramatically higher than biomanufacturers, are auditing their suppliers more frequently and implementing more dual-sourcing. They are also more likely to be verifying vendors' certificates of analysis, and specifically identifying secondary suppliers.

By contrast, biomanufacturers appear to be much more active than CMOs in demanding that their suppliers demonstrate higher levels of GMP/GLP compliance, implementing more comprehensive audits, verifying the origin of individual ingredients more carefully and holding more frequent meetings with vendors.

We find a divergence in actions on a geographic basis, too. U.S. respondents are for the most part more active than their Western European counterparts in quality supply management. Some of the larger disparities we found were in: Implementing more dual-sourcing (61.1% of U.S. biomanufacturers vs. 36% of Western European respondents); and Auditing more suppliers, including secondary suppliers (52.8% U.S. vs. 28% W. Europe).

OPTIMISTIC PICTURE

All told, our data paints a fairly optimistic picture. The frequency of batch failures is down to the lowest point in five years, and biomanufacturers are stepping up their supply chain quality control while complaining less of problems that can be traced to those vendors.

Despite its promise, PAT implementation remains slow and uneven, leading some to ask when this initiative will achieve its promise. Our data signals that perhaps the industry is finally ready to move to mainstream adoption of PAT. While intentions to implement may have outstripped reality in previous year, with improving economic situations and increased budgets, this may be changing. The success of PAT and QbD applications in pharmaceuticals will depend on better analytics, allowing biomanufacturers to make a strong business case for using these tools.

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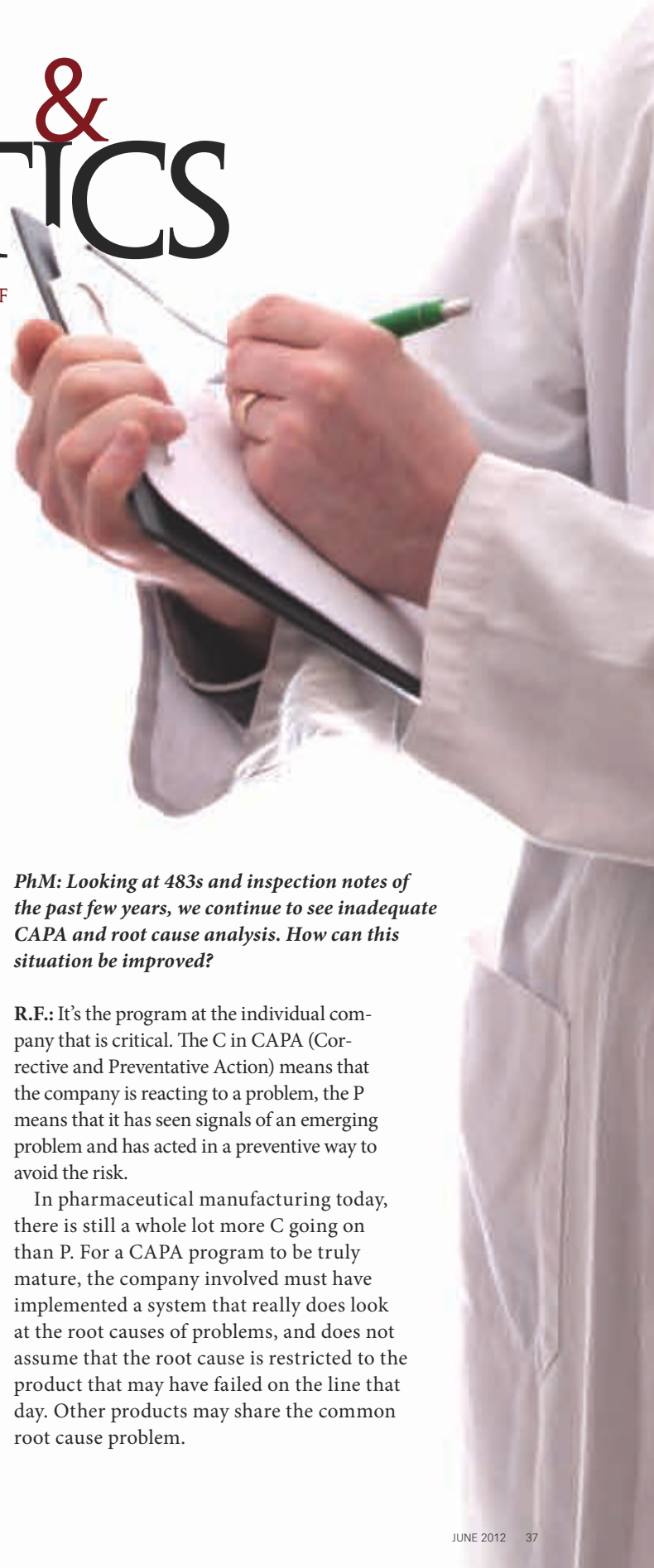
cGMPS & STATISTICS

BY AGNES SHANLEY, EDITOR IN CHIEF

FDA's Rick Friedman and Karthik Iyer explain why some manufacturers need to get a better grip on GMP-related statistics.



STATISTICS ARE critical to the pharmaceutical industry, from clinical operations through manufacturing. However, clinical and manufacturing statistics represent entirely different worlds. Where they might be well staffed on the clinical side, some pharmaceutical companies today aren't hiring qualified staff to analyze operations data, resulting in misapplied tools, inadequate CAPAs and superficial root cause analysis, all of which lead to financial loss and noncompliance.

Few people have analyzed these trends more closely than staffers at FDA's Office of Compliance, which must examine problem cases where inspectors have found inadequate compliance with CGMP.

In a recent interview, Rick Friedman, Associate Director, and Karthik Iyer, statistician and Senior Policy Advisor at CDER's Office of Manufacturing and Product Quality, now part of FDA's Compliance super office, discussed problem areas and areas where pharma might learn from the way other industries use statistics.

Representative of a new breed of regulatory professional at FDA, Iyer, who has been with the Agency for two years, has a B.S. in chemical engineering and an MBA, is certified by the American Society of Quality as a Quality Engineer and Six Sigma Black Belt, and spent over 11 years in the chemicals, refining and consumer products industries.

These industries, he says, use standardized methods to analyze root cause and have an understanding of the cost of poor quality. Below is an excerpt from that interview. (For more, visit PharmaManufacturing.com.)

PhM: Looking at 483s and inspection notes of the past few years, we continue to see inadequate CAPA and root cause analysis. How can this situation be improved?

R.F.: It's the program at the individual company that is critical. The C in CAPA (Corrective and Preventative Action) means that the company is reacting to a problem, the P means that it has seen signals of an emerging problem and has acted in a preventive way to avoid the risk.

In pharmaceutical manufacturing today, there is still a whole lot more C going on than P. For a CAPA program to be truly mature, the company involved must have implemented a system that really does look at the root causes of problems, and does not assume that the root cause is restricted to the product that may have failed on the line that day. Other products may share the common root cause problem.

Even though industry professionals know what CAPA is, generally, its practitioners within individual companies are not always the more experienced quality and production people, and in some cases, they're not always scientifically qualified to get to the true root cause of failures. As a result, some investigations end up being superficial and problems remain there, latently, until they show up later as causes of excessive variability, further batch failures, unexpected delays or shortages, all of which lead to financial losses.

[Philip B.] Crosby is famous for saying that quality is free. This is because a QA-oriented system allows an organization to prevent problems that are often very costly. If you're merely reacting, you can't assure the two essential objectives of any manufacturing operation: consistent product quality and customer supply.

PhM: Are there any lessons in determining root cause that pharma could learn from the petroleum and chemicals industries?

K.I.: Basic unit operations in the refining and chemicals industries have remained virtually unchanged since the 1920s and 1930s. In these industries, which use and produce dangerous chemicals, improvements have focused primarily on worker safety, with OSHA putting a microscope on chemical and refinery workplace safety practices, and EPA looking closely at environmental safety practices. Because they are also highly competitive commodity markets, product quality also became a key differentiator.

In petrochemicals and chemicals, safety concepts combined with the quality concepts advanced by Deming and Juran and merged into one, so the concept of CAPA is more robust in those industries. When chemical and petrochemical companies do an investigation, they use the same approach to determine the root causes of safety and quality problems, resulting in fairly robust processes. No matter what type of incident is reported to EPA and OSHA, regulators look to see whether a formal process has been set up or whether a proven methodology is being used. For example, two companies that I used to work for used a detailed investigative methodology that a third party private company created but a lot of chemical and petroleum companies use. The software package included a system to analyze root cause, offering structured methodology that is consistent, standardized, and calibrated across industries. So proven standardized root cause analysis methods do exist for manufacturing.

> In the end, any tool must be chosen with fitness of purpose in mind.
>
> **KARTHIK IYER**

R.F.: In this case, regulatory attention from EPA and OSHA helped accelerate the realization by petrochemical and chemical companies that improving root cause analysis was important for both safety and business reasons. For the drug industry today, a credible surveillance and enforcement presence that focuses on the effectiveness of a company's systems to analyze and resolve manufacturing problems has never been more critical to effectively regulate in a complex global environment..

PhM: Why does it seem that established practice in pharma has veered so far from the code of regulations? For instance, the GMP code requires statistically relevant sampling and never indicates that validation is somehow a three batch closed-end exercise.

K.I.: There are indications in our review of cases and FDA 483 trends that cause us some concern, although we (CDER Office of Compliance) do tend to review issues when there are adverse findings, and those practices are not necessarily representative of the whole industry.

R.F.: We have found that some firms have not sufficiently incorporated the basic staples of monitoring manufacturing operations that have been standard procedure for decades across the industries. This includes SPC and monitoring suitability of incoming raw materials.

The GMP regulations, as you mention, also reflect these basic expectations. But less regulated industries know they must do SPC and they must have reliable materials to maintain a consistent process. That's how they ensure manufacturing dependability and thrive as a business. They always want to improve because they want a competitive edge. In any industry, quality and compliance can be significantly impacted by the organization's commitment to robust product and process design, continual learning and

improvement, and sound lifecycle decision-making by including the needed subject matter experts.

K.I.: In the cases that come to us, we often see situations where qualified personnel are not there to analyze manufacturing statistics as the regulations require. There may be qualified people in the company, but they are not supporting that particular plant, or analyzing manufacturing data using the correct statistical tools.

R.F.: You need qualified people to perform this evaluation. How can you determine what a statistically relevant sample is if you're not trained in that area? These kind of specialized staff also are needed when evaluating the state of process control. So bringing the right people to bear in interpreting process trends and making relevant decisions is extremely important.

PhM: In the interests of process understanding, and better root cause analyses, wouldn't it be better to have QC and manufacturing more closely connected? What's FDA's position current on the practice of integrating some manufacturing and quality functions?

R.F.: In most device and drug industry, FDA expects an independence of quality from manufacturing units. It's a venerable concept that is rooted in many years of manufacturing experience that also goes across industries. For example, there has to be a final authority that determines whether the quality of a product lot is acceptable, and that's the quality department's duty. The EU and Japan have similar requirements.

When I'd go on plant inspections, at times the company's quality department would report to the operations vice president or plant manager. When quality is subordinate to operations, even if it is given final decision-making authority on paper, in reality I found it had to carefully pick and choose which of the significant product quality issues it pursued and corrections were frequently either slow or not instituted.

However, at some companies today, there appears to be a wall up between Operations and Quality Assurance. This creates a situation that is almost as problematic as having the two operations fully merged.

At recent ICH Q10 conferences that FDA co-chaired with the EU, we talked about whether quality and production work mostly as partners on a day-to-day

basis. Fundamentally, you can't achieve quality simply because the QA unit is there at the plant every day, but instead because the production unit builds quality into everyday operations, and the engineers, product development and R&D people build it into the design to begin with. But while that is a major part of the picture of how a state of control is achieved, there is much more.

The other part is where we see deviations or atypical events. And there must be strong commitment from the company's top management—irrespective of department —to document and investigate these. There's always something unexpected that can come up, there can be a lot of undetected variability in materials and operations. For instance, when equipment gets older, the equipment may actually fall out of control before the recalibration date. Or sometimes a significant, environmental or operator anomaly impacts the product but is not detected during the operation—so you hopefully catch the problem in the final QC test.

A production department is charged with supplying products to customers in a timely fashion and annual performance reviews are frequently based on the volume they get out the door. Perhaps because of this tension between timeliness and quality, I have seen cases where problems are, at least temporarily, swept under the rug. In contrast, an independent and empowered quality department should be able to put on the brakes, say "Don't ship this lot yet," and prevent substandard product from being released. The Quality department has the authority to make these final decisions and oversee the investigation. But production must nonetheless have a significant degree of ownership in the investigation, ideally including playing a critical role in identifying the root cause and leading implementation of an effective solution.

> Integration with Operations is needed, but Quality has to make the final call.
>
> **RICK FRIEDMAN**

So we hear from industry that a strong and routine partnership has been shown to be the most effective model for identifying and resolving problems. This partnership is characteristic of a healthy quality system. In the less integrated and proactive organizations, operations staff are not given incentives to document deviations, and some managers thus want to minimize documentation that QA would require. If you don't document deviations on an early basis, you can't address the problems that are starting to snowball, before you have the failure. So, ultimately, it's good medicine but I have heard that operations leaders may not always understand that at some companies.

PhM: But then QA might be missing operations data that's critical to process understanding. What should they do?

R.F.: Production management must believe in quality first, and quality departments should understand that they cannot do their jobs optimally, or properly investigate the root cause of quality failures, unless they have a good relationship with production. This organizational culture starts at the top of the company. Issues need to be surfaced and collaborative problem solving is critical. This is where the industry has started to mature. Today, there is more of a realization that integration between the two functions is needed, but Quality has to make the final call.

PhM: Is the pharma industry underutilizing statistical tools or using them incorrectly?

K.I.: From our perspective, we cannot make a statement that the entire industry is underutilizing statistical tools, but based on what we see at the Office of Compliance, there are four key areas where we find problems: product sampling, process capability, statistical process control, and analysis of variance.

PhM: Can analysis of out of trend data in Annual Product Reports aid process understanding and control?

R.F.: It's all about the P in CAPA. If a firm doesn't have a program in place to look for out of trend conditions, then they don't have an effective prevention program in place. ICH Q10 calls this the "process performance and product quality monitoring system." This guideline was written by EU, US and Japanese industry and regulators, and included this term to underscore the importance of monitoring daily operations and batch to batch performance to detect

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when processes start to drift. It's not only APR data that tell whether a process is about to fall out of control, but day to day monitoring of near term trends.

K.I.: Philosophically, firms agree that it is important to manage trends, and they have the right intent but in many of the cases we've seen, the wrong tools have been applied. For instance, we've seen cases where companies talk about an SPC chart. These charts can be set up for two different types of activities: a variable chart, for example, might be where you're measuring something continuous like tablet weight, so you might go from 2 micrograms to 2.1, to 2.3. The alternative is an attribute chart, in which you monitor the number of defects on a tablet. In this case, you are counting, for example, 1 or 2 blemishes per tablet or other defects. These are two different types of charts, and you can't use them interchangeably or compare one to the other. If you set up a chart that's counting and compare it to a continuous chart, you'll be comparing apples to oranges and you won't detect whether defect count has gone up or down. This goes back to the importance of having qualified personnel doing this work.
We've also seen cases where firms have applied specification limits as control limits on a control chart. That's a big no-no. The whole point of a control chart is to give you a signal of where you're heading toward a point where there's some probability of making offspec products.

R.F.: That's why there are usually inner control and outer control limits that are still within the specification. The cumulative variability of each operation in a process can, if it's not controlled tightly enough, exceed specification limit.

K.I.: Again, this doesn't reflect the actions of all drug companies. We don't want to indict the whole industry, but misunderstanding of cGMP-related statistics is a significant enough issue, suggesting that there is a lot of work to be done.

The firm may be making good product, but if they're using the wrong tool they might change parameters and then start manufacturing bad product. In the end, any tool must be chosen with fitness of purpose in mind.

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The Future? Let's Get Pumped Up

To survive, Steven Burrill tells Big Pharma, ignore the "gravel in the road" and embrace the disruption.

BY PAUL THOMAS, SENIOR EDITOR

AT A recent event in Chicago, the keynote speaker was introduced as the "Michael Jordan of biotechnology." In other words, the emcee said, there will never be another quite like him. The speaker being referenced was Steven Burrill, head of Burrill & Company, whose annual reports on the state of the biopharma industry have been best-sellers for more than 25 years.

Hyperbole, for sure, but Burrill's status as a biotech visionary is unquestioned and his keynote was befitting of the "guru" label often applied to him. His pronouncements and predictions were bold and sweeping.

All of the world's biggest problems—from climate change to energy sufficiency to food security—have biotech as their solution, Burrill began. "One thousand years from now, we'll look back and see this as mankind's greatest moment . . . Shame on us if we don't take advantage of this opportunity."

Burrill zeroed in on today's health care system, which he believes is essentially the same as it was 2,000 years ago. It is "episodic" in that we wait for disease to occur and then wait for doctors (today's "tribal healers") to tell us what to do. Too often the advice is wrong and the care doesn't work.

All that will change soon—in fact, by 2020, Burrill said. In a mere eight years, we'll move from a dysfunctional health care system to one that treats a "well population" more effectively.

This change won't come easily because doctors, pharmaceutical companies and other main actors within the traditional health care system "aren't going to vote themselves off the island voluntarily." But pharma will play a role, and is changing, albeit begrudgingly, says Burrill. The pressure on Big Pharma companies is only intensifying, he says. "It used to cost $200 million and seven years to get a drug to market," he said. "Now it takes twice as long and seven times the cost." This has resulted in layoffs and "massive dislocations," especially in R&D.

"Oceanliners called big companies are trying to move from a vertical orientation to a horizontal one and renting rather than owning everything." If they can't change fast enough, they'll become irrelevant.

"Guys like Jeff Kindler at Pfizer tried to take some of these oceanliners and turn them around, but how do they do that?" he asked. They are investing in areas such as over-the-counter drugs, generics, emerging market branded generics, biosimilars, licensing, and so forth. As a result, "Big Pharma doesn't look anything like it used to look like."

Ultimately, pharma's fate lies in its ability to truly innovate despite significantly greater barriers than in the past. One such roadblock, he noted, is FDA. "My friend [FDA Commissioner] Peggy Hamburg called me the other day and said, 'I have a problem.' And I said, 'I know: Everybody is trying to avoid you and get into other markets in the world and come to you later.' We have a system where FDA is going from being the gold standard in the world to becoming a late adopter."

"WE ALL DRANK THE KOOLAID THAT PERSONALIZED MEDICINE WAS GOING TO BE THE SAVIOR OF OUR INDUSTRY."

Despite its unfulfilled promises, personalized medicine still provides the greatest hope for change and for Big Pharma to rediscover success. "We all drank the koolaid that personalized medicine was going to be the savior of our industry," Burrill said. "We were going to have designer drugs overnight."

This hasn't happened, of course. "But if you stand back for a minute," he said, "we've moved from a uniformity of disease to understanding the vast variability of patients" and moving from an "episodic sickness-care" world to one of preemptive and increasingly personalized medicine.

"It's not a personalized medicine problem" to date, he added. "It's spurious science. There's gravel in the road, but don't underestimate that we're going to improve our knowledge and information." When that happens, personalized medicine will truly take root.

Ever the optimist, Burrill made sure to infuse the audience with as much of a *carpe-diem* attitude as he could. "This is an extraordinarily opportunistic time," he said. "You ought to be pumped up about it."

Will everything really change for pharma and healthcare by 2020? Doubtful. Burrill's full of a lot of bluster, to be sure. But that morning in Chicago he earned his speaker's fee. It felt good for a few hours to be pumped up about the future.

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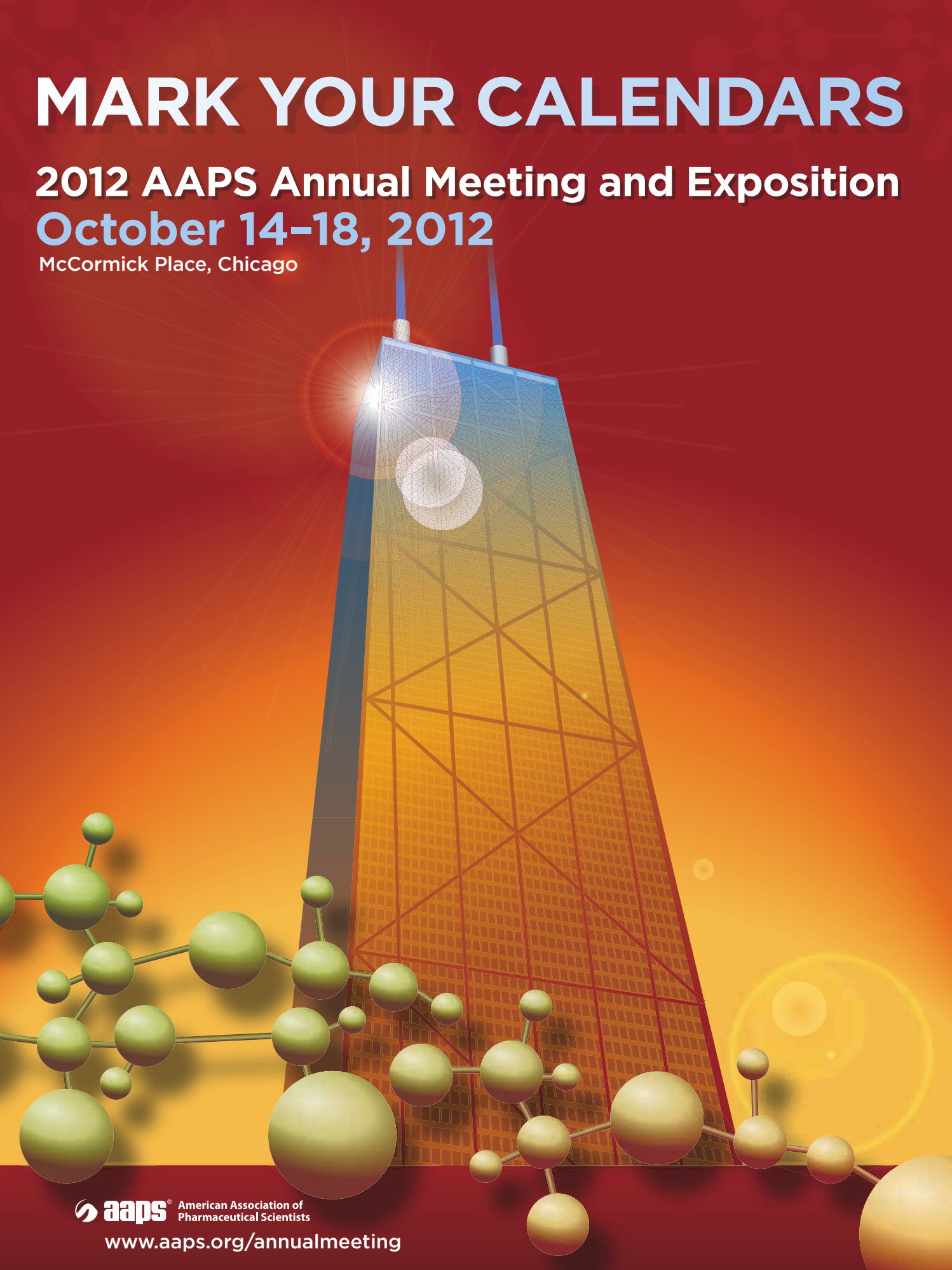

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Quick Contaminant Detection IN FILTERABLE BIOPRODUCTS

A new method allows microbial detection to take place from two to five times faster than with traditional methods

By Anne Baumstummler, Renaud Chollet, Hervé Meder, Céline Rofel, Adrien Venchiarutti and Sébastien Ribault, Millipore SAS

TESTING FOR microbial contamination in production processes is necessary to monitor product quality. However, traditional microbiological methods are slow and require several days to obtain results.

The microcolonies fluorescent staining method (MFSM; Milliflex Quantum, EMD Millipore) described in this article enables detection of microbial contaminants two to five times faster than traditional methods. This rapid microbiological method combines membrane filtration with a universal, enzymatic fluorescent staining of viable and culturable microorganisms. The procedure is nondestructive, allowing downstream specific identification following a positive result. MFSM consists of three steps:

- Sample filtration;
- A brief incubation on media to yield microcolonies;
- Staining of microorganisms and counting of microcolonies with a light-emitting diode (LED) system.

Microorganisms are labeled directly on the filter with a non-fluorescent substrate that is cleaved by intracellular microbial enzymes. Only metabolically active microorganisms with membrane integrity that retain the fluorescent product are stained. The fluorogenic substrate used is a non–fluorescent viability marker that is cleaved

STERILE WATER ARTIFICIALLY CONTAMINATED WITH ATCC OR ENVIRONMENTAL GERMS

MICROORGANISMS		INCUBATION CONDITION	INCUBATION TIME REQUIRED FOR MILLIFLEX QUANTUM DETECTION
Escherichia coli	ATCC 8739	TSA 32.5 +/- 2.5°C	8 hours
Pseudomonas aeruginosa	ATCC 9027		12 hours
Bacillus subtilis	ATCC 6633		8 hours
Staphylococcus aureus	ATCC 6538		12 hours
Candida albicans	ATCC 10231	SDA 22.5 +/- 2.5°C	24 hours
Aspergillus brasiliensis	ATCC 16404		30 hours
Caulobacter spp.	Environmental strains	R2A 32.5 +/- 2.5°C	30 hours
Micrococcus lylae			16 hours
Ralstonia spp.			24 hours

Table 1. Incubation conditions and time required for detection using MFSM.

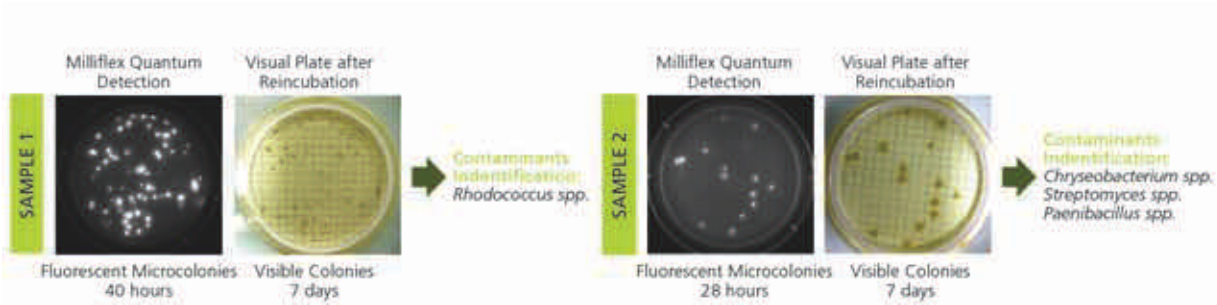

Figure 1. In-process, non-sterile water samples from pharmaceutical plants.

by nonspecific intracellular enzymes resulting in a fluorescent product. Accumulation of fluorescence inside cells is an indicator of microbial metabolism activity and membrane integrity. The dye is diluted in a staining buffer allowing cell membrane permeabilization and thus dye introduction into cells.

In the study summarized here, we examined MFSM and compared it to the traditional analysis method, epifluorescence microscopy (EM), to detect *Bacillus cereus*, *Staphylococcus epidermidis* and *Propionibacterium acnes* in CHO cell cultures.

We filtered sterile water artificially contaminated with ATCC or environmental germs or in-process non-sterile water samples from pharmaceutical plants over mixed cellulose ester membranes. After incubation on Milliflex cassettes prefilled with Tryptic Soy Agar (TSA), R2A agar at 32.5 ± 2.5 °C, or Sabouraud Dextrose Agar (SDA) at 22.5 ± 2.5 °C, the membranes were transferred onto a cellulose pad soaked with staining solution and incubated for 30 minutes at 32.5 ± 2.5 °C. Fluorescent microcolonies were counted using a specific LED system. After detection, membranes were reincubated on media for traditional plate count (viability assay) and contaminants identification using the MicroSEQ platform (Applied Biosystems). The compendial method was performed in parallel, and a plate count was done after a seven-day incubation. Table 1 summarizes details. Figure 2 shows results from the in-process, non-sterile water samples from pharmaceutical plants.

EM was performed with CHO cell culture at 2.5 x 10^6 cells ml^{-1}. Contaminated cell culture samples, spiked, and sterile CHO medium samples were treated with mammalian cell lysis solution and filtered through black polycarbonate filters (25 mm diameter, 0.22 µm pore size; EMD Millipore). Membranes were transferred onto cellulose absorbent pads (25 mm diameter; EMD Millipore) soaked with 500 µl of staining solution (200 µg ml^{-1} 5(6)-carboxyfluorescein diacetate, 0.1% n-Octyl β-D-glucopyranoside, 0.5% sodium hexametaphosphate, 50 mmol l^{-1} sodium acetate,

1.25 mol l^{-1} Lithium chloride and 10 mmol l^{-1} Rubidium chloride in water at pH 6.2) and incubated at 37°C for 30 minutes. Polycarbonate filters were mounted on a black mixed cellulose ester filter placed on a microscope glass slide, wetted with saline solution and observed under an epifluorescence microscope.

For MFSM, contaminated cell culture samples, spiked, and sterile CHO medium samples were treated with mammalian cell lysis solution and filtered through mixed cellulose ester membranes (Milliflex, 47 mm diameter, 0.45 µm pore size) in 0.9% NaCl water. After filtration, membranes were placed onto Trypticase Soy Agar plates and incubated at 37°C in aerobic conditions for *B. cereus* and *S. epidermidis* and in anaerobic conditions for *P. acnes*.

After the incubation period, filters were placed onto cellulose absorbant pads soaked with 2 ml of the staining solution described above. After a 30-minute incubation at 37 °C, filters were inspected with an LED system. Membranes were reincubated on TSA plates at 37 °C to allow growth and viability assessment.

The compendial method was performed in parallel and included filtration of samples through the same mixed cellulose ester membranes and incubation on TSA plates at 37 °C for visual counting of colony forming units (CFU). Fluorescence and CFU counts obtained after reincubation were compared to the compendial method. The fluorescence recovery and viability recovery parameters were calculated as shown in Equations 1 and 2 (above right).

CHO cell cultures ranging from $4.2x10^6$ to $5.2x10^6$ cells ml^{-1} were spiked with each of the three microorganisms and analyzed with MFSM using the incubation times determined previously.

Equations 1 and 2

$$\text{Fluorescence recovery (\%)} = \frac{\text{Fluorescence count}}{\text{Compendial method count}} \times 100$$

$$\text{Viability recovery (\%)} = \frac{\text{CFU count after reincubation}}{\text{Compendial method count}} \times 100$$

Fluorescence recoveries conformed to the acceptance criteria, showing that the MFSM gave comparable results to the compendial method.

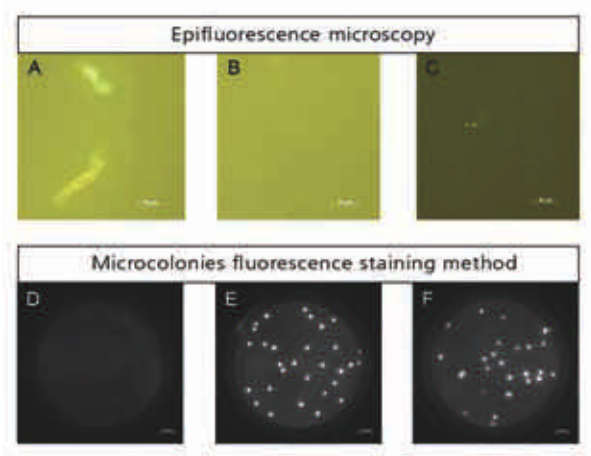

Figure 2. Detection of ***Bacillus cereus*** with epifluorescence microscopy and MFSM. For the latter, membranes were incubated on TSA plates during eight hours at 37°C before staining and reading. Non-spiked CHO cells treated with the mammalian cell lysis solution (A and D); CHO cells spiked with ***B. cereus*** and treated with mammalian cell lysis solution (B and E), CHO medium spiked with ***B. cereus*** (C and F). (Note that for epifluorescence microscopy, the picture corresponds to a 10-fold higher contamination level.)

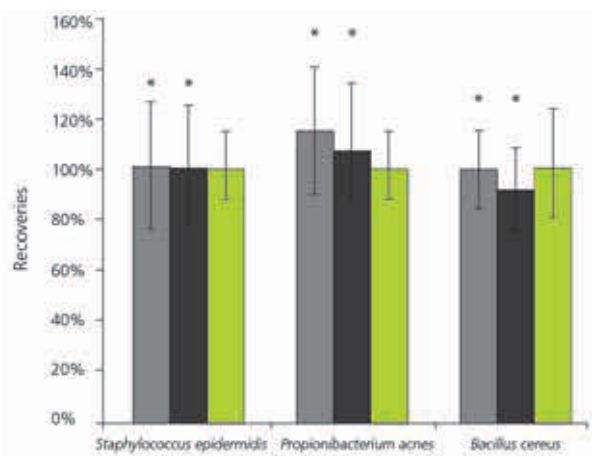

Figure 3. Detection of ***Staphylococcus epidermidis***, ***Propionibacterium acnes*** and ***Bacillus cereus*** in CHO cells cultures with the MFSM: comparison between fluorescence and viability recoveries and compendial method. Mean of three independent tests (five replicates per test). Light gray = fluorescence recovery, dark gray = viability recovery and green = compendial method. *Not statistically different from compendial method counts with P values of 0.841, 0.844, 0.068, 0.159, 0.904 and 0.198 from left to right (t-test, $P > 0.05$, n=15).

Stained membranes were reincubated on TSA plates and the viability recoveries also conformed to the acceptance criteria. Results of the three assays were repeatable.

FILTERABILITY AND BACKGROUND

The sample volume filtered for epifluorescence microscopy varied between 0.5 ml to 2.5 ml; even if the same culture was split onto different membranes, the filtered volume was variable. The maximal filtered volume, corresponding to approximately 1.3 x10^6 CHO cells, can be considered as the maximal capacity of the polycarbonate membrane before clogging. The mixed cellulose ester membrane allowed consistent filtration of the entire treated sample volume very quickly. The filtration capacity of the polycarbonate membrane appeared to be 50 to 90% lower than the cellulose membrane.

With epifluorescence microscopy, non-spiked treated CHO cells yielded a great deal of fluorescent debris and a very high background (Figure 2A), which interferes with the detection of, for example, *B. cereus* (Figure 2B). Since observation was difficult in the presence of cells, *B. cereus* was spiked in CHO medium. The fluorescent background was removed; but it was still difficult to observe bacteria on the polycarbonate filter. The detection of the microorganisms was only possible when increasing the number of contaminants retained on the filter by 10-fold (Figure 2C). Microorganisms spiked in the mammalian cell culture were easily detected with the MFSM, without any background or media interference (Figure 2D-F). Background noise was minimized by lysing the CHO cells before the filtration using the mammalian cell lysis solution; this buffer eliminates CHO cells while minimizing the impact on microorganisms. Similar results were obtained for both methods with *S. epidermidis* and *P. acnes* (data not shown). Figure 3 shows the mean of the three fluorescence and viability recoveries for each microorganism compared to traditional recovery. For all three microorganisms, results obtained with the MFSM were not statistically different from the traditional method. After reincubation, membranes were used for successful identification with API strips (bioMérieux), MicroSeq platform (Applied Biosystems) and Vitek system (bioMérieux). This study suggests that MFSM can consistently be applied to cell culture samples in one fifth to one half the time required for traditional approaches. At the same time, it is non-destructive, and thus compatible with downstream identification.

ABOUT THE AUTHORS

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Thinking Too Linearly

The idea that "the product is the process and the process is the product" can either result in sameness, or true control.

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

BIOPHARMACEUTICALS ARE now center stage and a hotbed of activity in the pharmaceutical industry. For mature, small-molecule-dominated companies dealing with the patent cliff, biopharma is a new lifeline. Many generic companies are investing in and planning to make biosimilars (Article p. 23).

Biotech advances made biopharmaceutical manufacturing possible. But, where innovation has been seen in screening and other technologies designed to identify chemical entities to treat disease, little has changed in the way that biopharmaceuticals are manufactured. A biopharmaceutical manufacturing process must be extremely responsive to the nature of proteins. Its inefficiencies are in yield, the high cost of manufacturing and downstream processing.

Innovation in vaccine manufacture has stemmed from knowledge gained from the therapeutic protein industry, but some of the myths and "best practices" of vaccines have crept into the manufacture of proteins, the main one being the idea that "the product is the process and the process is the product."

Rather than resulting in feedback control, this phrase has usually delivered process sameness. Even pharmaceutical Quality by Design failed to dislodge this mindset. The case studies and examples being presented or published rely on the tried and tested rather than provide a solid basis for process control.

Biopharmaceuticals' challenges and opportunities are somewhat different from those of small-molecule manufacturing. Biosimilar guidances are sensible and not too daunting; new biological entities are numerous; the products are very profitable even when the processes not very efficient and yields low. Is this scenario all that different from the small-molecule sector, where profit margins concealed inefficiencies? Shouldn't its past be a warning for biopharm's future?

Major challenges are already here, evidenced by a burgeoning number of biosimilar manufacturers. The impact of regulations on startup costs will force these new companies to innovate. Those that survive will be lean and mean. Consider Samsung, which plans to launch biosimilars by 2015, offering generics at half the current prices of name-brand biopharmaceuticals.

The manufacturing challenges of yield and downstream processing are still with us. The old way of dealing with them has been to scale up. The clever way of dealing with yield is to scale down.

Our industry has been very shy about embracing change, justifying its response as concern about regulations. Regulations per se are not the cause, but enforcing adherence to rigid practices is. Where is the manufacturing innovation in biopharmaceuticals? For example, the low-risk flu vaccine lends itself to continuous manufacturing, yet bio-continuous manufacturing does not feature in any discussion. Why?

SHOULDN'T SMALL-MOLECULE PHARMA'S PAST BE A WARNING FOR BIOPHARM'S FUTURE?

I believe we fail to develop efficient processes because we are not willing to deviate from our prior knowledge, from a rigidly defined and enforced development process, that unravels a product rather than delivers what has been desired and planned for.

In the *Harvard Business Review* recently, Tim Brown wrote about an alternative to the tried-and-true process that could invigorate pharmaceutical development. "The design process is best described metaphorically as a system of spaces rather than a predefined series of orderly steps. The spaces demarcate different sorts of related activities that, together, form the continuum of innovation. Design thinking can feel chaotic to those experiencing it for the first time. But over the life of a project, participants come to see . . . that the process makes sense and achieves results, even though its architecture differs from the linear, milestone-based processes typical of other kinds of business activities."

He goes on that design projects must ultimately pass through three spaces: inspiration, ideation, and implementation. For biopharma, the inspiration is clearly there and many companies are already in the ideation stage. Will they get to the implementation stage? Can we stop thinking so linearly, and save biopharm from the lackluster fate of small-molecule manufacturing?

SOURCING SOLUTIONS FOR ENVIRONMENTAL MONITORING

Ask the Right Questions

Accurate answers to the wrong questions pose risks and unnecessarily drive up costs.

IT SIMPLY makes sense for drug manufacturers to invest in technology to monitor labs, chambers, cleanrooms, warehouses, and other critical spaces in their facilities. But with no shortage of suppliers offering systems for tracking temperature, humidity and other key parameters, how do you know where to turn and who to trust? Which technologies and environmental monitoring systems (EMS) will meet your business and quality needs now and well into the future? This article outlines an approach for sourcing an effective real-time environmental monitoring solution—one that will meet your requirements near- and long-term.

By Ken Appel, Independent Life Science Consultant

WHERE TO START: WHO ARE YOUR CONSTITUENTS?

Start with a systematic approach that targets your priorities for meeting business, quality, and regulatory requirements. Seek council from throughout your organization. Chances are the solution will involve multiple responsibilities across your company, including quality assurance, facilities engineering, IT, operations, metrology, and purchasing. Including them in your project team from the start will pay off down the road.

DEFINE THE PROJECT

Using data gathered from all parties, categorize requirements based on the risk to the business and product quality as specified by the Quality Management System. The result should contain a set of minimum requirements and a group of others relative to their importance to the company and various departments. Once this is done, needs can be coalesced into a defined project. State the rationale for replacing or adding a new system and, at this point, refrain from specifying how to meet stated challenges.

DEVELOP A URS

While writing a User Requirement Specification (URS) is beyond the scope of this article, there are a few basic concepts to keep in mind. A URS should contain agreed-upon elements that will provide a consistent reference for vendors. It will document what you need the system to do. The project scope should have boundaries on the size of the facility, campus, or locations you want to monitor. The URS also needs to state the monitored environments such as warehouses, freezers, water quality systems and measured parameters such as temperature, humidity, pH, and conductivity. A supplier's approach may vary on the number of sensors, types of parameters and their locations. Clearly state your requirements. In fact, use the language of the FDA—it "must" or "shall" have (fill in the blank).

WHAT QUESTIONS SHOULD YOU ASK?

The evaluation process often works in stages, especially when there is insufficient information to distribute a request for proposal (RFP). To assist this process you can

send a request for information (RFI) to multiple suppliers. The questions below can serve as a template.

I. Questions about the Supplier's Business

Customer Depth

1. *How long has your company supplied environmental monitoring systems to GxP facilities?* If it is a new entrant to the market, you want to know it.
2. *How many of these systems have been installed to date and what percentage is GxP regulated installations?*
3. *Who are three customers in related organizations that can be contacted for evaluation purposes?* At a minimum, this lets you know that they have reference sites to visit.
4. *How does your company rate itself in terms of customer support?* This question tells you whether a supplier has a process for measuring customer satisfaction.

Business Depth

5. *What resources—dedicated, contracted, or both—are used to install, set up and validate the installation?*
6. *What maintenance capabilities does your company provide?* You want to know the basics if they provide warranty, repair, and calibration. (See system questions for details about support and calibration.)
7. *What training is available for users and administrators and what documentation is provided?*
8. *What are the responsibilities of the customer to prepare for installation?* The answer will provide insight into how organized the supplier is.

Quality Systems

9. *What quality systems and requirements documentation does your company employ to ensure continuous improvement (e.g. ISO, certifications, accreditations)?*
10. *What is considered a revision to the system and the typical release period for these revisions?* Too frequent updates may signal a problem in their understanding of market needs or can indicate quality problems.
11. *When was the last time your product development process or calibration lab was audited by a customer? How many times per year on average does this occur?*

II. Questions about the EMS

Infrastructure

1. *What is the range of sensor points that the platform can handle and what are the performance tradeoffs with increasing size?* This provides one indication that the system can conform to changing business needs. The system should scale from your initial project—50 sensors for example—to handle foreseeable growth.
2. *What connectivity options are available (wired and wireless 802.11 or 802.15)?* Depending on the type of facility, however, there may be occasion to mix hard wiring with wireless communications (WiFi or RF).
3. *How are data protected during a power failure, network interruption or both?* Missing data is a quality issue.

Alarming and Notification

4. *What is the flexibility for setting alarm limits, who can be notified, and by what means?*
5. *What notification is available during a power outage, network interruption, or both?* What happens when a freezer alarm triggers, for example?

Reporting

6. *How does the system generate reports, and who can create and receive them?*
7. *What types of reports are available and how are they customized?* Records should be available for different purposes and responsibilities. For example, a facility engineer may want a 6-month trend of data to develop a maintenance schedule for storage equipment.

Figure 1. A correctly sourced environmental monitoring system (EMS) provides the proper balance between quality, compliance and cost.

Computerized System Validation—Data Integrity

8. *How does the system ensure compliance with electronic records in terms of data alteration, unauthorized access and other data integrity measures?* No supplier can claim in advance the system is compliant since this can only occur when it is installed.
9. *What audit trail information does the system provide, how can it be sorted, and can the audit trail be deactivated?* Industry guidance recommends the system be incapable of disabling the audit trail.
10. *How is sensor (or instrument) calibration performed and what information is reported to prove traceability?*
11. *How is the system qualified?*

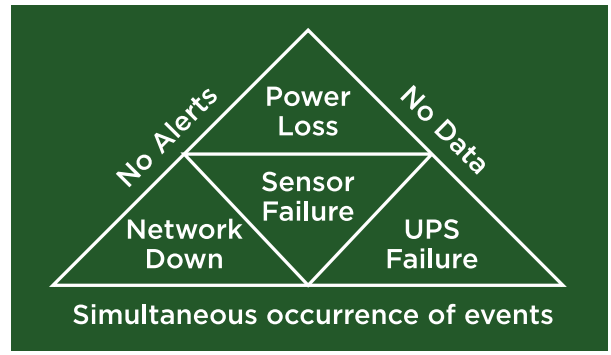

Figure 2. The perfect storm—concurrent failure of facilities and backup—can render even a "failsafe system" vulnerable to lost data or delayed alerts. Understanding these risks allows you to plan for contingencies.

Cost of Ownership

12. *What is the typical time and resource requirement for adding a sensor or moving it to another location?*
13. *What support services are available including typical response time when there is a problem?* Support services are like insurance. You don't necessarily want to use them but want answers when there is a problem.
14. *What mechanisms ensure that sensors or instruments maintain accuracy?* Investigate beyond the NIST certificate by understanding the supplier's measurement practices. A system with stable and repeatable measurements between calibration periods can provide payback.
15. *What options are available for recalibration?* Options can include on-site near sensors, in a calibration lab, performed by the customer or the supplier.

There are other questions you can ask about the finer details of system operation. Comfort level increases with seeing the real thing even after you have received a sales demonstration. When you reach a point of due diligence that satisfies your criteria, ask the supplier to ship a demo system. And be sure you have staff committed to using it. There is nothing that takes the place of hands-on experience by future operators of the system.

About the Author

Ken Appel has provided marketing and market development in human safety regulated industries for over 15 years. He is a contributor to the bio-pharmaceutical industry on topics such as computer system validation, chamber qualification, warehouse mapping, environmental monitoring, and cold chain good distribution practices, and is a member of ISPE and PDA. He holds a B.Sc. in Chemistry from the University of Massachusetts at Amherst.

MOTOR TRENDS

The latest on permanent magnet motors and other powerful trends in pharma.

By Paul Thomas, Senior Editor

Baldor's RPM AC, a salient pole permanent magnet (PM) rotor motor

SUPERIOR TECHNOLOGIES do not always win out. That's been the case with permanent magnet (PM) motors, which offer improved control and efficiency over traditional AC induction motors. PM motors are great for certain pharma needs, says John Malinowski, senior product manager at Baldor Electric Company—e.g., motors for cooling tower fans, or for variable torque-load pumps or fans that run 24/7 (see photo, right). Even slight boosts in efficiency can make for vast energy and cost savings over the long haul. Yet the trend towards PM motors has slowed, he notes. They rely upon rare-earth neodymium magnets, the market for which is primarily controlled by Chinese producers. Thus, the magnets are expensive.

"PM motors are not replacing AC induction motors for general purpose motors as had been expected," Malinowski says. "Some manufacturers are investigating redesign of PM motors using alternate material that is more readily available and at a more favorable cost. Unfortunately, the new materials may not have the same magnetic properties and could add additional steel and copper to the design and even reduce efficiency levels." Other "super premium" technologies have also been introduced that provide efficiency above that of the standard NEMA Premium, Malinowski says. Two such motors are synchronous reluctance and switched reluctance, which offer good efficiency (though not equal to that of PM motors) while not using magnets or copper in their rotors.

Will the magnet monopoly in China continue? China has raised its rare-earth magnet production quotas, which should help stabilize prices, Malinowski notes. And the U.S., Canada, Russia, and South Africa are beginning mining and material processing capabilities, so the next few years should see magnet prices come down.

The market for specialized motors for pharma and biopharma continues to grow. Shown here is the XP stainless steel washdown duty motor from Stainless Motors, Inc.

In the meantime, Malinowski reminds manufacturers seeking efficiency improvements to look beyond the motor. "It is easy for a user to simply replace an older inefficient motor with a same sized NEMA Premium efficient motor and gain 2-8% efficiency," he says. "It is not the best solution that would be available if the whole system were analyzed."

Higher efficiency speed reducers are one simple example of how to look at a mechanical component and raise system efficiency, he says. If a conveyer motor is driving through a high-reduction double work reducer, the reducer's efficiency may be as low as 50%. "Let's say that conveyor requires a 10 HP motor to provide enough torque for the load," Malinowski says. "If we were to switch to a high-efficiency helical or helical bevel reducer, that would have an efficiency in the mid-90's [%], the motor to drive the load could be reduced to a 5HP size, with a huge savings in energy use."

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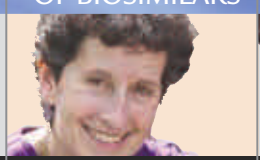

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Lead, Follow, or Get Out of the Way!

On LinkedIn, I was amazed to learn that QbD was to "become mandatory" in January. Did I miss the memo?

BY EMIL W. CIURCZAK, CONTRIBUTING EDITOR

LIKE MANY of you, I've become very active on LinkedIn discussion groups, and the "discussions" over process analytical technology (PAT) and pharmaceutical Quality by Design (QbD) continue to amaze me. In the eight years that the PAT Guidance has existed, we are still defining and dickering over what "is" is.

I wonder how many commentators on PAT have even read the guidance through, even once. From many of the negative comments I've seen, I'll assume the source is ignorance rather than disagreement of its tenets. (After all, as the old Latin phrase goes, people damn what they don't understand (*damnant quod non intellegunt*).

Another problem is that many respondents see QbD as being "the same as GMP." Of course, they *always* and *already* follow GMP so their problems are not problems at all, and all will be well.

Again, ancient Roman Tibullus had a saying for that, "Credulous hope supports our life, and always says that tomorrow will be better." (Or, if you prefer, *Credula vitam spes fovet et melius cras fore semper dicit.*)

QBD TO BECOME MANDATORY NEXT JANUARY?

Sometimes one learns of amazing and surprising things on the Web. On the USP Discussion Group, I was surprised to learn that QbD will become law in January 2013. Did I miss that memo?

The proof was a YouTube videotaped interview with Dr. Lawrence Yu of the OGD/FDA, in which he explained that some examples will be published online to help generic manufacturers follow QbD. (Yes, I listened to the whole thing).

With input from the public, Dr. Yu expects to require some QbD features in submissions in 2013: i.e., target product profile (QTPP), product design and understanding, process design and understanding, control strategy, including justification. What will be optional will be Design Space (DS) and PAT, the heart of any true QbD submission.

When I asked for references to either a draft Guidance or 21 CFR reference, a group member posted the ICH Q8, 9, and 10 Guidances. (Which, as with all Guidances, indicate these are consensual, allowed, not legal rules.)

To be fair, Dr. Yu does speak with a bit of an accent and the people commenting on the interview are from non-English speaking countries, so there may have been some misunderstandings. However, as Yogi Berra once said, "Any verbal contract isn't worth the paper it's written on." Perhaps someone should have checked the actual, written rules before assuming.

I fear that one of the largest problems is the diversity of the pharmaceutical industry. We have a multitude of countries with numerous regulatory agencies and multinational companies, all working in secret.

DENIZENS OF LINKED-IN AND THE BLOGOSPHERE CAN'T EVEN SEEM TO AGREE ON WHAT PAT OR QbD MEAN.

The vast majority of the management-types still think QbD, when they approve of it, gives their companies a competitive edge and will not share the full knowledge with "the enemy." Much like my field of NIR, the basics of PAT and QbD are not universally taught in bastions of knowledge ("colleges" to my friends).

SPARKS OF HOPE?

However, there seem to be some sparks of hope. If this year's IFPAC annual meeting in Baltimore was an indicator of the future, more companies are opening up about *how* they did PAT/QbD and *which* products they performed the work on and *what* equipment they used. This is encouraging.

Some very nice work is being performed at some universities and was presented; again, not only specific, but (are you sitting down?) relevant to what may be used for actual process control and product development. While still theoretical, the research work is also useful! (Have I fallen down the rabbit hole?)

Given price restraints put in place by countries with national health systems, expanding generic presence, expiring patents, and various other challenges, market conditions are forcing us all to approach QbD as the common practice. We may all be approaching it from different directions, but, perhaps, despite all the confusion, there is a faint light on the horizon. What do you think?

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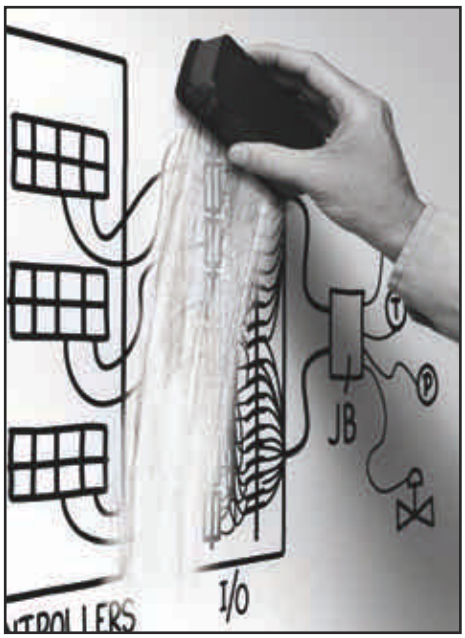

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