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VOLUME 11, ISSUE 8

Pharmaceutical MANUFACTURING

THE DRUG INDUSTRY S VOICE FOR MANUFACTURING EXCELLENCE

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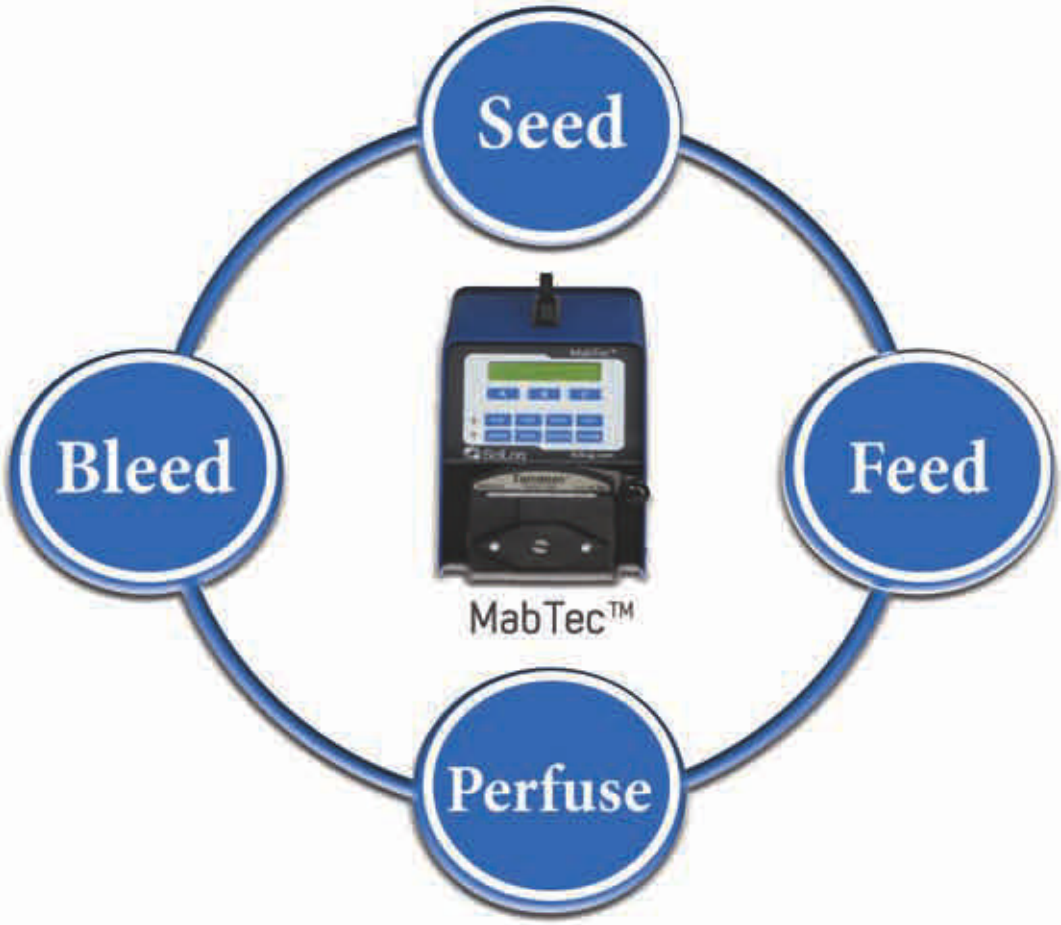

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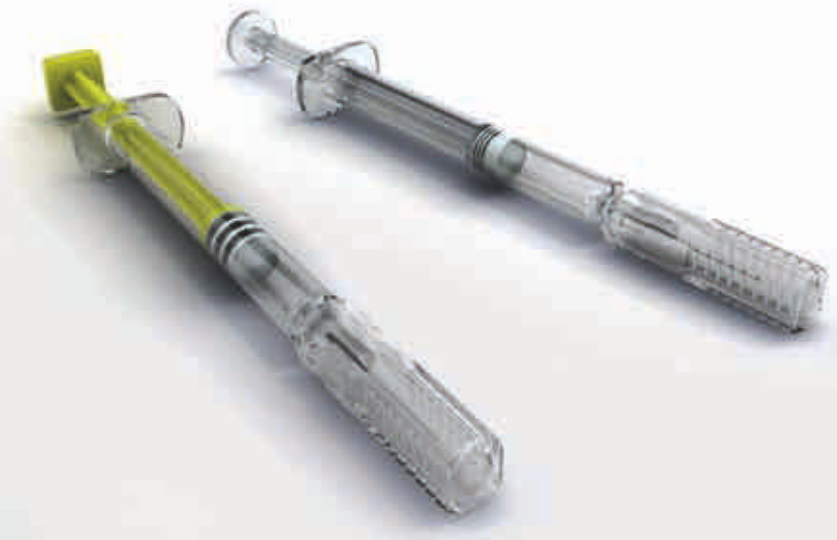

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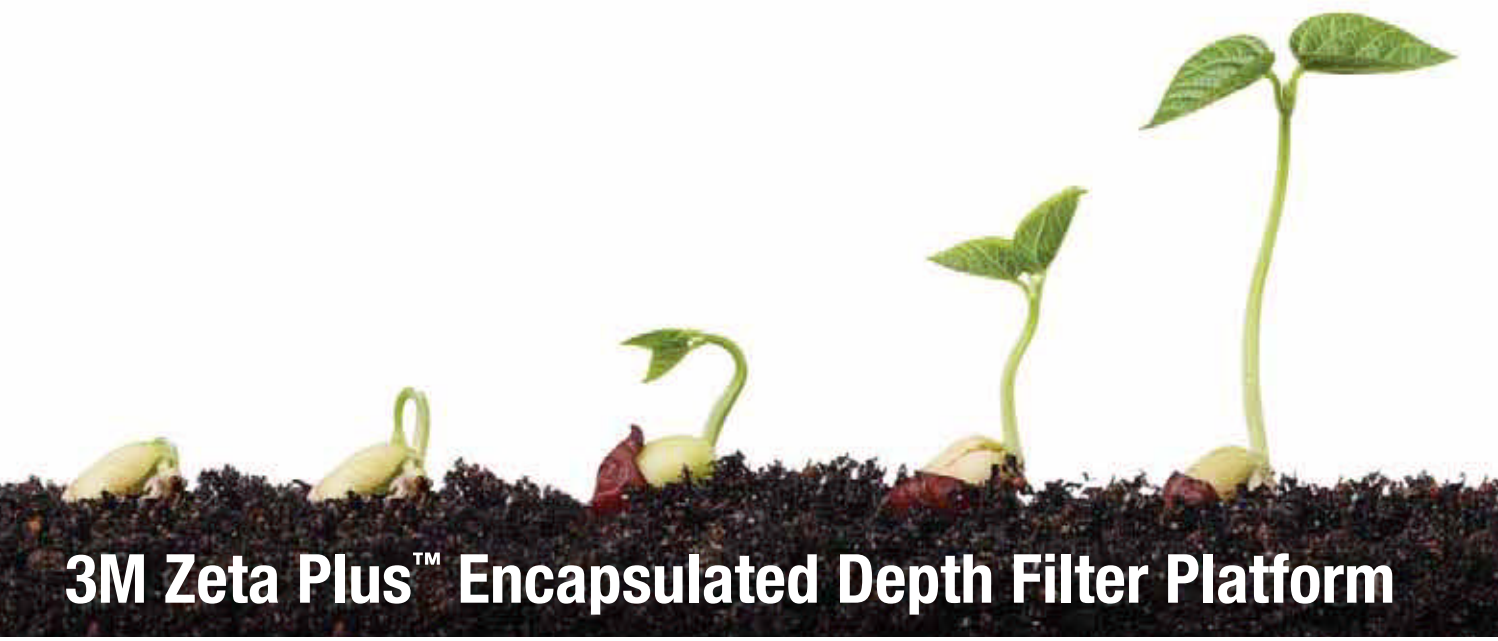

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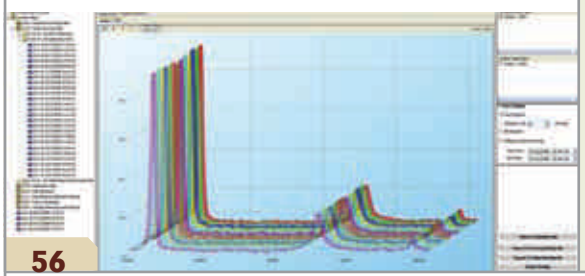

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Departments

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Are You in Control?

Pharma recalls due to supplier quality issues have increased by 16%/year since 2007

IT'S NO secret that pharma is outsourcing more of its core manufacturing and development operations. In the U.S. alone, pharma outsourced more than $10.7 billion worth of business last year, according to Frost and Sullivan, whose analysts expect the market to grow by 7-9% per year over the next four years.

Given current economic realities, nothing can (or should) stop this growth, but something has to stop the quality problems stemming from CMO and supplier quality gaps. Over the past five years, McKinsey & Co. analysts note, the number of pharmaceutical and medical-device recalls due to supplier quality problems has increased by 16% per year (article, p. 45). Consent decrees, forced plant shutdowns and 483s stemming from supplier issues have also increased.

Today, many pharmaceutical manufacturers face the daunting task of developing internal and external risk and quality management systems at the same time. This is not easy when internal operations tend to be siloed. Perhaps some comfort can be derived from the fact that models exist for setting the right foundation. Years ago, the company formerly known as Wyeth developed metrics and systems for evaluating suppliers as its own internal Lean, Six Sigma and continuous improvement programs evolved.

But there are limits. As McKinsey consultants point out, pharmaceutical manufacturers have little visibility into their contract partners' supply chains, at least beyond the first few tiers. Remember what happened just a few years ago, when an offshore CMO's spot purchase of a raw material led to tragedy on a global scale? Observers note that the heparin recall was only a harbinger of things to come, if CMO quality systems are not clearly understood and synchronized with those customers.

We surveyed readers last month to get some idea of their progress in synchronizing their own quality systems management with that of their key contract partners. 173 readers responded, suggesting some trends (see cover story, p. 22, for more).

There were some encouraging signs. For one thing, most respondents said they closely define process validation and change control requirements for their CMOs, while 52% use risk management tools, both internally and with suppliers. Of these tools, FMEA was the most widely used, by 58% of respondents, while 51% said they used process capability analysis and 41% described using QbD approaches with contract partners, for projects that begin at earlier stages.

There were signs of some disconnects, too. At a time when QMS and related software options are growing, 13% say they have linked their QMS and other IT platforms with those of their contract partners.

Most respondents said knowledge management was the most challenging aspect of working with contract partners. However, when asked how frequently they communicate with contract partners, 18% said "monthly," 31% "weekly," but 40% answered with a vague "it depends."

INCREASED OUTSOURCING WILL ONLY MAGNIFY AND REFLECT INTERNAL QUALITY **AND COMMUNICATION GAPS**

Could a simple failure to communicate be at the root of contract partner issues? In BioPlan's Ninth Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production, for instance, biopharm CMOs noted the fact that clients often failed to build in sufficient time for projects; that they focused on cost containment by doing limited development runs, but still expected manufacturing success; and that they failed to communicate effectively or plan the tech transfer process.

Could better and more frequent communication be one simple way to improve control over contract partners and risk? Are there ways to harness more modern methods, and the latest IT and automation?

Nothing ventured, nothing gained. But, clearly, much stands to be lost, for patients and for reputations, if nothing is done. PM

AGNES SHANLEY, EDITOR IN CHIEF
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USPS number (023-188)

Social Media: Sanofi Style

Sanofi-Aventis is writing its own social media rules for Big Pharma

MICHELE VACCARELLO WAGNER, SENIOR EDITOR, DIGITAL MEDIA

A BIT of a broken record, but FDA, now three years after the 'Promotion of FDA-Regulated Medical Products Using the Internet and Social Media' hearing was held, has still not issued any official guidance for social media policy, strategy and customer interaction for the pharma industry.

Big Pharma has since been treading lightly on social media channels, and companies like Sanofi have even found themselves in prickly legal situations. In 2010, Sanofi's cancer division suffered a PR nightmare after a patient posted complaints and photos on the group's unmonitored Facebook page. The importance for creating a social media outline and strict company guidelines may be a defensive move more than anything for Sanofi, but other companies can learn from its mistakes.

Sanofi chose to focus its social media efforts on diabetes management, and with such a large community of people already living with the disease and sharing online, Laura Kolodjeski, Sanofi's diabetes community manager, feels that creating a channel for those living with the disease to help, inspire and educate others was the best use of the company's social media efforts. Sanofi's experiences not only help the online community become more in-tune with Big Pharma, but also will help pharma companies, and even FDA, lay the groundwork for functional, yet compliant, guidelines that will help to benefit both company and consumer.

THE GUIDELINES ACCORDING TO SANOFI

1. Be Transparent

Sanofi suggests that a company's social media presence should aim to build a community of trust and transparency. Attaching a photo of the administrator or giving the channel a personal voice can help members and followers relate to the people of the company and not just the idea of a faceless company.

Kolodjeski also recommends outlining clear-cut rules for the forums, free from legal jargon, which align with the company's marketing goals for the page.

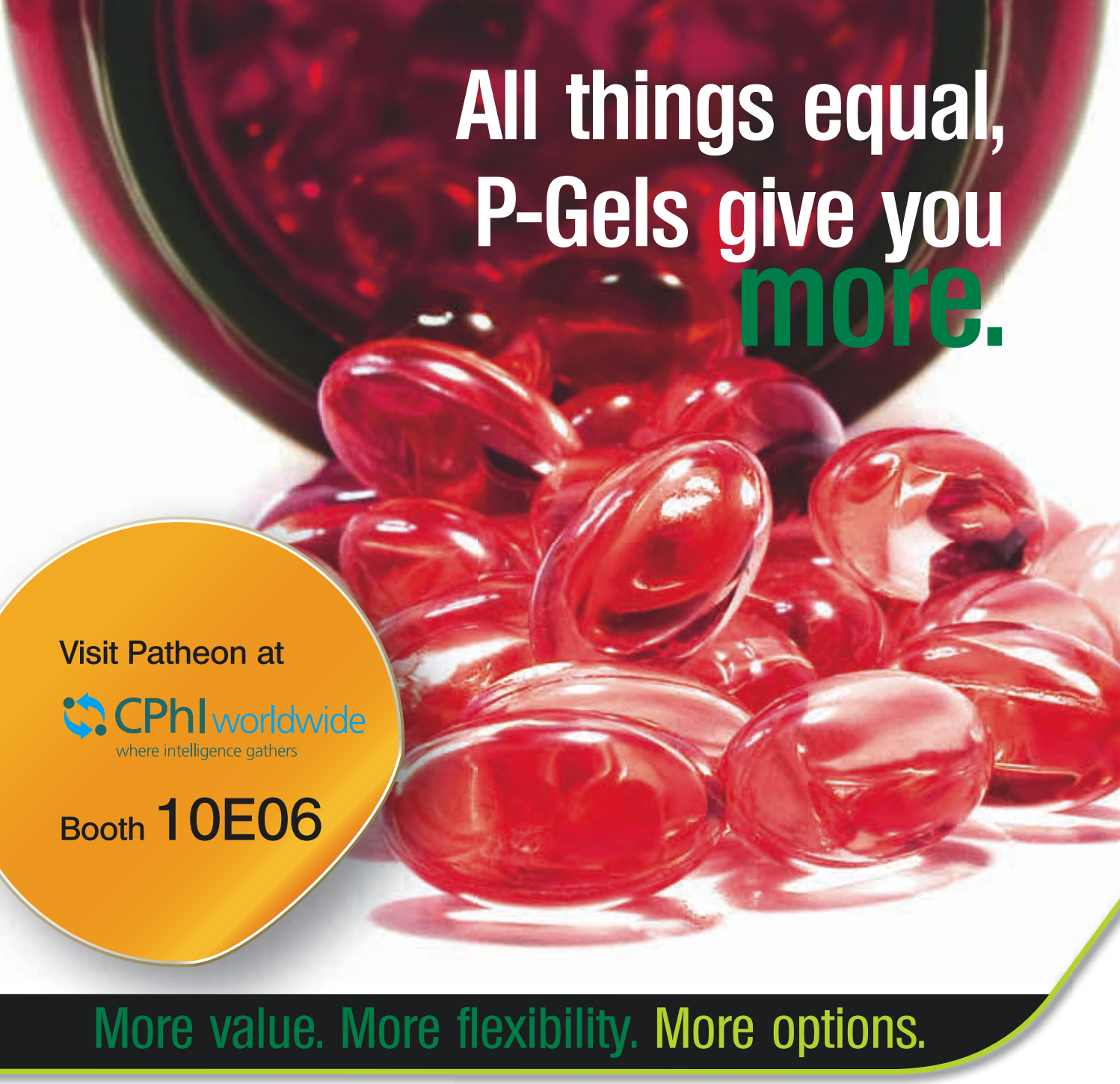
2. Let Users Shape Expansion

When Sanofi's Twitter and Facebook handles launched in September 2010, the company noticed that several top niches from each channel that could use their own venue began expanding their pages based upon the community's reaction and participation. Offshoot pages such as highlights, inspirational messages, topic blogs and education and informational pages emerged as ways to keep users engaged and improve their community experience.

3. Give Users Even More Control

On Sanofi's educational and informational social media pages, users are encouraged to submit their own entries, helping inform newcomers of established disease terminology and site practices. The company also recommends contests/giveaways that both engage the audience and help the treatment of the disease. In addition, Sanofi launched iBGStar, an iPhone/iPod plugin, that serves as a personal blood glucose monitor. Users can share results with family or email them to health care providers.

While FDA may never establish its Social Media Guidance, companies like Sanofi's successes (and mistakes) can help establish a road map for other companies' social media participation, and in turn, better serve the pharma consumer.



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What Drives Pharma's CMO Partnerships?

Quality is the top selection criterion, recent research suggests, but regulatory compliance is becoming more important

BY AGNES SHANLEY, EDITOR IN CHIEF

QUALITY IS the main reason why pharma companies select a specific contract manufacturing partner, although regulatory compliance is becoming more of a factor, according to recent market analysis. The market research firm, That's Nice (New York, N.Y.), which has been studying the pharma outsourcing space for the past several years, found that quality was the top selection criterion for CMOs this year. "It's hard to distinguish between the two, because the concept of quality encompasses regulatory compliance," says Kate Hammeke, director of market intelligence at That's Nice.

However, in this year's most recent survey of the market, regulatory compliance came in as the third most important CMO performance metric, up from fifth place last year. (Table)

Recently, biopharmaceutical manufacturers have had a number of cross-contamination problems occur at their facilities, which led to warning letters and at least one prominent consent decree. Other research suggests an increased focus on compliance in this sector. For instance, in BioPlan's 9th annual report and survey of biopharmaceutical manufacturing capacity and production, released earlier this year, 63.5% of respondents cited CMO compliance with operating company quality standards and ability to handling cross-contamination issues effectively as the two top issues on their "very important" list.

Other top requirements cited this year were for CMOs to "provide standard performance metrics," and "provide lead times sufficient to cover tech transfer," according to BioPlan.

BioPlan data showed fill and finish, analytical and toxicity testing, plant maintenance and validation services as the top areas for biopharmaceutical

CMO Referral Sources	Overall	Big Pharma	Biotech
Industry Research	55%	58%	57%
Consultants	54%	55%	56%
Peer Referrals	49%	45%	49%
Trade Shows/Events	40%	32%	42%
Periodicals / Publications	28%	23%	32%
Web Searches	19%	15%	19%
Online Directories	18%	14%	19%
Other	5%	7%	4%

Outsourcing Drivers	Overall	North America	Europe
Quality	1	1	1
Reliability	2	2	2
Regulatory	3	3	6
Productivity	4	4	3
Affordability	5	5	4
Innovation	6	6	5

FUNNY PHARM

"It's a good thing Viagra is not a Controlled Substance!"

— Grace Scheibner

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

outsourcing this year. Over the next two years, the biopharmaceutical manufacturing decision makers who responded to BioPlan's survey say they expect to outsource significantly more in analytical testing, validation services and fill and finish as well as API biologics manufacturing.

Spending on outsourcing for manufacturing and R&D should increase by about 9.3% this year, BioPlan estimates.

That's Nice's research, meanwhile, shows the greatest demand for consulting, with 48% of pharma and biopharma companies saying they plan to contract with consultants for key projects. Higher than average growth was also expected for analytical services, which 40% say they will outsource; clinical research, a growth area for 38%; and bioanalytical services, which 34% cited as a growth area.

Focuses differ depending on geographical region. In established markets, such as the U.S., Europe and

COMPLIANCE QUIZ

Welcome to Compliance Quiz, which focuses this month on cold chain management. This month's quiz focuses on Part 11 and the Predicate Rules. Answers are below, right. (Find a full quiz and answer details on PharmaManufacturing.com.)

1. Predicate rules are FDA regulations that were created _____ CFR 21 Part 11 at a time when records and signatures were still made with _____ and _____.

a) after, charts, stamps
b) prior to, paper, pen
c) before, pre-approval, witnesses
d) after, hopes, prayers

2. The two CFR titles relevant to Pharmaceutical manufacturing are:

a) Title 21 Food & Drugs, specifically Chapter 9, The Federal Food Drug and Cosmetic Act (the Act)
b) Title 42 The Public Health and Welfare, specifically Chapter 6A, The Public Health Service Act (PHS)
c) All of the above
d) None of the above

3. 21 CFR Part 11 came into being to allow _____ rules to be satisfied by a computer system that creates and stores records or signatures.

a) GMP
b) GCP
c) GLP
d) all of the above

4. True or False? Part 11 determines record creation, content, signature requirements or retention period, or Original vs. Copy to be archived.

TRUE
FALSE

5. Which of the following is NOT regulation on digital or electronic signatures?

a) US E-sign Act (2000)
b) EU Directive 1999/93/EC on Electronic signatures
c) 21 CFR Part 11
d) North American Electronic Signatures Act
e) Uniform Electronic Transactions Act (UETA)
f) US Digital Signature And Electronic Authentication Law (SEAL)

6. Records and Signatures are subject to Part 11 IF:

a) The record is required by a predicate rule
b) The record is in electronic form
c) There is an electronic signature on a predicate-required record, regardless of whether the signature is required
d) It's an electronic submission to the FDA, i.e. IND, NDA
e) All of the above

Answers
1.B 2.C 3.D 4.FALSE 5.D 6. E

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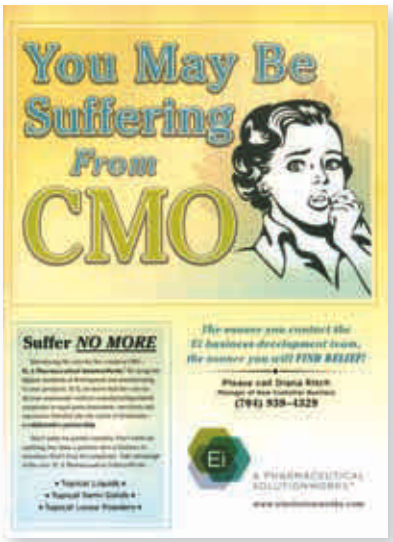
Japan, That's Nice's recent research suggests that the top areas for outsourcing were analytical services, with 69% of companies planning to outsource; bioanalytics, with 63%; regulatory support with 62%; fill and finish, with 60%; blending with 60%; and stability storage and testing, with 59%.

In emerging markets, the top outsourcing areas were: Chemical synthesis and cytotoxic drug development projects with 27%; packaging with 21%; and data management, drug delivery and fill and finish with 20%. Clinical research accounted for 20%.

That's Nice also rates CMOs in less tangible areas such as customer awareness and customer perception. One company singled out for advertising with impact was Ei Solutions (Image).



One of CMO's advertisements referred indirectly to outsourcing issues.

WINNERS OF THE 2012 AICHE AWARDS FOR QBD

The American Institute of Chemical Engineers (AIChE) has selected winners of the 2012 award for outstanding contribution to the field of pharmaceutical Quality by Design (QbD), both of which will be presented at the 2012 Annual Meeting in Pittsburgh. This year's winners are:

Dr John Lepore, Merck & Co., for his many contributions to advancing QbD, his role in helping draft ICH guidance on design space, criticality, modeling and control strategy, and Dr. Christine Moore, FDA, for her QbD contributions at FDA, and previously, at Pfizer, Searle and Pharmacia.

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Focusing on the End Game at Vetter

A lifecycle focus, emphasizing commercial manufacturing, defines a true CDMO, says managing director Peter Soelkner

BY PAUL THOMAS, SENIOR EDITOR, WITT-KIEFER

AS THE challenges of technology transfer and process scaleup underscore the need to stop throwing processes "over the wall" to manufacturing, the term "contract manufacturing organization" (CMO) has morphed into "contract development and manufacturing organization" (CDMO).

Is the term a misnomer? Are CDMO partners achieving true alignment with their operating pharma company customers? In a recent interview, Peter Soelkner, managing director of the parenterals specialist, Vetter Pharma-Fertigung and Co. KG, and Vetter Pharma International, discussed the issue and outlined his company's philosophy and approach. A chemical engineer with an MBA, Soelkner believes in taking a holistic view of the parenteral lifecycle, but always focusing on the end game: commercial manufacturing.

PhM: CDMO has become a popular acronym in pharma outsourcing circles. How would you define it, and how does Vetter fit this category?

PS: Many companies use the term because it suggests that they will help customers maximize the potential of their product, from the earliest stages of development through to commercialization. At Vetter, we know that the right choice of CDMO can make the difference, not only between success and failure of an individual product, but also the survival of the company that makes it.

We believe that you can't claim to be a CDMO simply because you work on both development and manufacturing of parenterals with customers. There is a need to focus on the ultimate goal: long-term market supply, and to add value all along the product lifecycle.

We start this process at the earliest stages of development, with a view to later stages of development, to our clients' potentially changing needs at various stages, for instance, attracting investors; providing licensing-out opportunities; or even, in some cases, being acquired outright by a larger company.

We've seen that some companies that use the term CDMO give little thought to commercialization efforts required for the drug. We like to support products as they move from phase to phase, but always remain focused on the ultimate goal: long-term market supply.

PhM: CDMO suggests a holistic approach to drug development and commercialization. What are some best practices at Vetter that best illustrate this approach? Is Vetter more integrated now than it was 5-10 years ago?

PS: We did not claim to be a CDMO for a long time. That is because the nature of our assignments has changed quite radically over the past 10 to 20 years, becoming more complex, along with the compounds themselves and our clients' needs.

Today, our customers are increasingly doing R&D and marketing in-house, but turning to us, not only for aseptic filling support, but also associated development activities. As a result, over the past decade, we have continuously

expanded the range of development services we offer, from early development phases through commercialization.

Our approach is to incorporate integrated multifunctional project teams into the process from the start of any customer project. These teams include senior specialists in process development and implementation, as well as experts in the areas of commercial manufacturing and quality assurance.

We also involve experienced people from our drug development laboratories, downscaling first, reproducing in small batches what we can later successfully apply to the larger context of commercial manufacturing. This allows us to scale up faster and more efficiently.

PhM: Apart from members of this team, do you have anyone assigned to "follow" specific drugs along their lifecycles?

PS: The key to any product's success is adequately supporting tech transfer from clinical development to long-term commercial manufacturing. To support this effort, Vetter relies on a continuous partnering relationship, which results in an integrated approach to projects.

The core element to this strategy is our key account management philosophy. Key account managers (KAMs) serve both as partners and as interfaces between our customers and the Vetter Development Service, as well as Vetter Commercial Manufacturing service divisions.

They are charged with making sure that products move efficiently from early drug development phases through to long-term lifecycle management. Our KAMs are well-integrated into project teams and are familiar with all of the critical pharmaceutical processes.

They create multifunctional teams that are comprised of experts from all areas of the process and ensure that well-trained scientists and engineers are working together. This approach allows for more efficient problem solving, which in turn time to clinic, and ultimately time to market.

A well-versed team can work more efficiently and tap into multifunctional expertise to enable the best use of money, time and human resources.

Other team members, from production and quality control, stay with the products after the project has been transferred into market production.

To be a really good CDMO means being there throughout all stages of a drug's development and

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PETER SOELKNER

lifecycle, providing necessary support at all times. This will provide the customer with valuable time and resources to concentrate on research and development as well as marketing.

PhM: How does Vetter optimize tech transfer between its different facilities, and those of clients, to ensure that data and product knowledge are transferred seamlessly and effectively?

PS: The process of tech transfer is one of the most important aspects of our business and a key focus of both our Development Service and Commercial Manufacturing areas at all our locations. Our goal is seamless transfer of data and project knowledge, and a solid foundation for tech transfer throughout any project.

Each project has a clear structure in place, which includes teams that are accountable for strict quality-control procedures, regulatory standards and evolving technologies.

Each development team is led by a highly experienced project manager who is aware of the day-to-day realities of production. Each project manager can support both clinical filling as well as the transition to commercial manufacturing and market supply. In addition, we make sure that all departments relevant to commercial manufacturing are involved in the projects from an early stage. Plus, we elaborate clear and complete documentation. All data are available to people responsible via our central IT systems.

PhM: How do you handle data management so that critical information is robust and can be easily accessed throughout the product lifecycle?

PS: We continuously invest in modern IT, including Electronic Batch Records system. We've recently introduced TrackWise to document SOPs, change processes, complaints, CAPAs and other key data. A system like this gives all those on any project team permanent access to critical data at a central place.

Working with validated processes, we can generate up-to-date reports and trend analyses. Additionally, the workflow can be tracked precisely, allowing for parallel work processes and various escalation steps.

In order to establish efficient company planning and optimize supply-chain processes, we have been using a customized SAP solution since 2008.

PhM: How are analytical and microbiological services integrated and scaled up along with the product?

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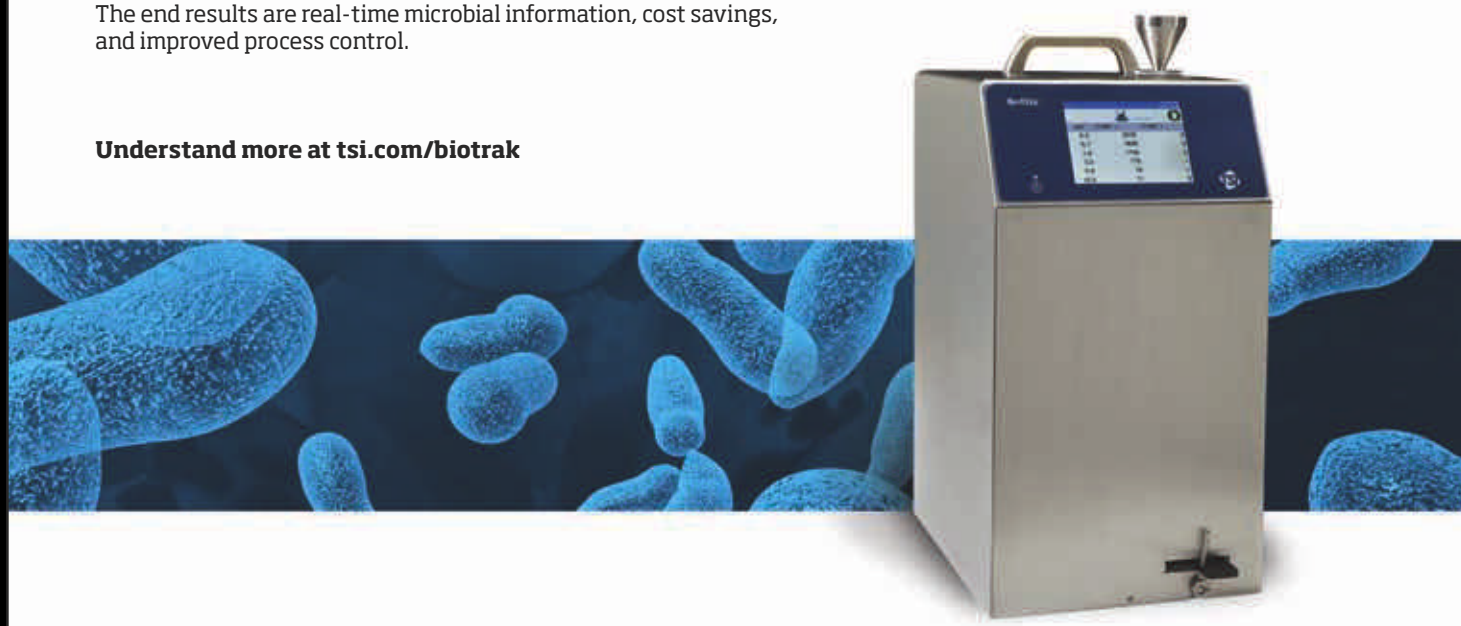

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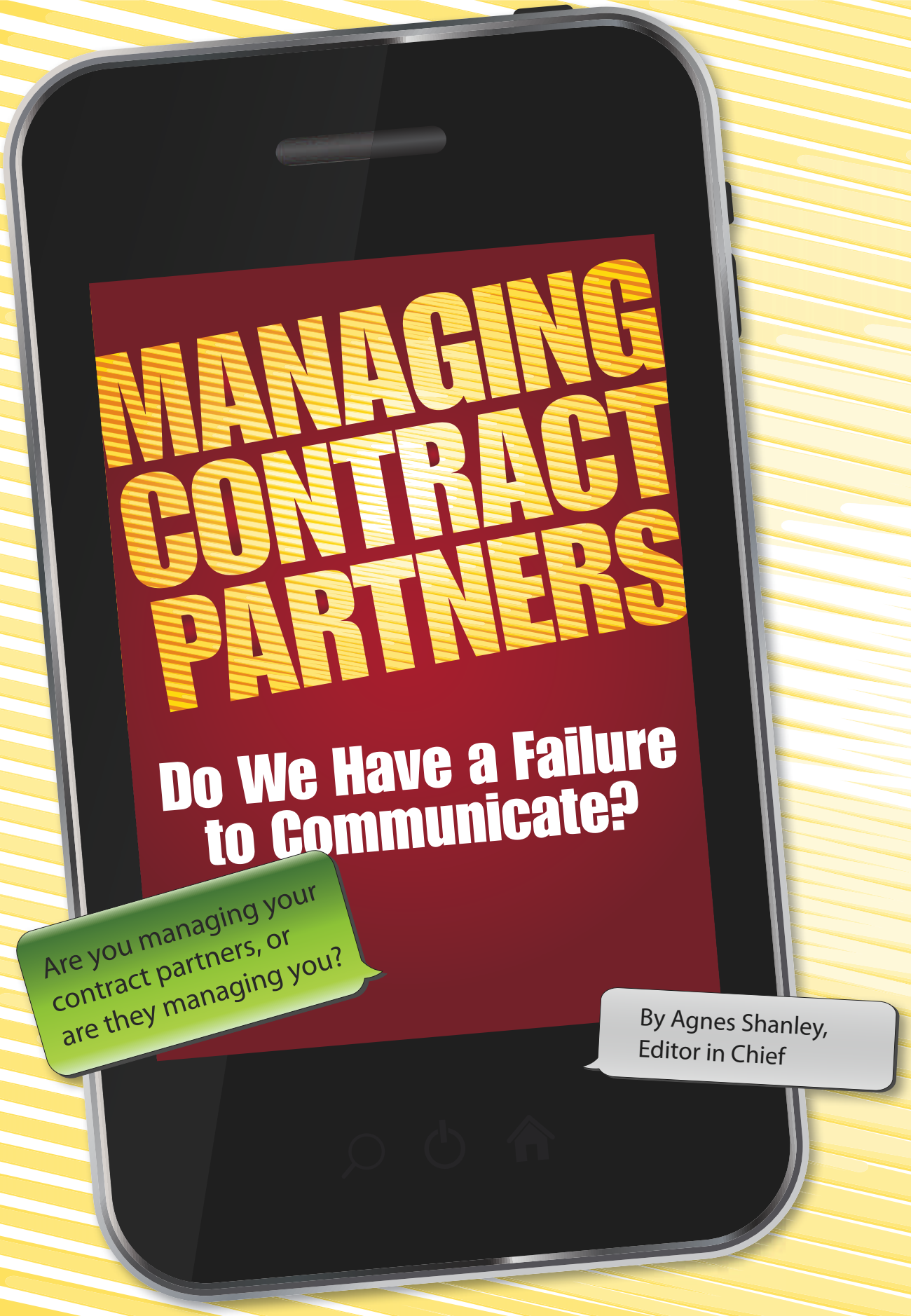

MANAGING CONTRACT PARTNERS
Do We Have a Failure to Communicate?
Are you managing your contract partners, or are they managing you?
By Agnes Shanley, Editor in Chief

AS COMPETITIVE pressures increase, nothing can stop the pharmaceutical outsourcing juggernaut. What started off as a "back office" practice for business, IT, HR and real estate management has become well established in manufacturing, and the use of outsourcing continues to grow in other strategic functions, including R&D and clinical.

(For more information, see article on p. 11)

Developing an accurate assessment of the pharmaceutical outsourcing market's size is nearly impossible, says Nigel Walker, managing director of That's Nice (New York, N.Y.) whose Nice Insight market research program studies the evolving contract pharmaceutical services market closely.

A wide range of companies offer services from tiny, privately held and extremely niched players to generic drug manufacturers and even big pharma companies.

The market research company Frost & Sullivan estimates that the pharmaceutical contract services market is roughly $10.7 billion in the United States alone, and growing by roughly 8% per year [1].

While pharmaceutical manufacturing and development outsourcing has increased, so have pharmaceutical recalls and other regulatory issues, including 483s and consent decrees (Figure 1).

Observers say this parallel growth is no coincidence. Over the past five years, McKinsey & Co. consultants have found there has been a 16%/yr increase in pharmaceutical recalls that can be directly traced to quality failures on the part of suppliers or contract partners (for more, see article on p. 45).

Paradoxically, in surveys, operating pharmaceutical companies say that quality is the top reason they select a contract partner. CMO's ability to comply with regulatory requirements is another one of their top selection criteria. [2,3]

Michael Long, from FDA data

Regulators continue to emphasize the need for better risk management. "There has been an evidentiary shift that places the burden on the industry to prove appropriate levels of risk management," said Michael Long, director of consulting services for Concordia ValSource, LLC (Downington, Pa).

In the future, he says, pharma supply chains may more closely resemble those of the automotive industry, with Tier 1 and 2 suppliers. However, in the short term, Long says, expect more questions from regulators surrounding risk management, product and process knowledge, he says [4].

Not only regulators, but observers and experts within the industry are calling for much stronger outsourcing governance [5]. The subject is complex, touching on risk management, staffing, training, tech transfer and communications. Are drug manufacturers ready for the challenge?

In this article, two industry experts comment on the issues playing out right now, and suggest best practices. The article also examines results of a recent reader survey, which sheds some light on how drug manufacturers are responding to the challenges of contract supplier oversight.

RISK MANAGEMENT 101

Clearly, many are at an early stage in developing risk management strategies. "Even though ICH Q9 was published six years ago, drug manufacturers are just starting to find their footing in the areas of risk management, quality by design, and quality systems," said Long. Their progress, he says, depends on how advanced they are in applying risk management tools and concepts.

"If you do not have an adequate quality system in place, with adequate controls, all the product and process development and the process understanding in the world, may go to waste," he told attendees at PDA's annual meeting earlier this year in Phoenix.

In addition, he says, some professionals have fundamentally misunderstood the concept of a "risk-based approach," Long said. "It is not a gift card for reducing testing and other precautions," he said. "Instead, it requires a balance between identifying and mitigating threats, while taking advantage of opportunities. It should never become a hammer in search of a nail, and all systems must be evaluated if it is to be robust."

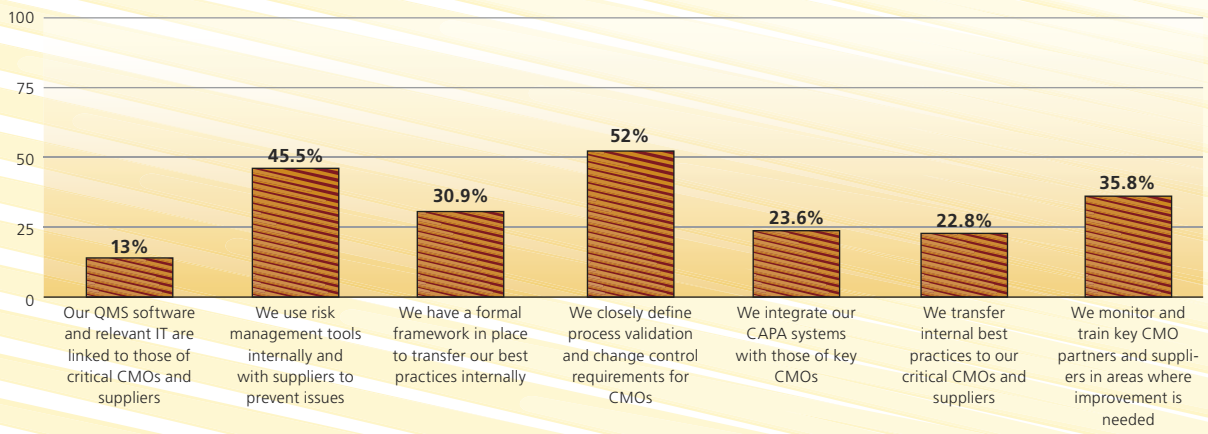
Managing contract manufacturers requires asking two key questions, according to Hedley Rees, consultant and founder of the U.K.-based consultancy, Biotech PharmaFlow, who established and chairs the Drug Industry Modernization group on LinkedIn and whose extensive book on optimizing pharmaceutical supply chain management was published two years ago [6]:

1) Do I understand the extent of my obligations to manage my CMOs?
2) Have I the right processes in place to deliver on those obligations?

All manufacture and testing carried out at third parties must be treated as if it were carried out by the drug manufacturer itself, Rees said, and the working supply chain must comply to regulations at every stage. This means:

- Investigating out-of-specification results and appropriate (root cause) corrective and preventive actions

HOW CLOSELY ARE YOUR QMS AND THOSE OF YOUR CMOs AND SUPPLIERS LINKED?



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"Contracts must closely spell out such widely ranging activities as corrective and preventive action (CAPA), technology transfer, operation of interfacing quality systems, specific mitigations emerging for risk assessments as well as newer approaches, such as the adoption of a pharmaceutical Quality by Design (QbD) approach," Rees said. "If your contract did not spell out alignment, it may not happen."

The best approach, he said, is to view outsourcing as a specific case of procurement, and to remember that it is a strategic, organizational function. Rees urges the following:

1) Identify and involve all stakeholders in the outsourcing process, from the start, and do not leave key issues to either the procurement department or the CMC group.
2) Beware of checklist Quality Agreements based on legal boilerplate. The commercial and technical terms for the agreements (Supply and Quality) must form part of the tender and the pre-contractual negotiations. Terms should be based on the practical ways you will work together to meet your mutual obligations.
3) Remember that power shifts after contracts are signed, especially if you are entering a single-provider arrangement. If anything important is left out of the contract, such as the requirement that certain information be provided by the contract company on a regular basis, then you will have no reason to expect it because the contract partner is under no obligation to provide it.

HOW ARE WE DOING?

Is the typical pharmaceutical manufacturer developing the right approach to CMO management? *Pharmaceutical Manufacturing* surveyed readers to get a snapshot of contract partner management practices. Over 173 industry professionals responded to the survey, results of which are highlighted below. (For more information, check www.pharmamanufacturing.com.)

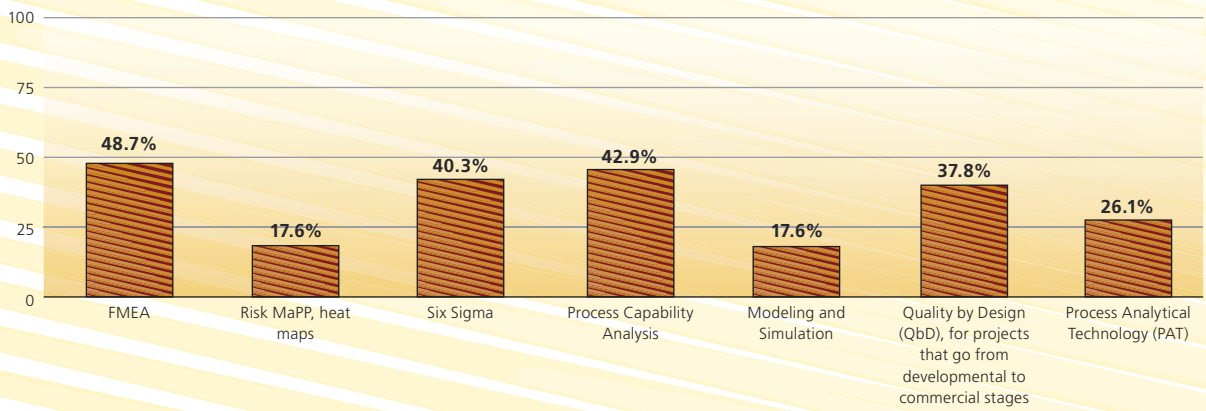
When asked how closely they synchronized their internal quality systems with those of CMOs and suppliers (Figure 2) 64% of respondents said they defined process validation and change control requirements closely for their CMOs; 46% said they used risk management tools internally and with suppliers.

In addition, 36% said they monitored and trained CMO partners in areas where improvement was needed, and 31% described having a knowledge transfer process available, to transfer internal best practices to their contract partners. Twenty-four percent said they had integrated CAPA systems with those of their suppliers.

Fewer respondents are using technology to facilitate con-nection to CMOs; 13% said they had connected QMS and other IT platforms to those of conract partners and suppliers.

As far as specific risk management tool kits and methods are concerned (Figure 3), 49% of respondents said they were using failure modes and effect analysis (FMEA), 43% are using process capability analysis, 40% are using Six Sigma, 38% say they use QbD, and 36% report using process analytical technology (PAT).

WHAT METHODS ARE YOU USING TO MANAGE POTENTIAL CMO AND SUPPLIER RISK?



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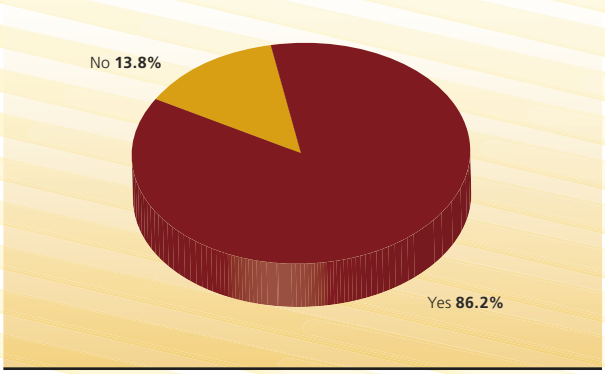


Eighty-six percent of respondents said they have a formal process in place to monitor the source and quality of raw materials critical to product quality bought by suppliers. (Figure 4) The remainder did not.

On the positive side, most respondents to the survey said they have a system in place for monitoring the quality performance of critical CMOs and suppliers. Sixty-one percent said they hold regular meetings with contract partners, 58% send senior quality staffers to visit supplier sites, 58% say they review relevant manufacturing and process monitoring data regularly; and 20% have set up dashboards to monitor KPIs for contract partners.

When asked to define their biggest challenges in managing CMOs, most respondents (30%) cited knowledge transfer; 24%, process validation; and an equal number, change control. In addition, 23% said that risk management was their top challenge, 21% reported monitoring, 15% CAPA coordination and 14% tech transfer. "Someone always seems to be asleep at the switch," wrote one. Another described high attrition rates at smaller CMOs, with poor knowledge transfer the result.

"If you don't have a quality and technical rep on site for each batch produced at a CMO, there are items that don't get documented at the same time, so resulting deviations aren't always documented efficiently."

Among other issues respondents cited:

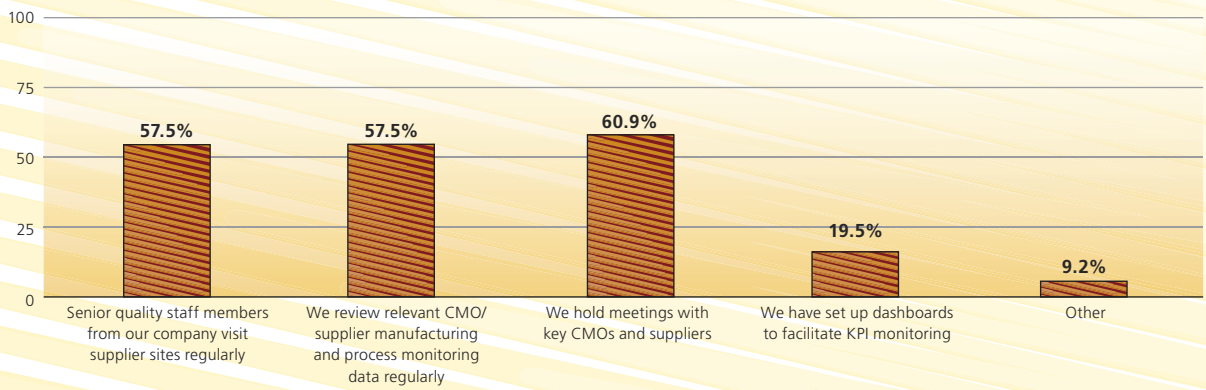
- A lot of manufacturing and quality data for CMOs can only be seen during on-site visits
- CMOs need to prevent process drift and poor decisions by management
- Insufficient knowledge of CMC issues
- Wrote one respondent, "It can be difficult to ask informational questions from most of our suppliers. They are reluctant to provide helpful information for fear of incriminating their own products."

Other respondents noted that, given limited internal resources, it was becoming more difficult to maintain close and meaningful contact with suppliers. Said another "review of documentation alone does not provide a full picture of actual performance."

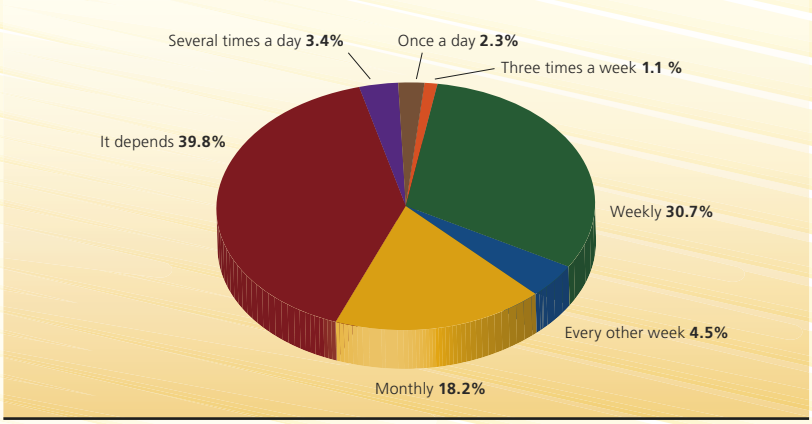
COMMUNICATION AND KNOWLEDGE TRANSFER

Communication, or the lack of it, has clearly become a factor in the overall CMO management picture. In the survey, 5% of respondents describe communicating with key contract partners at least once a day, 31% weekly, 18%

AFTER YOUR QUALITY AGREEMENT HAS BEEN COMPLETED, HOW DO YOU CONTINUOUSLY MONITOR THE PERFORMANCE OF YOUR CRITICAL CMOs AND SUPPLIERS?



HOW FREQUENTLY DO YOU FORMALLY CONNECT WITH YOUR KEY CMOs AND SUPPLIERS TO VERIFY THEIR PERFORMANCE AND QUALITY MANAGEMENT?



monthly, but 40% answered with a vague "it depends."

Relatively infrequent communication would appear to conflict with the stated goal of better managing knowledge and tech transfer, said Michael Long.

Pharmaceutical operating companies often fail to communicate adequately to their CMOs, as contract manufacturing companies reported in BioPlan's 9th annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production [7]. Eighty-six percent of the 302 pharma operating company and CMO professionals who responded complained that biopharm clients didn't build in enough time for projects, or communicate effectively, while 83% said they didn't plan their tech transfer process or recognize variability in process development.

Another complaint: 67% of the CMO respondents to BioPlan's survey said that their clients just "handed off a project" without planning for ongoing interactions. Some CMO respondents said that their pharma clients did not adequately use QA and QC expertise and expected CMOs to make regulatory decisions for them.

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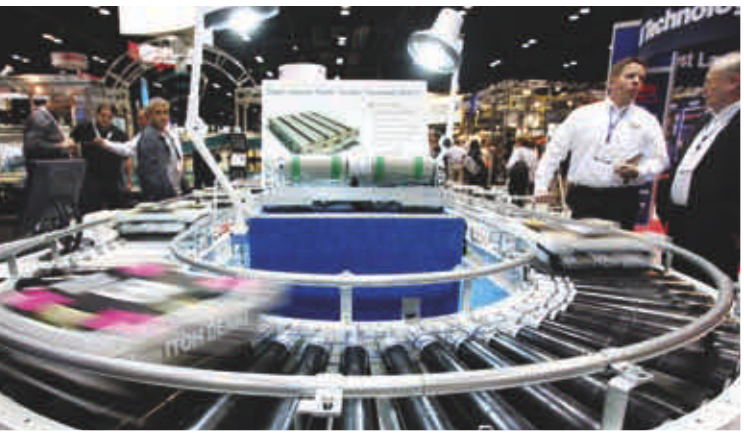

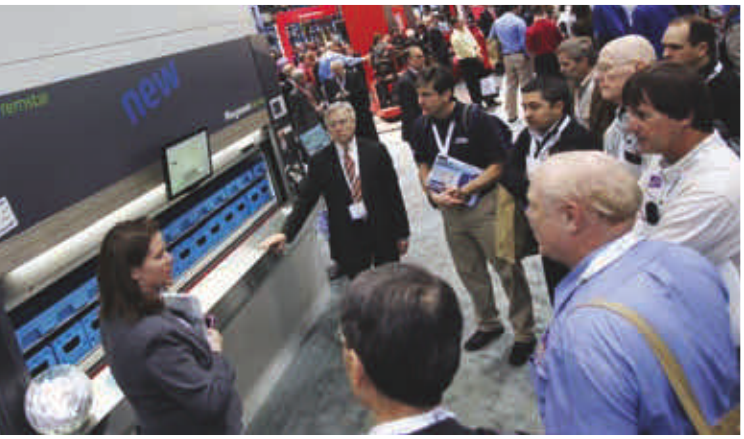

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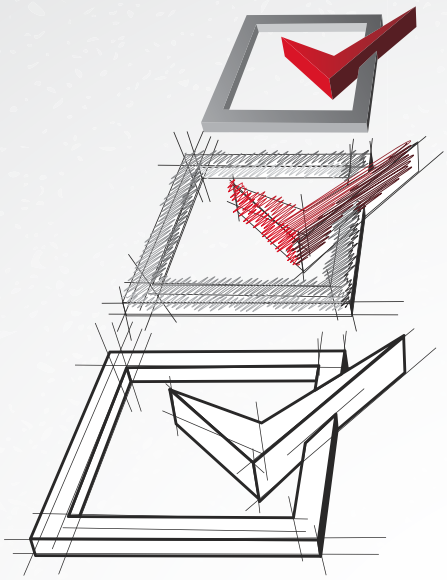


TRUST but Verify (Continuously)

FDA's Process Validation guidance calls for continuous process verification. Here's how to do it, and how automation can help

BY HEATHER SCHWALJE, EMERSON PROCESS MANAGEMENT

IN JANUARY of 2011, the FDA issued Guidance for Industry, Process Validation: General Principles and Practices. This document will affect how pharmaceutical manufacturers operate and presents them with a series of both challenges and opportunities.

The Guidance document, in its own words, "aligns process validation activities with a product lifecycle concept and with existing FDA guidance, including the FDA/International Conference on Harmonization (ICH) guidances for industry, Q8(R2) Pharmaceutical Development, Q9 Quality Risk Management, and Q10 Pharmaceutical Quality System. Although this guidance does not repeat the concepts and principles explained in those guidances, FDA encourages the use of modern pharmaceutical development concepts, quality risk management, and quality systems at all stages of the manufacturing process lifecycle."

The document defines process validation as "the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product." Validation activities are broken into three stages: Process Design, Process Qualification and Continued Process Verification.

This article will discuss the third stage, Continued Process Verification (CPV), the challenges and opportunities that this concept creates for pharmaceutical companies, and what this means to pharmaceutical manufacturers on a practical, day-to-day basis.

The guidelines identify three key program elements for CPV:

1. A system or systems for detecting unplanned departures from normal operation of the process designed to correct, anticipate and prevent problems.
2. An ongoing program to collect and analyze product and process data that relate to product quality, including evaluation of intra-batch and inter-batch variation. This data "should include relevant process trends and quality of incoming materials or components, in-process material and finished products. The data should be statistically trended and reviewed by trained personnel. The information collected should verify that the quality attributes are being appropriately controlled throughout the process."
3. Maintenance of the facility, utility and equipment qualification status: "Once established," say the Guidelines, "qualification status must be maintained through routine monitoring, maintenance, and calibration procedures and schedules."

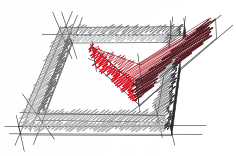
ALIGNMENT WITH ICH Q10

ICH Q10, Pharmaceutical Quality System (June 2008) is a tripartite guideline that describes "a model for an effective quality management system for the pharmaceutical industry, referred to as the Pharmaceutical Quality System." One of its major objectives is to establish and maintain a state of control: "To develop and use effective monitoring and control systems for process performance and product quality, thereby providing assurance of

continued suitability and capability of processes." To a large extent ICH Q10 embodies existing regional GMP requirements. Its coverage extends from development to manufacturing to product discontinuation.

Several key elements of ICH Q10 align with Continued Process verification as it relates to the "Manufacturing" stage. Two of the most important are:

- Knowledge Management, which ICH Q10 considers one of its two key enablers (the other being Risk Management) and is defined as a "systemic approach to acquiring, analyzing, storing and disseminating information related to products, processes and components." The data historians found in modern distributed control systems (DCSs), often in combination with an electronic batch record system, perform this function.
- Continual improvement of process performance and product quality, described in Section 3 of ICH Q10. Regarding the commercial manufacturing stage of the product lifecycle, ICH Q10 states "the pharmaceutical quality system should assure that the desired product quality is routinely met, suitable process performance is achieved, the set of controls are appropriate, improvement opportunities are identified and evaluated, and the body of knowledge is continually expanded."



Make sure that the process control strategy is appropriate, and that process, reporting and quality parameters are identified/assigned.

In order to meet many, if not most of the goals of all these guidelines, data collection and availability should be consistent and easily accessible to users. These goals can be achieved using current automation and business technologies that include Distributed Control Systems (DCS) and Manufacturing Execution Systems (MES). For example:

- Handling unplanned departures — A modern DCS has an alarm strategy and can be configured with preplanned actions to respond to unwanted changes in continuous data (e.g. temperature of a bioreactor). The system can provide exception reporting through its event/history log. Use of the DCS in combination with electronic batch records (EBR) would provide more granularity to exception reporting through viewing exceptions within context of the batch. Use of EBR in an integrated MES would provide the ability to reconcile and/or integrate data with separate deviation management systems. And finally, Process Analytical Technology (PAT) in-line instrumentation and modeling can be incorporated into the automation strategy to respond to and correct process deviations in real time.
- Process monitoring — A DCS collects a considerable amount of process data on an ongoing basis that includes critical process parameters from moment-to-moment loop control operations via reporting of trends. Additional process data may be generated outside of Manufacturing through Quality Control testing. Effective monitoring of the process requires both sets of data. Integration of an EBR with Laboratory Information Management Systems (LIMS) would provide a central repository for data when test results are provided back to the batch record. Potential delays in obtaining laboratory data should be considered as they affect the ability to respond to results in real time. Identification of PAT with online testing in key areas would contribute to the success of continued process verification where a response can occur in real time.

A final data set is required for raw material information from sources such as certificates of analysis from suppliers (COAs) and/or site release testing. If this data is collected in an ERP and/or LIMS system, it can also be integrated into a central repository to provide ease of use for process analysis.

- Maintenance of facility, utility and equipment — The data handled by a DCS can be used to monitor the health of the equipment and process. Alarm records and key utility and equipment performance parameters, as well as data from intelligent field devices, can be collected and analyzed. All of this data can be correlated with asset management and MES systems to aid in predictive/proactive maintenance.

As explained above, facilities that use modern distributed control systems already have access to the data required for Continued Process Verification. But in many cases, these systems collect an enormous amount of data that is useful in some ways, but is superfluous or irrelevant in others. How can Management decide what is important?

GETTING THE CONTROL STRATEGY RIGHT

The first step is to make sure that the process control strategy for the facility is appropriate, and that process, reporting, and quality parameters are identified and assigned. These include input parameters such as equipment settings (e.g. agitation rate) and output parameters

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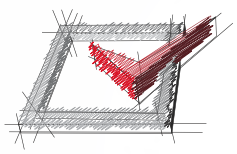
(e.g. pH achieved based on assignment and use of the input parameter agitation rate). How critical are each of these? Not all parameters are critical. The assignment of Critical Quality Attributes should be based on a careful risk assessment with risk to patient as the focus.

With the key parameters identified and the critical ones called out, it's time to define the statistical process control ranges based on live data (batches performed to provide enough sample size to provide assurance of control). Control ranges should be tighter than acceptance criteria.

In those key areas where analytical methodologies already exist, the next step is to implement PAT methods, incrementally. Note that much more data will be generated from the PAT methods than from manual laboratory methods. Where there may have been only one data point in a laboratory for a particular attribute, there might be hundreds of data points with a PAT method. What is the appropriate response to that? What is the appropriate sample frequency?

The quality of the raw materials also has an effect on product quality. What are the key attributes, whether received from vendor testing on a certificate of analysis (COA) or tested on-site as part of release process? It's important to evaluate current data collection methods to ensure these key attributes are funneled to the appropriate place for analysis.



Combine process monitoring data with the validation program to comply with CPV requirements and derive business/process benefits.

DEVIATION MONITORING

Earlier we mentioned deviation monitoring systems. It's important to make sure that deviation monitoring is kept in a single system, rather than maintaining bits of data scattered across systems. Keeping all the data together can help to ensure that all excursions are identified and that the associated data can be trended, so that reports can be generated from a single source. This requires a system with the flexibility to report issues and investigate. The decision to launch an investigation should be predicated on potential impact.

The deviation monitoring system should include the appropriate data fields and reporting mechanisms to reduce the effort expended on data mining. The system should be made available to the plant's MES to allow for real-time documentation and reconciliation of issues as manufacturing occurs. To make this possible, it's important to evaluate the deviation process workflow. Does the system require a minimum number of fields to be populated before a record can be saved (and therefore receive an identification number)? If so, are those fields appropriate for receiving data from an MES to have successful reconciliation?

PROGRAM DEFINITION AND PROCEDURES

Many companies already have strong process monitoring initiatives, but not all of them tie back to the validation program and have the appropriate quality oversight; the goal is to combine process monitoring data with the validation program to comply with CPV requirements and derive business and process benefits. The CPV program should be maintained in alignment with the master validation plans for each site and/or process. Note again, this is recommended for products after the initial validation has been done, so it can be implemented for a company's current commercial products once the appropriate reporting strategy is developed. In addition, if the output of the monitoring program is currently provided only to the technical staff, the audience list should be updated and a formal review program instituted to include the Quality Unit and other validation roles. The CPV program then becomes a robust mechanism for identification of improvements and obtaining collective agreement on implementation of changes.

The formal program should identify the frequency for reporting and identify the mechanisms for investigation and follow-up. This should include the definition of the audience for reporting, as well as oversight by the Quality Unit. Typically, the process, roles and responsibilities would be defined in a Standard Operating Procedure under GMP requirements to ensure consistent process and training.

Where real-time data from DCS, MES and/or PAT cannot be employed or a company is not ready to make that leap, it is still possible to achieve CPV through incorporating laboratory data into the program. The frequency of reporting may differ based on lag time to receive results, but analysis and improvement opportunities may be derived on a real-time basis rather than traditional batch review during release processes; with additional benefit derived when data is evaluated batch to batch instead of evaluating only a single batch.

In short, the drivers behind FDA's most recent process validation guidance represent good science and facilitate continuous improvement on the part of suppliers; both are critically important factors to the needs of the patients and the reputation of the industry. The guidance challenges pharmaceutical manufacturers to achieve Continued Process Verification.

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IN SEARCH OF CLARITY:
Troubleshooting Depth Filtration

Some common scenarios (and their root causes)

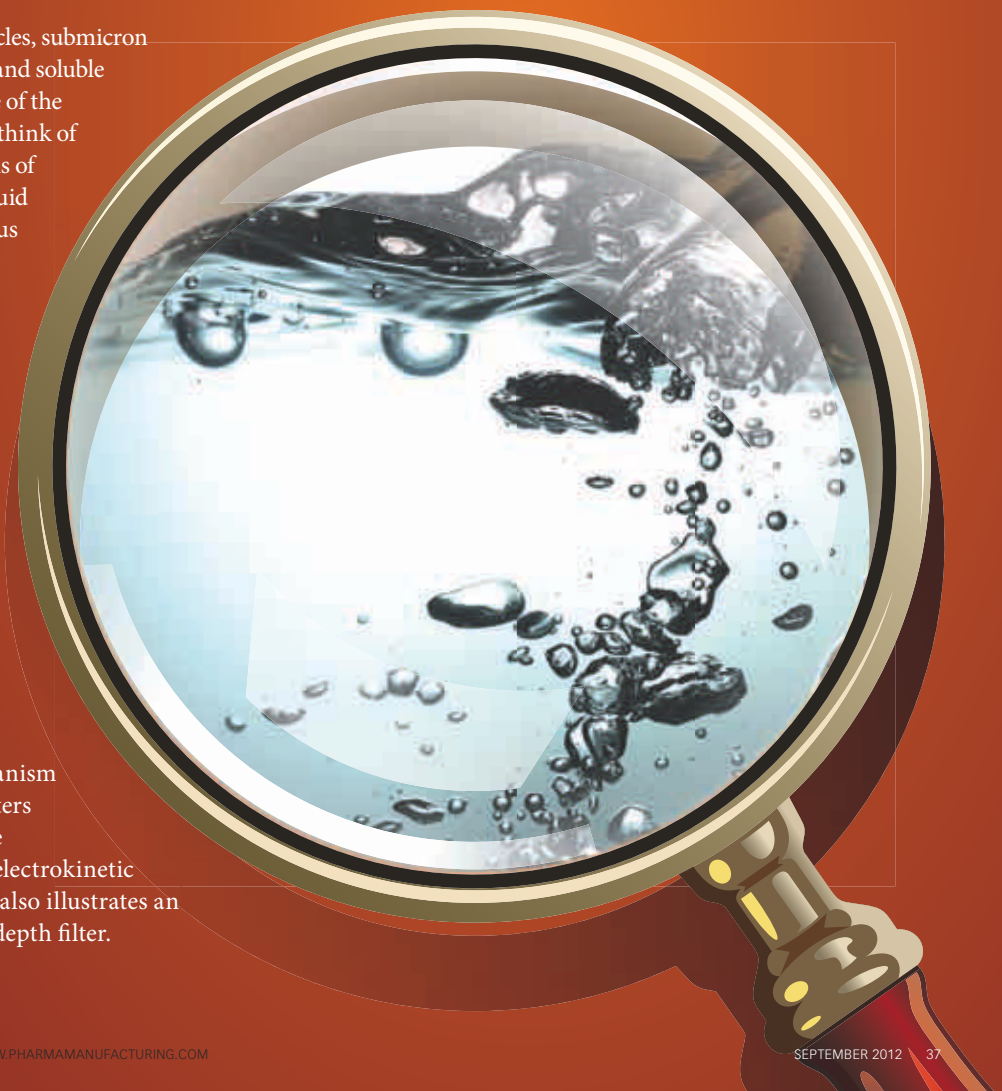
BY BRITTANY NIXON,
3M PURIFICATION, INC.

THE CORRECT selection of depth filters can significantly improve the productivity of any cell culture purification process. However, if the filtration is not optimized early on, problems such as low product recovery, premature plugging, an excess of DNA and Host Cell Protein (HCP), and lack of scalability can occur, resulting in major problems downstream. Optimizing depth-filter performance requires a clear understanding of the specific fluid characteristics and batch-to-batch variability. This article will summarize basic requirements for optimizing selection.

Depth filters remove particles, submicron particles, colloidal material, and soluble material by taking advantage of the depth of a particular media (think of a sponge) to enable high levels of contaminant removal. The fluid must travel through a tortuous path before it is able to reach the other side. Figure 1 illustrates the flow of fluid through depth-filter media.

It is logical to assume that contaminants that are larger than the filter pore size would easily be removed by mechanical filtration. This mechanism is also referred to as sieving, straining, or size exclusion.

However, the removal of contaminants such as DNA and HCP is less intuitive. Another purification mechanism that operates with depth filters is adsorption, attracting the contaminants using either electrokinetic or surface affinity. Figure 1 also illustrates an adsorbed particle within a depth filter.



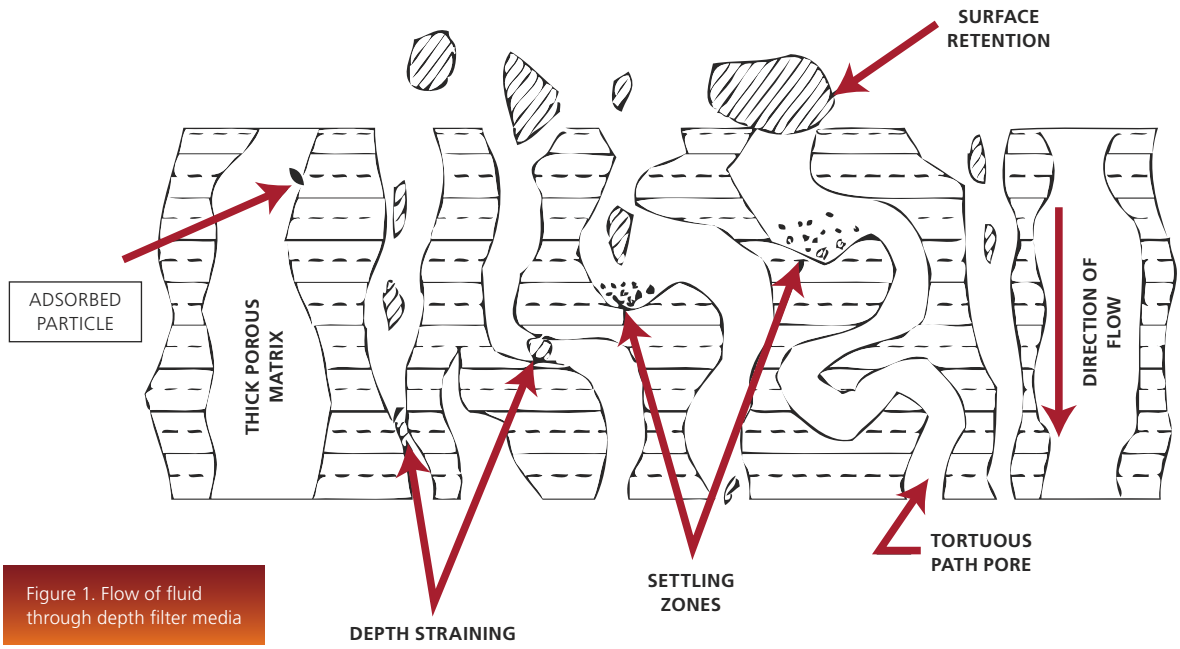


Figure 1. Flow of fluid through depth filter media

The electrokinetic effect present in charge-modified depth-filter media makes removal of these submicron particles, colloidal material, and soluble contaminants possible. Depth media are designed and manufactured with various pore structures and surface modifications. Figure 2 shows the results of testing of a charge modified depth media under the same conditions as a non-charged modified media. The results show that both filters perform equally at the mechanical removal of large particles, while the charge modified filter is more efficient at removal of submicron particles through adsorption. Pore surface chemistry also plays an important role for the removal of contaminants. The removal mechanism works by selecting a filter that has a pore surface energy lower than that of the contaminants. Thereby, the contaminants, driven to reduce their surface energy, would be attached to the pore surface of the depth filter and removed from the liquid stream.

To select the optimum depth filter, it is necessary to research commercially available filter media. There is a wide range of depth-filter media available including but not limited to:

- positively charge modified for removal of negatively charges species
- carbon impregnated for specific adsorptive properties
- high silica for lipid removal
- low pyrogenic for pyrogen-sensitive applications

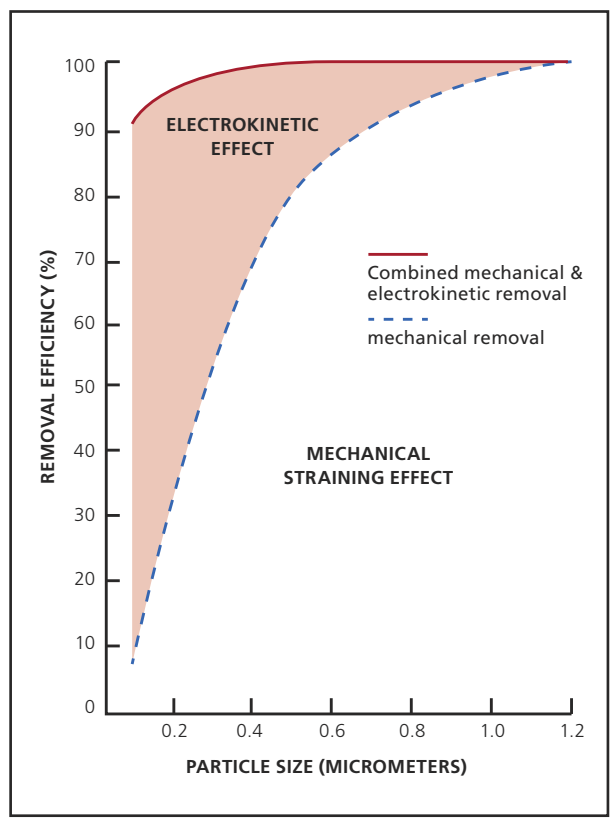


Figure 2. Results of testing of a charge-modified depth filter

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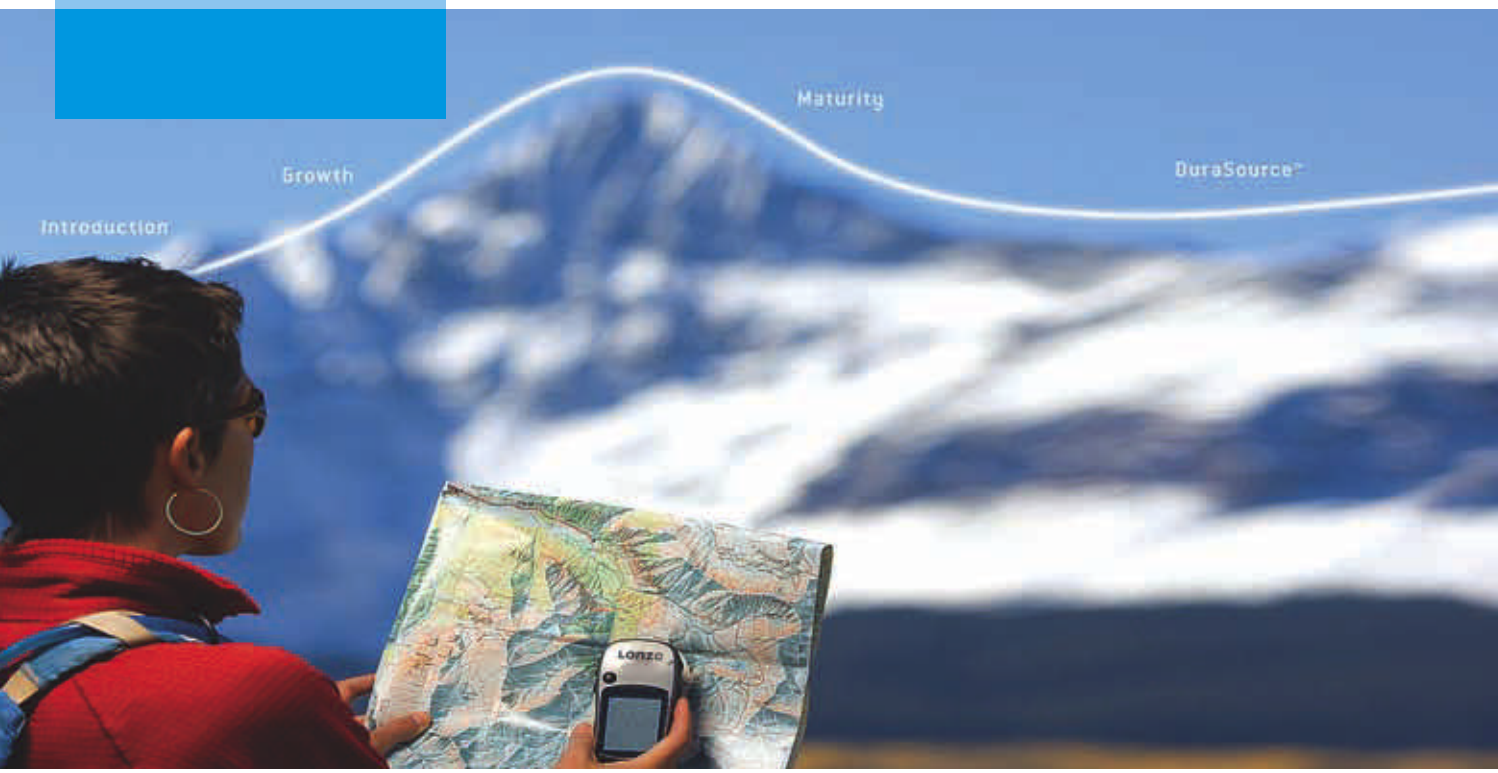

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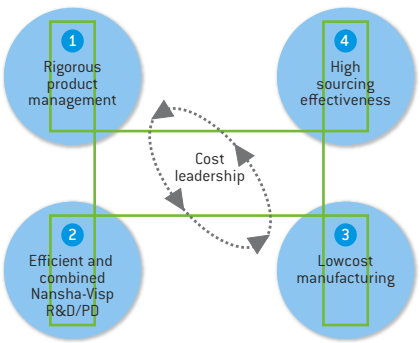

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Depth filters are nominally rated, since there is no one standard contaminant that can be used to challenge all filters and address the complexity of cell culture media compositions. Therefore, it is necessary to test several filters for each application.

In filter optimization, the main goal is to maximize filter capacity. In this regard, dual layer products take advantage of gradient pore size structure within a filter. The larger pore-size filter is placed upstream of the finer pore-size filter. Larger contaminants are captured within the upstream layer while smaller particles are removed by the downstream layer. As a result, a larger distribution of contaminants can be removed in a single step.

The first step in designing a filtration train is determining what needs to be removed or reduced and what should not be removed. Small-scale testing for each process and/or product is important. In many cases for mammalian cell culture, a few pore sizes of charged depth media in various configurations would be tested. In order to measure the effectiveness of the filter, data such as total cell density, viability, turbidity, and titer would be recorded just prior to filtration. During optimization, the differential pressure across each filter, the weight/volume of filtrate, and turbidity of the effluent is monitored until a terminal differential pressure is reached. The turbidity, titer, DNA concentration, and HCP concentration of the pooled filtrate would be recorded and product quality analyzed to determine the optimal filtration scheme.

Reviewing total cell density, viability, and turbidity is a quick way to review batch-to-batch variation. Titer data pre- and post-filtration will show if any product is being retained in the filter. Turbidity of each pool is an indicator of filtrate quality and depth-filter effectiveness, and should be compared qualitatively, especially when a sterilizing membrane filter is used downstream.

If the desired effluent quality is obtained, the next step will be to size the filtration train for a given scale. By analyzing the pressure drop and weight/volume data, throughput is calculated and is used for sizing a system. Throughput is represented as a normalized value with units of volume per unit area, commonly

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recorded in liters per meter squared (L/m^2). The value for filter throughput capacity is used to determine amount of filter area needed for any given size filtration.

For example, say that one liter is to be filtered with a 25 centimeter squared (cm^2) filter. When the experiment is completed, it could be recorded that 0.85 liters (L) was filtered when the terminal pressure drop was reached. This data could then be used to determine the filtration surface required for a 150-liter batch by dividing 0.85 L by 25 cm^2 filter area to get 0.034 L/cm^2 or 340 L/m^2. Next, divide the desired batch size of 150 L by the 340 L/m^2 capacity to obtain 0.44 m^2 of required filter area.

Filter throughput capacity depends upon the particular flow rate and grade/pore size of the depth filter that was tested. If the recorded flow rate during the small scale test was 7 ml/min, flow rate can be calculated for the 150 L batch. This is done by dividing the flow rate of 7 ml/min by the filter area of 25 cm^2 obtaining 0.28 ml/cm^2/min or 168 LMH, a commonly used "liters per meter squared per hour" unit. This value is used to determine the flow rate for any size filtration by multiplying filter area 0.44 m^2 and 168 LMH (74.1 L/hr = 1.2 L/min). Note that the exact 0.44 m^2 of required area could not always be available. The calculation should be repeated with the available filter surface area. Depth filters are designed in modules and next size up is usually recommended. This leads to some excess of filter area, or safety factor, which accommodates potential process and batch-to-batch variation.

Although every product and process is unique, generally the following statements will hold true:

- Lower flow rates per unit filter area lead to higher filter capacity (L/m^2).
- Smaller pore size and higher charged media are more effective in removing DNA and HCP.
- Cell morphology, total cell density, and viability of a harvest impact filter capacity.
- If using a positively charged depth-filter media, the product's isoelectric point (pI) should be greater than the pH to achieve the highest product recovery.
- Factors such as hold-up volume, scalability, ergonomics, and ease of use can vary by specific supplier and should also be considered when determining a filtration process.

There are many factors to consider when developing a filtration process for a product — titer, turbidity, DNA/HCP, and filter capacity. By executing small and mid-scale tests and understanding more about depth-filtration performance, a robust process can be developed which can provide consistent product quality, reliable results for scale-up, and shortening the process cycle time.

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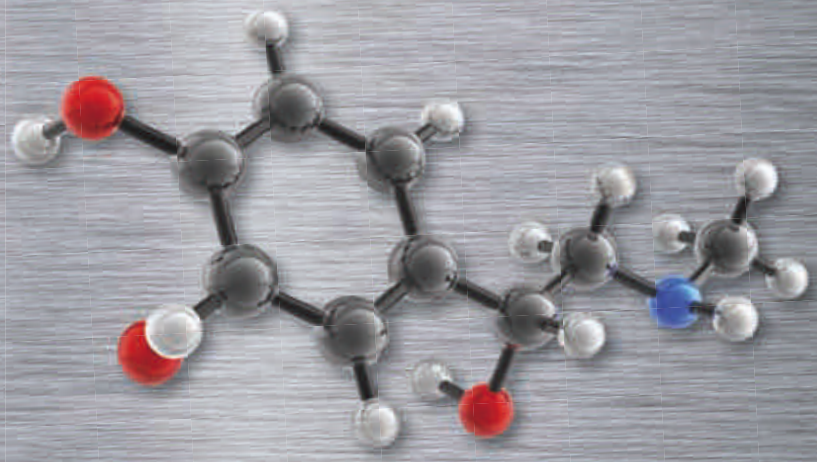

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Sometimes mistakes arise during scale-up phase, which have relatively simple solutions. Here are some examples:

Case 1. The first test performed showed a 98% product yield, and now it is closer to 90%. The filter media was exactly the same, the flow rate was the same, and the product/process was the same. How could the difference be explained?

Potential solution: There could be a number of different root causes, however, it likely had to do with the pre and/or post flush of the filter. Essentially, the product might not have been lost, but diluted with buffers which were used for the flush(es). A mass balance experiment can be done to verify if this is the case.

Case 2. In a two-stage filtration, it seems that terminal pressure drop is being reached earlier than expected.

Potential solution: A pressure gauge upstream of both filters will read the system pressure drop, the pressure gauge upstream of the second filter will read the second filter's pressure drop, and the pressure drop of the first filter will have to be calculated by subtracting the second filter pressure drop from the system pressure drop. It is likely that the system pressure drop is being recorded instead of the first filter's pressure drop. Note that each supplier has different specifications for maximum system pressure drop and individual filter pressure drop.

Case 3. In calculating the amount of pre-rinse needed for the filter, the value was 100 times the amount specified by the supplier.

Potential solution: It is likely that there was an error in unit conversion. Although there are 100 cm per meter, there are 10,000 cm^2 per m^2. It is critical to review calculations and unit conversions in order to ensure the accuracy of results.

ABOUT THE AUTHOR

Brittany Nixon is currently a Scientific Applications Support Service Specialist (SASS) at 3M Purification in the Life Sciences Process Technology Group. She assists many biotech companies in filter selection and optimization. She may be reached at b.nixon@mmm.com.

Reference

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Four Steps to Managing Supplier Quality

Success demands a proactive, collaborative and continuous approach

BY PARAG PATEL, JANICE PAI, JEHANZEB NOOR, AND RAMIT JAIN, MCKINSEY & COMPANY

WHILE QUALITY problems can be found in any industry, they have become more frequent recently in the pharmaceutical and medical-device space. As a result, more pharmaceutical manufacturers are paying greater attention to supplier quality. The most progressive operating companies are taking a proactive, collaborative, and holistic approach to supplier quality management. Their goal is to manage and support suppliers, just as they would their own production facilities, to reduce risk and build better partnerships with these suppliers.

It's not easy. Companies often tell us that they are struggling to master supplier quality — this is not due to a lack of effort, but because managing suppliers has become more challenging. There are several reasons for this, notably:

- Product complexity is rapidly increasing, making it more challenging to integrate suppliers into product development, manufacturing, logistics and service operations, and can also make it more difficult to resolve supplier quality issues.
- Globalization of the supply chain continues to increase complexity. Operating companies must now manage supplier quality across physical, cultural and language borders. Operating companies working with these partners often have visibility into just the first-tier of the supply chain, while significant potential risk resides deeper in the chain with sub-suppliers farther upstream.
- Regulatory demands continue to increase, as FDA and other regulatory agencies expect pharmaceutical companies to take full ownership of managing their suppliers. The past few years, supplier quality issues have been at the root of an increasing number of drug recalls (which have increased by 16 percent year-on-year for the past five years), as well as 483s, consent decrees, and forced plant shut-downs. At the same time, in the age of Internet and social media, coverage of any quality issues is widespread and almost instantaneous, increasing negative publicity and public opinion of the players involved.

Given all these heightened challenges in managing supplier quality, we took a closer look at more than 40 recent pharmaceutical quality incidents (many of which were at pharmaceutical and/or medical device companies) to discern common themes and identify a holistic approach to improving them. We found that more than 40 percent of these incidents were actually due to supplier quality issues. An in-depth evaluation of these supplier quality issues found three main root causes:

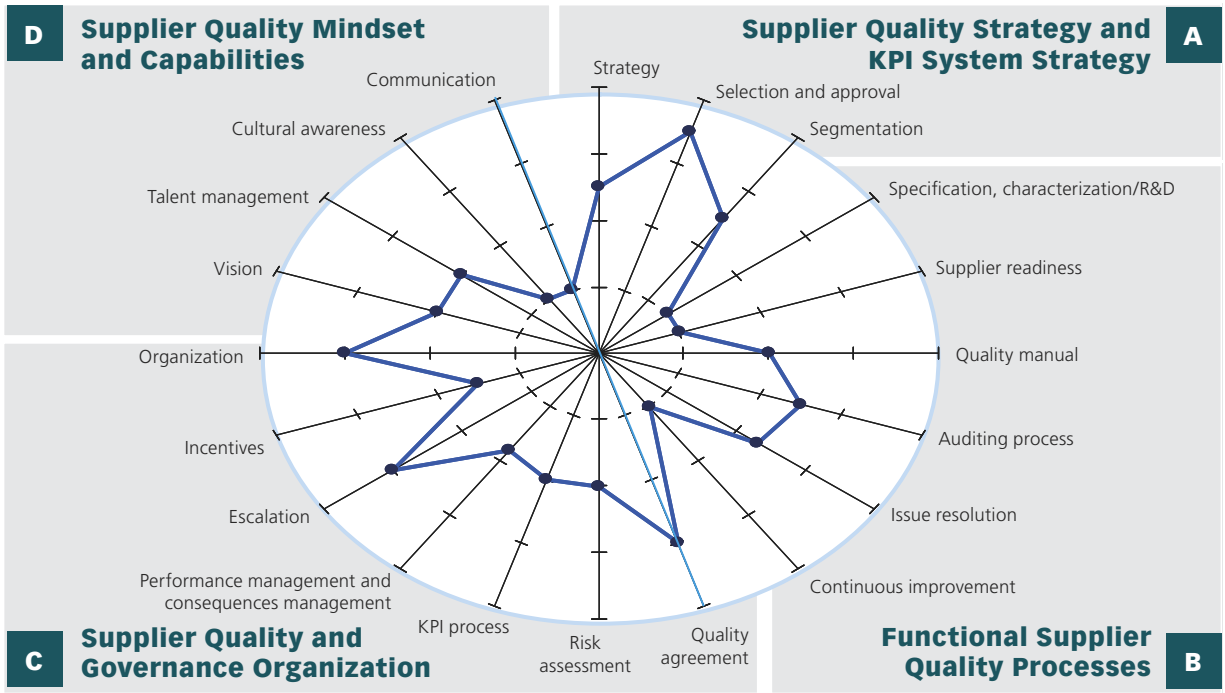
1) lack of collaboration in the design phase
2) lack of a robust quality system/KPIs at the pharmaceutical company and/or the supplier
3) lack of capabilities in supplier manufacturing facilities.

ENSURING SUPPLIER QUALITY IS NOT A QUICK FIX, BUT A JOURNEY THAT DEMANDS A HOLISTIC APPROACH

Managing supplier quality cannot be a quick fix. Instead, it is a multi-stage journey and requires a holistic approach based on four key cornerstones:

1) Supplier strategy and KPI system: Companies must ensure that their supplier quality strategy is aligned with their overarching corporate and purchasing strategies. They must focus their attention on strategically important suppliers, define clear targets, and measure their progress against those targets. Often, companies fail to segment their supplier quality programs, spreading their effort too thinly. This can leave them with only the resources for firefighting, and responding to day-to-day operational incidents, rather than taking the proactive and preventative actions that will drive deep improvements upstream.
2) Functional supplier quality processes: Companies need to define and apply a structured set of standards and processes (advanced product quality planning, part approval processes and root cause analysis standards, for example), both internally for themselves and for their suppliers.
3) Supplier quality organization and governance.
4) Supplier quality mindsets and capabilities: Focused communication efforts with suppliers are required to maintain attention on quality issues. But it is equally important to invest in getting the right people with the right skills and expertise.

An Internal Quality Diagnostic Can Help Identify Opportunities for Improvement



One large medical device company applied many of the techniques outlined above to uncover and rectify many of its supplier quality issues, summarized below:

- Diagnostic phase: First, the company identified the sources of supplier quality risk by conducting a full quality diagnostic across 20 critical dimensions of supplier quality. This company started with an internal diagnostic (Figure) using these 20 dimensions to identify improvement opportunities and prioritize its areas of focus. This evaluation highlighted areas where improvement was needed.
- Design phase/prepare for supplier assessment: The company developed a supplier assessment approach to evaluate the operating systems, management systems, and culture of its suppliers. The company's suppliers were also prioritized for evaluation based upon risk with the goal of balancing a reactive approach (i.e., address the recently "problematic suppliers) with a proactive approach (i.e., evaluate suppliers that could be "problematic" in the future). The company used criteria such as suppliers with recent recalls/complaints, suppliers linked to critical products, suppliers with highest spend, and other qualitative factors to rank suppliers and prioritize the evaluations. This helped to identify the first 15 suppliers to be assessed and improved. An in-depth evaluation toolkit (with scorecards across operating, management and culture systems) was built to conduct the evaluation, and a cross-functional evaluation team was selected and trained. Finally, the company communicated to the suppliers so that evaluation could be collaborative to uncover "win-win" opportunities.
- Implementation phase: An 18- to 24-month roadmap was built to roll out the assessments, build supplier capabilities and define internal requirements.

This new assessment allowed the company to go from a reactive, audit-based approach to a proactive assessment toolkit that could be applied across multiple franchises and products. The company has improved many of its internal practices, completed more than 15 supplier assessments with clear action plans to improve the suppliers' approach, and now is continuing to evaluate its other "high-risk" suppliers. Most importantly, there was a substantial improvement in the collaboration with suppliers that will continue to identify actions to reduce quality risks for both the suppliers and company itself in the future.

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QbD: To Be or Not to Be?

That is the question, but the answer may surprise you

BY CHRIS AMSTUTZ, DIRECTOR, LIFE SCIENCES INDUSTRY CONSULTING, EMERSON PROCESS MANAGEMENT

THE DEBATE over Quality by Design (QbD) and Process Analytical Technology (PAT) rages on in the pharmaceutical and biotech industries. Some companies have adopted these process improvement methodologies with great success, but most continue to drag their feet.

On the surface, it appears to come down to a cost issue: QbD and PAT cost too much to implement and the "old ways" seem to get the job done, so why bother? In other words, it's easier and less expensive to do nothing, especially since no one is forcing pharma manufacturers to do anything else.

But there's more to the issue than just cost. First, QbD and PAT are the right things to do because they benefit the patients who use pharmaceuticals. Today, these patients face shortages of critical products they need. At the source of some of these supply problems are manufacturing and quality assurance issues. PAT and QbD offer ways to prevent these problems from occurring in the first place.

Second, experience shows that QbD and PAT improve productivity, reduce waste and cut costs. It makes more sense for pharma companies to embrace QbD and PAT than to ignore them.

Proponents argue, with passion, that QbD and PAT are the right things to do and make good business sense, looking disdainfully at their powerful managers and asking why they cannot understand something so obvious.

The debate comes down to shareholders against stakeholders. Shareholders are the owners of the company — the stockholders, corporate owners, banks, brokers, and other entities who have a financial interest in the company's performance. They want the company to be profitable so that company share values will increase. Stakeholders are those who are affected by the company's actions or inactions. This includes but isn't limited to shareholders, company employees, suppliers and — most important of all — the patients who consume the company's medications.

Shareholders often treat other stakeholders as nothing more than background noise. In their view, even if they make business sense, QbD and PAT are related to production metrics. Thus, by definition, are of a lower priority than R&D, testing, distribution, record keeping and marketing, which, according to one recent estimate, outweighs R&D spending by 19 to 1.

Given a rapidly changing business landscape and pressure to maintain profits, their focus is on profitability, and they may feel that incremental improvements in production metrics, as achieved with PAT and QbD, may not be a strong enough economic driver. This can be particularly true if attaining production improvement requires changing a process and entails record keeping and regulatory costs. In the middle of this debate are the patients, the most important stakeholders.

CAN CORPORATE SOCIAL RESPONSIBILITY BREAK THE "STAKEHOLDER VS. SHAREHOLDER" IMPASSE?

Could corporate social responsibility be the catalyst to get pharma's shareholders and stakeholders to come together? Corporate social responsibility is much more than an empty buzzword today. As Web-based and social media influence opinion, companies and their leaders are held responsible for what they say and do — or fail to do.

Bad publicity already affects pharma companies, and pharma has had a lot of bad publicity lately. Could the idea of preventing negative impact on patients get senior management to embrace QbD and PAT, and recognize the potential benefits of many incremental improvements?

When done right, QbD and PAT will exhibit a postive ROI, benefiting all stakeholders. Emerson recently worked with a company that had a 15% reject rate for one product. It had been drying to a time spec and, as a result, product was being overdried, and wasted.

Changing to a real-time approach using NIR, and implementing a series of PAT pilot studies, the firm was able to evaluate the real-time measurement of critical quality attributes. As a result, the company identified $2 million in annual cost savings by implementing PAT on secondary process operations — another example that shows QbD and PAT are the right things to do.

The firm is not only smart, but also socially responsible. But perhaps the concept of being more responsive, and responsible, to patients will end this debate and usher in a new era of QA and operations.

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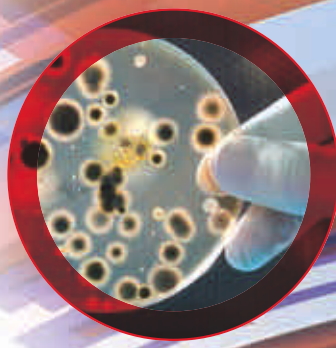

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- Confirmed speakers from the *FDA*:
  - **John Metcalfe**, PhD, Senior Microbiology Reviewer, *CDER, FDA*
  - **Marla Stevens-Riley**, PhD, Senior Microbiology Reviewer, *CDER, FDA*
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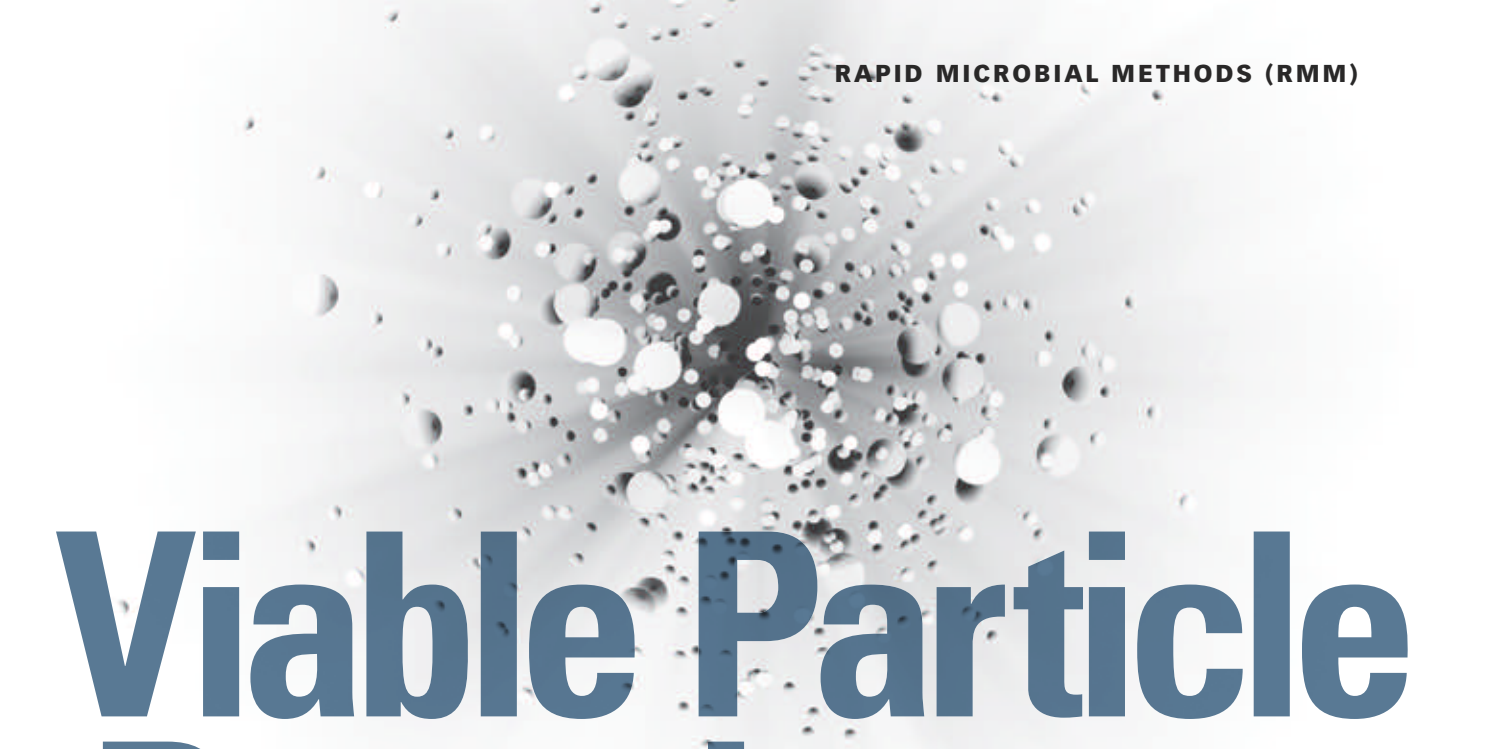

Viable Particle Detection

CHALLENGES & OPPORTUNITIES

Particle counters offer opportunities, but show a need for updated guidance

BY DARRICK NICCUM, TSI INC.

RAPID MICROBIOLOGICAL Methods (RMM) have intrigued pharmaceutical manufacturers for several years. The benefits of RMM are well established: They enable better insight into the manufacturing process by providing microbial information much faster than the compendial methods that take multiple days to provide results. Most currently available RMM instruments are laboratory-based and significantly reduce the time to obtain microbial results from a collected sample. Several manufacturers have recently introduced real-time viable particle detectors similar to that shown in Figure 1.

Real-time viable particle detectors use optical techniques to determine particle viability on a particle-by-particle basis. This capability provides for:

- Trending of microbial content in the manufacturing environment.
- Instantaneous notification of microbial contamination events.
- Enabling segregation of potentially exposed product.
- Rapid initiation of root cause investigations.
- Providing input to Process Analytical Technology (PAT) based process control measures.
- Potential for real-time product release.

While real-time viable particle counters offer significant potential benefits, they also present some new challenges to industry and regulators. This article will address the unique challenges associated with evaluating, testing and validating this new family of RMM instruments.

REAL-TIME VIABLE PARTICLE DETECTION 101

Real-time viable particle detectors use the intrinsic fluorescence of microbial constituents associated with cell viability to analyze environmental particles entrained in the aerosol sample flow path. When excited by ultra violet laser light, the metabolites associated with cell viability fluoresce and emit light at a higher wavelength than the excitation wavelength. Principal microbial fluorophores associated with cell viability are tryptophan (excitation peak ~280 nm, emission peak ~340 nm), NADH (excitation peak ~340 nm, emission peak ~450 nm), and riboflavin (broad excitation ~350-450 nm, emission peak ~530 nm).

The most common excitation source for portable viability detectors is the 405 nm laser diode. The technique is non-specific. Organism specificity is not obtainable due to the complex composition of the viability metabolites and the resulting fluorescence signal. Laser induced fluorescence (LIF) has been used in

military and homeland defense threat-detection products since the late 1990s. It has only recently been adapted for use in the pharmaceutical manufacturing environment.

Real-time viable particle detectors have several key operating parameters: sample flow rate, aerosol efficiency, sensitivity and false positive rate.

Sample flow rate is the amount of air that the instrument analyzes. Higher flow rates enable better characterization of manufacturing environments and reduce the time required to meet mandated sample volume requirements. Aerosol efficiency is the ratio of the number of particles present in the manufacturing environment compared to the particles that reach the instruments analysis engine.

Sensitivity and false positive rate describe the ability of the real-time viable particle detectors to measure and differentiate viable particles from non-viable particles. Sensitivity is the ability to measure low numbers of viable particle counts. A false positive occurs when a non-viable particle is classified as a viable particle. False positives can occur due to the non-specific nature of the LIF technique. Additionally, non-viable particles such as pollens, skin flakes, and paper dust have fluorescence properties and create optical signals that must be addressed during instrument design. Typically, higher sensitivities result in higher levels of false positives. These key operating parameters should be considered and addressed when evaluating and validating real-time viable particle detectors.

Figure 1. BioTrak real time viable particle detector

Due to the low intensity of the fluorescence signals, real-time viable particle detectors that have sample flows greater than approximately 5 liters/minute must reduce the flow to increase the fluorescence emission intensity. Aerosol concentration is the enabling technology incorporated into high flow rate detectors. Aerosol concentrators utilize particle inertia to concentrate the larger particles of interest into a lower velocity flow volume. The incoming sample flow is separated into a high (major) volume flow that is exhausted from the system and a low (minor) volume flow that is analyzed. Small low-inertia particles follow the high-volume flow path while larger high-inertia particles follow the low-volume analyzed flow path. Figure 2 illustrates the operating principles of a concentrator.

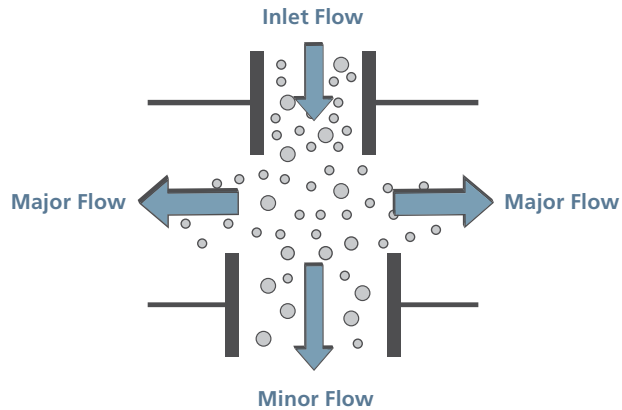

Figure 2. Aerosol Concentration: Small particles follow the major flow path and are not analyzed; large particles with greater inertia follow the minor flow path and are subsequently analyzed.

Two key parameters define concentrator performance: aerosol efficiency and D50 cut point. Figure 3 shows aerosol efficiency on the Y-axis and particle size on the X-axis. Aerosol efficiency is the ratio of the particles in the minor (analyzed flow) flow versus the total number of particles present at the inlet of the concentrator at each given size.

The D50 is the particle size, where 50% of the particles contained in the incoming flow are carried forward into the low volume analyzed flow. The efficiency is the percentage of incoming particles above the D50 carried forward into the low volume analyzed flow. The diversion of smaller particles into the exhaust flow is not a major concern since the majority of biological particles range in size from 2 to 10 microns. The efficiency is an important parameter since not all the particles in the incoming sample are analyzed, their numbers are reduced by the efficiency of the concentrator. Active air samplers are characterized in the same manner.

The detection efficiency of the viable particle detector is as important as its aerosol efficiency. All real-time viable particle detectors on the market today are based on intrinsic fluorescence, which is non-specific due to the variability of the quantity of fluorescent metabolites in microbiological organisms. Adding to the complexity of the viable particle detection is the fact

that some non-viable particles also have fluorescence properties. The detection performance of viable particle detectors is usually a tradeoff between its sensitivity (i.e. its ability to detect low levels of viable particles) and the amount of false positives that it generates when exposed to naturally occurring environments comprised of both viable and non-viable particles. Currently available viable particle detectors use different analysis techniques and incorporate different optical input parameters. Thus, different instruments will have different performance characteristics in terms of sensitivity and false positives. Sensitivity and false positive performance is extremely difficult to characterize in controlled laboratory conditions due to the variability of particles that are present in the manufacturing environment. Adding to the uncertainty are the known deficiencies of the compendial method: which agar should be used, what incubation temperature and time should used, and the recognition that Viable But Non Culturable (VBNC) organisms exist.

REGULATORY GUIDANCE

With the exception of real-time viable particle detectors, the majority of current RMM instruments are operated in the microbiology lab and speed up the process of analyzing microbial content of previously obtained environmental or product samples. The guidance given in USP 1223, EP5.1.6, and PDA TR33 was developed based on laboratory test methodologies. The key evaluation criteria given in TR 33, USP 1223 and EP 5.1.6 consist of:

- Accuracy
- Precision
- Specificity
- Detection Limit
- Quantification Limit
- Linearity
- Operational Range
- Robustness
- Repeatability*
- Ruggedness*

*(*mentioned in USP <1223> only)*

The guidance documents describe serial dilution test methodologies to generate challenges so the RMM can be compared to the compendial plate culture method. Laboratory-based challenge inoculums can be fairly well controlled, as can the ability to mix different microbes of interest to determine specificity and matrix effects. Generating controlled aerosol releases of known concentrations is considerably more difficult than serial dilution methodology. The experimental uncertainty

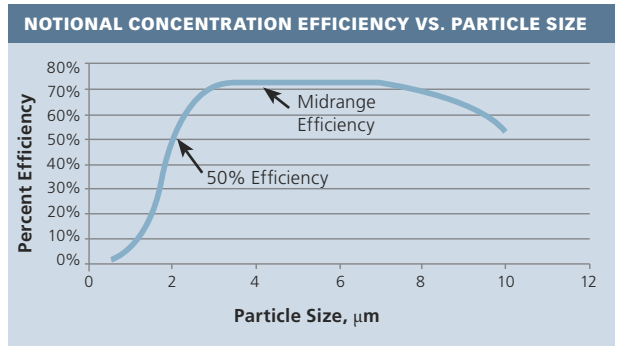

Figure 3. Concentrator Characteristic Aerosol Efficiency Curve

associated with aerosol challenges is considerably larger than that of laboratory-based methodologies. This raises into question whether the acceptable criteria stated in the guidance documents are directly related to aerosol-based instrument performance criteria.

ISO 14698-1 contains guidance for the characterization of active air samplers. ISO 14698-1 describes the generation of a known concentration of biological aerosols in a well-characterized aerosol chamber and comparing the colony counts obtained by the active air sampler with those collected by a reference filter. The ISO standard calls for the use of Bacillus subtilis var niger (Bg) spores for physical efficiency because it survives aerosolization and capture with very minimal loss of viability so colony counts are an accurate representation of physical particles.

Staphylococcus epidermidis is designated for biological efficiency testing since its survival rate is more representative of vegetative bacterial contaminants. The biological efficiency is intended to characterize the potential damage the active sampler could do to microorganisms. The test is difficult to perform as indicated by the fact that the Health Protection Agency (HPA) in the UK performs the majority of the independent characterizations of active air samplers according to ISO 14698-1. Vellutato recommends an alternative method for characterizing the efficiency of active air samplers using OPCs to measure the total number of particles present in exhaust of the air sampler versus the number of particles measured up stream of the sampler (Vellutato Jr., Arthur, Sampling Equipment, Chapter 18: Environmental Monitoring: A Comprehensive Handbook, Volume 1; Moldenhauer, PDA 2005). He also presents an excellent discussion pertaining to characterization of active samplers and the challenges associated with ISO 14698-1 guidance. Because real-time viable particle detectors sample environmental particles for analysis, their aerosol efficiency must be characterized in a manner similar to

that employed for active air samplers.

Existing RMM guidance evaluates performance of the method compared to compendial techniques post sample collection. As illustrated in Figure 4, a real-time viable particle detector is both a particle sampler and viability detector. Evaluation of real-time viable particle detectors must include the following critical factors:

- How the aerosol is introduced during routine operation as well as laboratory based evaluation.
- The aerosol efficiency of real-time viable particle detector.
- The aerosol efficiency of the active sampler used to obtain the comparison sample.
- The detection efficiency of real-time viable particle detector.
- The false positive rate of real-time viable particle detector.

Current RMM guidance does not appropriately address the critical performance parameters of real-time viable particle detectors. Current guidance focuses on comparing new laboratory-based methods to the compendial culture-based method. This guidance addresses the majority of post sample collection laboratory based RMM instruments. The established technique of serial dilution is appropriate for characterizing the key performance characteristics defined in the guidance. Real-time viable particle counters gain their utility from measuring aerosol viable particles. This introduces a significant source of uncertainty into the evaluation process. The uncertainty involves both the ability to generate well-controlled challenge aerosols in addition to having the aerosol efficiency of both the active air sampler and the real-time viable particle detector well characterized. Finally, how the challenge aerosol is introduced to the real-time viable particle detector is critical and can have a large influence on the reported results.

Establishing the Limit of Detection (LOD) is a challenging task for several reasons. It is extremely difficult to generate stable, low concentrations of aerosolized viable particles. Additionally, the LOD of an aerosol instrument is determined by count and sampling statistics. The LOD is influenced by the sample volume, sampling time, detection efficiency, and the relative aerosol efficiency of both the reference aerosol collector and the real-time viable particle detector under test. It is difficult to apply and evaluate single particle detection to aerosol instrumentation. There are aerosol generation methods that can generate single particle challenges.

Single particle generation equipment produce a series of single particles that can be directed into the inlet of the real-time viable particle detector and measured allowing single organism capability to be claimed. It should be noted that the test methodologies do not correspond to how the instrument will operate in the manufacturing environment. Evaluating LOD and single particle detection capability requires a discussion of sampling statistics, flow volumes, and particle concentrations in order to establish the correlation between the laboratory experiment and real-world performance.

Current RMM guidance does not adequately address evaluation and validation of real-time viable particle counters. The guidance criteria are generally applicable, but the test methodologies do not adequately

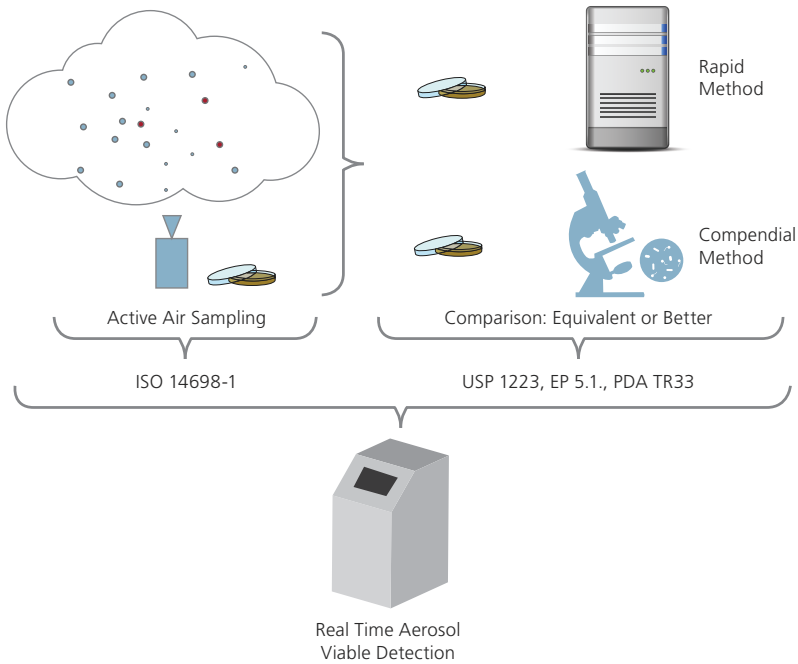

Figure 4. Guidance for Evaluating Real-Time Viable Detectors

address the unique characteristics and challenges associated with aerosol instrumentation.

The key performance criteria given in USP <1223>, EP 5.1.6 and PDA TR33 are applicable, but the test methodology and performance limits require refinement and clarification.

The challenges associated with evaluating this new family of RMM instrumentation are directly related to the benefit they offer to the manufacturing process: The ability to measure for the presence of viable organisms on a real-time basis. The FDA aseptic processing guidelines states: "Manufacturers should be aware of a device's air monitoring capabilities, and the air sampler should be evaluated for its suitability for use in an aseptic environment based on collection efficiency, clean ability, ability to be sterilized, and disruption of unidirectional airflow" (Guidance for Industry Sterile Drug Products Produced by Aseptic Processing-Current Good Manufacturing Practice FDA 2004). Similar awareness and understanding needs to be developed for real-time viable particle detectors. Characteristics such as sample flow rate, aerosol efficiency, sensitivity, and the false positive rate should be considered and evaluated. In order for the full benefit of this new technology to be realized, collaboration between vendors, industry, and regulatory authorities is required to define and implement better test methodologies to characterize and validate them.

The ability to monitor for the presence of viable particles on a real-time basis offers tremendous benefit to the pharmaceutical manufacturing process. However, the real-time aerosol-based viability measurement does not lend itself to current RMM guidance developed for post sample collection laboratory-based instruments. Methodologies that consider the unique nature of the measurement must be developed through active dialogue between instrument vendors, industry and regulatory bodies. The benefit offered by this new family of RMM instruments is well worth the effort.

ABOUT THE AUTHOR

Darrick Niccum is a Senior Global Product Manager-Biotechnology for TSI Inc. He has been involved in development of particle detection instrumentation, including fluorescence based viability detections for 12+ years. He can be reached via DNICCUM@TSI.com.

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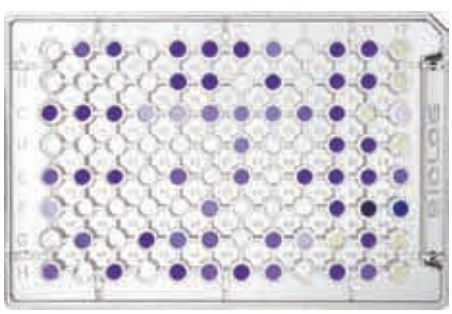

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DEPLOYING PAT FOR MANUFACTURING:

A Practical Guide

Taking a structured approach, let's redefine PAT as the Practical Application of Technology

DESPITE THE many operational and cost-saving benefits provided by Process Analytical Technology (PAT), its adoption in the life sciences sector has been slow. There are many reasons for this: natural resistance to change, perceived cost, complexity, risk, regulatory concerns, depth and length of commitment required, and deployment methodology, which is not clear to all. This has meant that PAT deployments may take too long.

BY MARTIN GADSBY, DIRECTOR, OPTIMAL INDUSTRIAL AUTOMATION LTD

The challenges facing PAT implementations are many. First, people generally do not like change. Second, people may fear that the implementation of PAT may adversely affect roles and responsibilities. Third, regulatory requirements still have to be met at a time of great change, but the FDA has created opportunities for streamlined registration of such changes. Fourth, PAT deployment calls for a wide range of skill sets. Fifth, a detailed yet pragmatic and risk-based approach is required. Sixth, the correct and appropriate PAT technologies are essential for project success. This article will focus on these last two challenges.

Developing the underpinnings for successful PAT deployment is a two-phase process. Phase 1 is concerned with process model and knowledge building — control is seldom of concern at this stage. For this phase, the requirements are typically a univariate data-acquisition system, spectral instruments, an MVA package, and a PAT data-management system. Phase 2 deals with control model building and control with PAT. For this phase, all the items listed in Phase 1 are required, plus a control system.

Step 1: Target Product Identification

PAT Implementation Strategy is all about knowing where to start and what questions to ask. If the project is going to be related to a new product application, typical questions would be: Can I produce without PAT? What are the benefits of using PAT, and how do I quantify them? Do I apply PAT at the R&D, PD or production phase? In existing product applications, the questions are fundamentally different. Typically they include: How do I work with the regulator on an existing process? What are the potential

financial, quality and timing gains? What are the risks and how do I mitigate them? An often unspoken concern also relates to answering the question, what happens if the PAT process reveals that my existing quality isn't to the standard that I always thought it was?

Step 2: Unit Operation Identification

Of even more importance is the question of which process to start with. Should the easiest or most complex be targeted? Alternatively, what about the process with the highest potential financial or quality gains? Or should it be the process that is likely to be the fastest to deploy? The outcome of this targeting strategy is critical.

As a general rule, no matter whether the PAT implementation is going to be on a new or existing product, for your first PAT implementation, you should choose a unit operation that is not too complex and where the PAT deployment can be carried out in a timely fashion. Even if only modest financial or quality benefits are gained, provided the project can be delivered in a timely fashion, then it is better to follow this route than one where the financial or quality gains are much greater but will take much longer to deploy. If the first project becomes protracted, then the sponsors can lose heart and interest. This will only give PAT a bad name with managers and ensure delays in its further adoption.

By taking this conservative approach, the first project will be invaluable in terms of learning and will make further projects much more straightforward. You can then move on with confidence and experience to the more complex projects that may deliver more financial and quality gains. Further key recommendations are that PAT should be employed as soon as possible in the process development cycle, because PAT models developed early on in the development cycle can be very beneficial to the development cycle as a whole.

Step 3: Regulatory and Human Resources Acceptance

Engagement, both with the regulatory authorities, and with the staff concerned is vital to any PAT project's success. Staff needs to be advised of the strategy and objectives of the project to ensure buy-in. By engaging with the regulator early on, you can establish a dialogue in relation to your intentions and agree upon the way forward.

Step 4: Put Team in Place

An in-house audit is necessary to identify all the available in-house skills and engage them on the project, while also identifying skill sets that are missing. Any gaps can be filled either via recruitment or by connecting with an appropriate PAT services provider.

Step 5: Data Acquisition Technology

The next step is to identify the Critical to Quality Attributes (CQA) for the chosen target unit operation, and also the CQAs for the up and downstream processes. What also must be considered at this stage is that future CQAs may affect the choice of instruments made at the present. For example, it may be more cost effective in the long term to purchase a multi-head instrument that can also be used on an up or downstream process.

From identification of CQAs, the next step is to determine how the raw data for determining the CQAs is to be measured. This invariably requires the selection of one or more instruments that output multivariate (spectral) data and this may need to be combined with univariate data. Instrument vendors or consultants can be of great assistance in determining the best instruments and the finer details relating to sampling position, probe types, sample sizing and the like.

Step 6: Data Management and MVA Technology

At this halfway stage of the implementation strategy, the next action is to identify the optimum PAT data management product. Without a data management platform, the model building will take much longer, and there will be huge problems maintaining control of all the data that is to be processed in a way that is acceptable to a GMP process and regulator. The PAT Data Manager should be instrument neutral — use the most suitable for the process; it should also be neutral as far as control system and multivariate analysis (MVA) packages are concerned, so that there won't be a need to upgrade your control system. Other key requirements are cost effectiveness, scalability, ease of configuration and flexibility. Next, identify the optimum MVA package.

Step 7: Design Experiments for Model Building

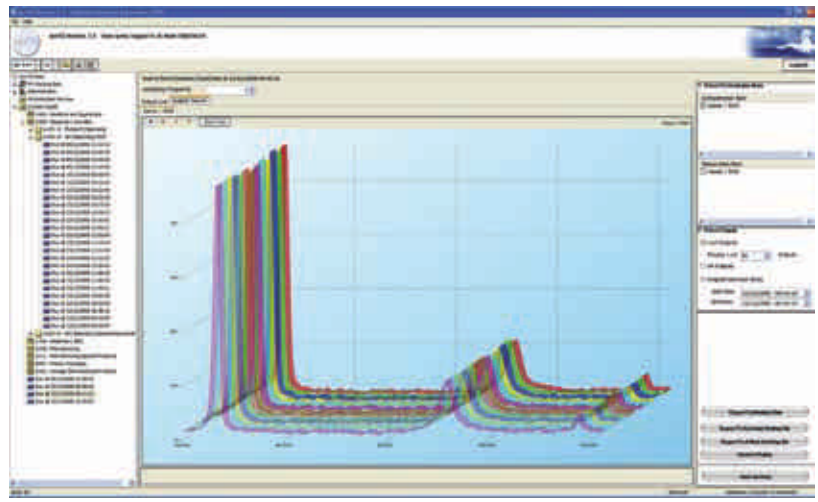
Once the data management and MVA packages are decided upon, the stage is set to design the experiments required for model building. Before embarking, it is important to bear in mind that, as the understanding of a process grows, the choice and number of CQAs may change. The experiments themselves should be optimized using Design of Experiments (DoE), and all data should be saved.

Data acquisition and data association are key activities at this stage. As regards data acquisition, both time-synchronized univariate and multivariate data need to be collected using the PAT data management product, and physical samples for off-line analysis in the laboratory have to be taken during the experiments at known points in time. It is very important for all the asynchronous data sources to be synchronized by your PAT data manager in order to

ensure that all the data gathered at any one point in time is valid.

The time synchronization of physical sample taking is also critical to ensuring that the data for model building is correct. The samples that have been gathered should then be analyzed retrospectively in a laboratory and the results added back into your PAT data manager and associated with the real time product data gathered at the precise moment that the sample was taken.

The multiple data sets of raw data and laboratory results are then collated together as a group within your PAT Data Management product and then exported to your MVA package. All model building is executed within the MVA package, and the model is then imported into the PAT Data Management product. By controlling the export of data and import of model directly between your PAT Data Management product and the MVA package, the provenance of the model is assured as all of the audit data can be stored together with the model. Without a full creation history then the value of a model is significantly reduced — potentially it will only be suitable for non-GMP operations.



Optimal Automation

Historical data, maintained in the PAT data management system, will be critical to building the models you need. Don't strive for perfection at first, or you will add to the cost and timeframe, and turn off management support. Instead, build a workable model that ensures adequate quality.

Step 8: Process Model Testing

The model, or models, that are produced by the processes in the previous step are loaded into instances of a real time prediction engines, typically supplied by the MVA vendor, but managed for real-time use by the PAT data management package. Here, one can save time by testing models initially against historic raw data and comparing the "live" results against laboratory results that had not been used in the model building, i.e., a "virtual" process can be run. In addition, multiple models may be tested concurrently.

When running the actual process, the operations are very similar to those executed during the model building phase, i.e., at known and recorded points in the process samples are taken for retrospective analysis. The results are then compared with the historical CQA output value that the real time engine generated at the exact time that the sample was taken.

If the model is not generating the correct results, it needs to be refined. This can be done by gathering more data and laboratory results to optimize the model design and then repeating the testing regimen. However it must be pointed out that at this stage the model will not be perfect. You should apply the 80:20 rule — if the model is capable of being used to make product that is of acceptable quality (not optimized, but adequate), then use the model and move on.

Support for PAT projects can be lost at this stage if users focus too closely on optimizing a model. PAT embraces continuous improvement, so by definition, the models will not be perfect from day one. However, after gathering the data from many batches over many months or years, the models can be continuously improved to optimize financial and quality gains.

If too long is taken at this stage, then project sponsors will tire of waiting and there is a real risk that the project will be canceled and all future PAT projects will be vetoed for years to come.

Step 9: Develop Understanding

For a true PAT system, developing process understanding is essential. Experiments should be designed to show how in real time the CQAs change with varying control parameters and raw material input quality — the parameters that are critical to the target CQAs — the Critical Control Parameters (CCPs) are therefore derived. The process should be run with all real-time data being recorded by using the PAT Data Management system and being displayed in real time by this same package.

By running the process in this way, you will be able to study the effects of input process parameters on your CQAs in real time, plus you will be able to retrospectively analyze the

results to develop understanding of the mechanistics of the process. When the understanding has been derived then it will be possible to predict how a CQA will change when an input parameter is changed.

Step 10: Develop and Test Control Models

The process understanding derived from Step 9 is used to design and build the Control Model. At this concept stage, running the control model from within the data management product can have advantages. For example: Running multiple instances of control model in open loop can speed up the development process, however there is no reason why it shouldn't at this stage be deployed in your control system of choice .

Initially, the process should be run in open loop. An initial "soft" option, (if possible and permitted by the process) is to use manual control derived from instructions from the control model. Provided that the parameter change demands are within the licensed allowable operating envelope of the process, then automatically prompted manual control can be undertaken to test the control model's validity.

Running in open loop at this stage, and with all "traditional" testing in place, offers the major advantage that the model development or improvement exercise can sometimes be undertaken during normal production. In this mode, all salient events are recorded in the data-management system, and the results analyzed, retrospectively, to adjust the control model as necessary. Then, with the model refined, an attempt should be made to run the process with full PAT control in place, initially on trial batches. If the "soft" option is not possible then control model testing will have to be conducted solely on trial batches.

The control model is then optimized as necessary; once again applying the 80:20 rule. When finally fit for purpose, the model can be deployed onto the production control system. At this stage of the implementation process, PAT will have proved its worth and gained buy-in. It is now time to identify the next unit operation (or product) where PAT can be used, and repeat the process.

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Martin Gadsby is Director of Optimal Automation Ltd., which offers the synTQ data management software as well as vision systems. He can be reached at mgadsby@optimal-ltd.co.uk.

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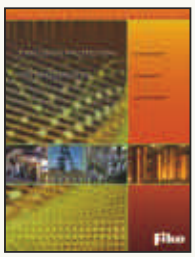

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EQUIPMENT & CUSTOM SERVICES

PAT's O. Henry Paradox

At a time when new PAT hardware is introduced at conferences, companies are sending fewer people to find it

BY EMIL W. CIURCZAK, CONTRIBUTING EDITOR

MY EDITORS think I'm working at conferences, when I am actually having fun looking for new products to talk about. Little do they know, this is something I'd do for free. There's nothing like searching for the latest gizmos and gadgets at Pittcon and other instrumentation conferences. What drives me are curiosity and the desire to try something new and/or improved (no matter what vendors say, no product can simultaneously be both).

As more industry professionals recognize that process analytical technology (PAT) and pharmaceutical Quality by Design (QbD) can help ensure quality products, these "toys" take on greater importance. If we are to achieve true process control, new instruments become the heart and soul of pharmaceutical product quality assurance.

Recently, I was reminded of how many good analytical tools I had seen when my editors asked me to evaluate reader nominations for *Pharmaceutical Manufacturing*'s first Innovation award. It made me think of one of my favorite short stories by the writer, O. Henry.

You may be familiar with this classic, "The Gift of the Magi." A young husband and wife, without much money, want to buy each other very special Christmas gifts. The woman has long, luxurious hair, so her husband plans to buy a beautiful comb. His greatest treasure is his pocket watch, for which she wishes to buy him a chain. In short, she sells her hair to buy his chain while he sells his watch to buy her a comb. What, you may ask, does this have to do with analytics and pharma?

As the pharmaceutical industry comes under increasing pressures from all quarters (generics, an insecure supply chain, stricter enforcement of regulations, the advent of biosimilars), it is caught in an O. Henry paradox of its own, as far as analytical equipment is concerned. As new equipment is introduced at conferences, companies are sending fewer people to those events to find it. In addition, key conferences are being scheduled at exactly the same time. Consider the fact that AAPS and ISPE conferences overlap this year.

The theory seems to be that all we need to do is search the Internet for new analytical instruments. This thinking is seriously flawed for several reasons: first of all, most of the really imaginative new products are from start-up companies that don't have Web pages. And, sadly, the "geeks" who build the new instruments seldom have marketing abilities. So, if you stick to Web searches, chances are good that you'll never find that "perfect" answer to your problem.

If you want to peruse a slick, well-crafted Web page, look up one of the "traditional" (read: "large") instrument companies. And, yes, sometimes the biggies come up with something really new and different. They offer new products based on 1) glacial improvement of existing products (slowly upgrading, say, pumps or columns, or spectrometers) over time or 2) the acquisition of small innovator companies. A couple of the big companies offer hand-held spectrometers, for example, because they bought the companies that initially invented and made them. At least now you hear more about those products.

PHARMA HAS LOST TECHNICAL EXPERTS, AND THOSE WHO COULD ACTUALLY USE THE LATEST ANALYTICAL TOOLS

Some of these innovators are one-product companies, and I confess that I'm biased in favor of those who make one thing as good as it can be, rather than having it get lost in a bag of treats and hope people will go with "good enough." There is so much competition for development money when there are dozens of products that any one may not advance very far in any given year. But, I digress.

Due to massive cutbacks in headcount, there is a good probability that there will not be someone who can actually employ the "latest widget," even if he or she was able to discover and buy it. The double-whammy here is loss of technical expertise AND loss of warm bodies to employ the technology. The apparent cost savings has a point of diminishing returns, and short-term gains will only come back to bite managers later.

There is still a need for conferences that connect end-users with innovators. When there is no stage for small, innovator instrument companies, will the biggies continue to innovate? If this trend continues, it can only slow the industry's adoption of PAT, QbD and more modern methods of pharmaceutical manufacturing and quality assurance.

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