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Beyond SOPs

Bringing the rigor of QbD to analytical method development

AS THE philosophy and techniques enshrined in Quality by Design (QbD) become second nature to the pharmaceutical industry, their application is spreading. Analytical method development is a current area of focus. The process of developing, validating and deploying analytical methods closely parallels product development and can similarly benefit from the systematic and scientific approach that QbD promotes. The dependence of pharmaceutical development and manufacture on robust analytical data intensifies the need for rigor in analytical method development and increasingly a QbD approach — Analytical QbD (AQbD) — is seen as the way forward.

THE GOAL IS TO DEVELOP

In analytical method development the goal is to develop, validate and deploy a method for making an analysis that will deliver the information required, in all the instances that it is required to do so. The starting point is to identify exactly why the measurement is being made; in the same way that the starting point for conventional QbD is to identify clinical performance targets for the product. Once this is established, the process is one of understanding and learning to control those aspects of the measurement method that define critical elements of analytical performance. This closely mirrors the QbD model of working toward a fully scoped design space.

INTRODUCING THE PRINCIPLES OF QBD

A useful starting point for examining AQbD is to return to the generally accepted definition of QbD, which was originally presented in International Conference on Harmonization document Q8(R2). This states that QbD is:

"A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management …"

Figure 1 shows the QbD workflow that represents this systematic approach. The first step is to identify the Quality Target Product Profile (QTPP), the definition of what the product must deliver. The subsequent steps of QbD involve identification of the variables that must be controlled to deliver the defined product performance, and the best way of implementing that control.

CONTINUOUS IMPROVEMENT WRAPPER

Determination of performance-defining Critical Quality Attributes (CQAs), and the Critical Process Parameters (CPPs) and Critical Material Properties (CMAs) that control them, comes first. Definition of the design space follows. The design space is the operating envelope for the process. It encompasses the defined ranges for the CPPs and CMAs that ensure the CQAs will be achieved consistently. Defining the

By Paul Davies and Paul Kippax, Malvern Instruments

control strategies needed to maintain operation within the design space is the final step, but the entire workflow is wrapped within a process of continuous improvement across the lifecycle of the drug. Indeed, a major attraction of QbD is that its application permits ongoing optimization within the design space without requiring further regulatory approval.

ICHQ8 (R2) does not specifically mention analytical method development. However, the underlined phrases in the original QbD definition (above) have direct resonance when looking to apply a structured, rigorous approach to developing analytical methods. This resonance has prompted the evolution of Analytical Quality by Design (AQbD).

TRANSFERRING QBD TO ANALYTICAL METHOD DEVELOPMENT

FDA guidance on the application of AQbD [1] highlights the potential benefits of transferring QbD to analytical method development. The proposal is that AQbD will lead to the development of a robust method that will be applicable throughout the lifecycle of the product. Just as with QbD, being able to demonstrate adherence to AQbD will be associated with a certain degree of regulatory flexibility, providing the freedom to change method parameters within a method's design space, referred to as the Method Operable Design Region (MODR).

The starting point for AQbD is an Analytical Target Profile, or ATP, which is directly analogous to a QTPP (Figure 1). The ATP defines the goal of the analytical method development process, linking the output of the method to the overall QTPP. Identifying why the analytical information is required, what it will be used for and when, helps to formulate the ATP. Supplementary targets for performance characteristics, such as precision and reproducibility, stem from a more detailed analysis of these needs.

The next step is to identify a suitable analytical technique. This must be done with reference to the needs defined in the ATP. Once the technique is identified, AQbD focuses on method development and includes detailed assessment of the risks associated with variability associated with:

- Analyst methods
- Instrument configuration and maintenance
- Measurement and method parameters
- Material characteristics
- Environmental conditions

This assessment identifies the CQAs, the parameters that impact the ATP. A Design of Experiments (DOE) approach is then adopted to define the MODR. This is the operating range for the CQAs that produces results that consistently meet the goals set out in the ATP. Once this is defined, appropriate method controls can be put in place and method validation carried out following the guidance in ICH Q2.

Figure 1: QbD workflows for product development and the analogous workflow for analytical method development.

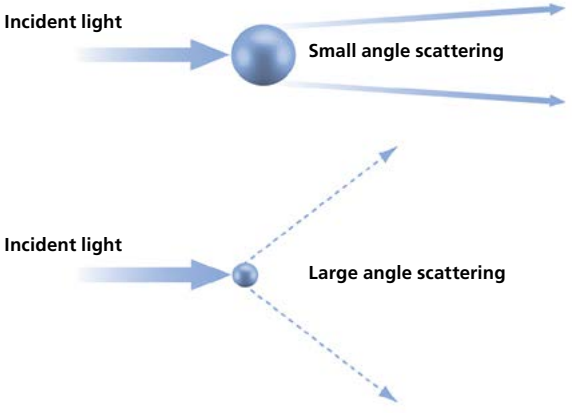

Figure 2: Laser diffraction analyzers determine particle size from the pattern of scattered light produced as a collimated laser beam interacts with particles in the sample.

Like QbD, AQbD works on the principle of recognizing and handling variability by understanding its potential impact. By identifying an analytical design space, rather than applying a fixed set of measurement conditions, it enables a responsive approach to the inherent variability encountered in day-to-day analysis throughout the lifecycle of a pharmaceutical product. This delivers an analytical method that is robust in daily use and which also substantially reduces the potential for failure when the method is transferred from, for example, a research laboratory through to QC. The root causes of method transfer failure can usually be traced back to insufficient consideration having been given

to the nature of the routine operating environment and a failure to capture and transfer the information needed to ensure robust measurement. Applying AQbD overcomes these issues and has the potential to eliminate costly mistakes.

DEVELOPING A PARTICLE SIZING METHOD

Addressing a specific analytical challenge helps to clarify what the application of AQbD looks like in practice. Consider the scenario of measuring the particle size distribution of a micronized active pharmaceutical ingredient with the goal of assessing its suitability for downstream processing and bioavailability for a solid oral dose product.

In this situation the ATP is the measurement of particle size distribution at a defined point in the process, in a way that is precise enough to ensure the material will perform to expectations. In practice, the required level of precision may exceed that which is laid down in the US and European Pharmacopoeias [2, 3], but for simplicity we will assume that the USP and Ph. Eur. acceptance criteria are adequate. Many techniques are available for particle size distribution measurement, but laser diffraction is the method of choice for most pharmaceutical applications. So we will base this AQbD example on laser diffraction particle size measurement.

INTRODUCING LASER DIFFRACTION

Fast, non-destructive and amenable to automation, particle sizing by laser diffraction is a technique that has been tailored in modern instrumentation for high productivity, routine use. In a laser diffraction particle size analyzer, the particles in a sample are illuminated by a collimated laser beam. The light is scattered by the particles present over a range of angles, with large particles predominantly scattering light with high intensity at narrow angles, and smaller particles producing lower intensity signals over a much wider range of angles. Laser diffraction systems measure the intensity of light scattered by the particles as a function of angle and wavelength. Application of an appropriate light scattering model, such as Mie theory, enables particle size distribution to be calculated directly from the measured scattered light pattern.

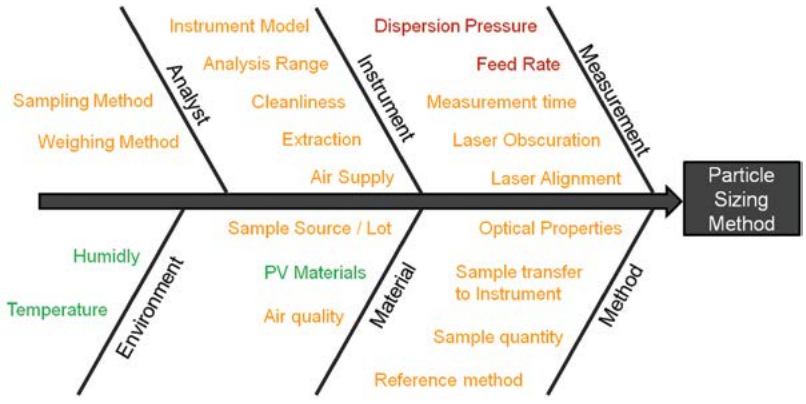

Figure 3: Output of an assessment of the key parameters for a dry dispersion method. Items shown in green are noise factors within the method; those in orange are control factors; whereas those in red must be investigated experimentally to determine the MODR.

Laser diffraction involves relatively little sample preparation, but it is essential to present the sample in a suitably dispersed state to generate data that are relevant. In our example, the need is to measure the primary particle size distribution of the active pharmaceutical ingredient. This means that any agglomerated material present must be dispersed, prior to measurement, to ensure consistent and relevant results. Here then the parameters applied to ensure complete dispersion are CQAs, variables that have a direct impact on the quality of the results. Investigating dispersion in a systematic way is therefore a primary objective when it comes to defining the MODR for a laser diffraction method.

SCOPING THE MODR

When it comes to dispersing a sample for laser diffraction particle size measurement, there is a choice to be made between dry powder or liquid dispersion. Dry dispersion is the preferred option because it:

- Enables rapid measurement to be made,
- Is well-suited to moisture-sensitive materials,
- Accommodates relatively large sample volumes, enabling reproducible measurement of poly disperse materials, and
- Is environmentally benign, as the use of organic liquid dispersants is avoided.

Although dry dispersion offers these advantages, it is not suitable for all sample types. Dry dispersion involves entraining the sample within a high-velocity air stream. The process of entrainment subjects the particles to substantial shear energy and promotes particle-particle/particle-wall collisions, dispersing any agglomerates. Friable materials may be damaged by this process. It may also be hazardous to handle highly active ingredients in this way because of the risks associated with aerosolization. Some samples are therefore better suited to liquid-based measurement.

Figure 3 shows some of the CQAs associated with a dry method for a micronized API powder. In dry dispersion, the air pressure applied during entrainment of the sample is the

lever that is used to control the input of energy into the dispersion process. This identifies it as a CQA. Another consideration is the sample feed rate, as this determines the amount of material which passes through the venturi during the dispersion process and therefore the efficiency of dispersion. It also defines the concentration of a sample, which in turn can have an impact on the measurement process itself. If particle number/density is too low, then the signal to noise ratio during measurement may be unreliable. Conversely, a high particle density increases the risk of multiple scattering, where the light interacts with more than one particle prior to detection, a phenomenon that complicates the calculation of particle size. Feed rate, therefore, tends to be the other CQA when using dry dispersion for laser diffraction particle size measurements.

So, working on the basis that dry dispersion is suitable for our model sample, and that the above assessment is realistic in terms of identifying the CQAs for the method, one of the steps needed to scope the MODR is to determine how air pressure influences the results of the analysis. The experiment that delivers the necessary data is commonly referred to as a pressure titration.

Figure 4 shows results from two pressure titrations. These were carried out using the Mastersizer 3000, which has a number of modular dry dispersion units that allow the intensity of dry dispersion to be matched to the sample. The upper of the two plots was measured using a dry dispersion unit fitted with the system's standard venturi disperser, while the lower plot was generated using a venturi designed to provide high dispersion energies.

The aim with dry dispersion is to completely break up any agglomerates present, without causing damage to the primary particles. The results show that with each venturi increasing pressure decreases particle size. This

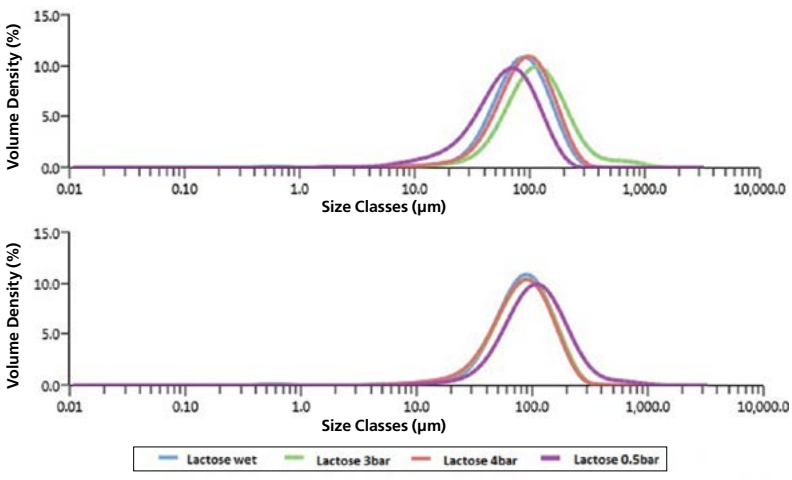

Figure 4: Pressure titration data for a lactose formulation. A comparison of liquid (blue) and dry measurement shows close agreement at a compressed air pressure of 3 bar with the standard venturi (upper plot) and at 1 bar with the more aggressive venturi (lower plot).

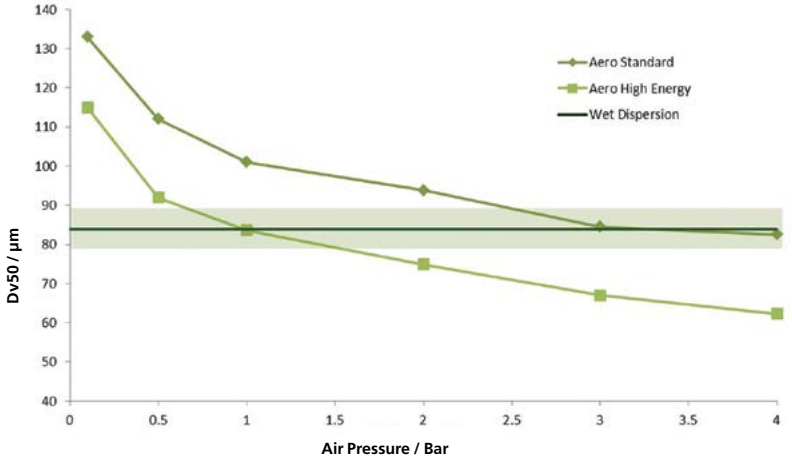

Figure 5: Plotting measured particle size as a function of air pressure for each venturi disperser. Shaded region shows where the results are in agreement with the reference method to within USP<429> guidance. The standard venturi disperser delivers a wider MODR.

raises the question of how to determine whether a given pressure is breaking up agglomerates as required, or is causing damage to primary particles. A comparison with a reference liquid dispersion measurement helps to answer this question since liquid dispersion very rarely results in particle damage.

Results from liquid measurements are shown in blue in Figure 4. These indicate that the standard venturi disperser delivers complete dispersion at a compressed air pressure of around 3 bar, whereas using the high energy venturi disperser an air pressure of around 1 bar is required.

These data suggest that it would be possible to use either of the venturi tested. However, by plotting particle size as a function of air pressure for each venturi (Figure 5) it can be seen that the standard venturi is the better option. This plot shows that the MODR is larger with the standard venturi than with the high energy disperser.

These results show that with the

Figure 6: Mastersizer 3000 measurement manager, showing a dispersion trend.

Figure 7: Measurement data quality advice provided in the Mastersizer 3000 software.

high energy disperser any variation in air pressure will have a significant effect on particle size, compromising the ability of the method to meet the ATP. Using the standard venturi, on the other hand, the particle size results are reasonably consistent across the pressure range 3 to 4 bar. This venturi will therefore deliver an inherently more robust measurement. The MODR associated with its use can be determined, in terms of suitable air pressure, on the basis of these data.

METHOD VALIDATION

The data shown in Figure 5 enable the selection of a dispersion pressure which would be expected to deliver robust results. To ensure that a proposed method meets the ATP, it is essential to verify that any variability in the way the method is applied does not shift the precision of the results outside the intended limits. This requires the method to be validated, following the guidance outlined in ICH Q2.

Two concepts are central to confirming that a particle sizing method is fit for purpose: repeatability and reproducibility. Assessing repeatability involves duplicate measurements of the same sample. It therefore tests the precision of the instrument, and the consistency of the sampling and dispersion process. Reproducibility is a broader concept that also encompasses multiple operators or even multiple analytical system installations.

Both the USP [2] and EP [3] recommend acceptance criteria for reproducibility testing. A Coefficient of Variability (COV) of less that 10% is suggested as acceptable for the median (Dv50) particle size or any similar value which is close to the center of the particle size distribution. This figure rises to 15% on values towards the edge of the distribution, such as Dv10 and Dv90, the particle size below which 10 and 90% of the population lies on the basis of volume. These limits are doubled for samples containing particles smaller than 10 microns because of the difficulties associated with dispersing such fine powders.

In our example then, where the acceptance criteria for the results are based on pharmacopoeial guidance, robust definition of the MODR requires that any source of variability does not take data reproducibility outside these limits. For example, the precision of air pressure control during dispersion is a function of the analyzer. If air pressure, a CQA, is controlled to within +/-0.1 bar, it is necessary to conduct experiments to determine the level of variability that this introduces in terms of the repeatability and reproducibility of the measured data. All potential sources of variability must be investigated in this way.

TOOLS TO EASE AQBD

As with QbD, AQbD places the emphasis on fully understanding a process, rather than simply focusing on a set of conditions that work for certain sample types. The potential rewards of this approach have already been highlighted, but gaining the necessary understanding is inextricably linked with more extensive experimentation. Tools that can alleviate the burden associated with this research are therefore to be welcomed.

Figure 6 shows a screen shot from the Mastersizer 3000 illustrating the Measurement Manager tool. This is a software feature that provides real-time feedback which indicates the impact of changing an analytical parameter. Parameters can either be modified by the user in real-time as part of a manually controlled measurement or they can be set within pre-defined measurement sequences within the software's SOP-player tool. This tool provides the first step towards full automation of the method development process.

In addition to aiding with the process of method development, there is also a requirement to ensure that the data collected are reasonable and therefore reflect the

capabilities of the analytical technique in terms of both resolving product changes and delivering reproducible results. Here, tools to assess the quality of the data are extremely valuable, helping to guide the user towards the definition of a good method.

Figure 7 shows the output of the Data Quality assessment tool provided in the Mastersizer 3000. Advice is given relating the measurement process (e.g. instrument cleanliness and alignment) and also the analysis process (e.g. the goodness of fit between the light scattering data acquired by the instrument and the optical model selected to calculate a size distribution from these data). This helps to address many of the method control issues highlighted in Figure 4. Software advances such as these can therefore make a big difference when it comes to the application of AQbD, and they substantially ease the analytical burden associated with its implementation.

LOOKING AHEAD

A decade or so ago the introduction of standard operating procedures (SOPs) was groundbreaking, but analytical method development is now moving beyond simply defining a fixed set of measurement parameters. AQbD invites analysts to establish a robust MODR, a safe analytical working space. Working within the MODR ensures that results consistently meet defined quality criteria while at the same time providing the flexibility to respond to routinely encountered variability. The understanding that comes with scoping the MODR secures robust application of an analytical method across the product lifecycle and substantially eases method transfer.

As with QbD, AQbD holds out the attraction of greater understanding, but brings with it the burden of a broader research remit. However, advances in instrumentation, most especially in software, can make a major contribution when it comes to efficient scoping of the MODR. Features such as real-time feedback on the stability of a measurement and the impact of changes, for example, and the ability to automatically step through a series of SOPs, can help to substantially lighten the analytical burden, enabling analysts to reap the benefits of AQbD more easily.

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[2] General Chapter <429>, "Light Diffraction Measurement Of Particle Size", United States Pharmacopeia, Pharmacopoeial Forum (2005), 31, pp1235-1241

[3] General Chapter 2.9.31, "Laser Diffraction Measurement of Particle Size", European Pharmacopeia.

WHAT'S TRENDING IN PHARMA IT

OPERATIONAL TRANSPARENCY AND OPTIMIZED PROCESSES FROM LAB TO PLANT FLOOR TO EXECUTIVE SUITE AND BACK ARE DRIVING IT INVESTMENTS

BY STEVEN E. KUEHN, EDITOR-IN-CHIEF

CHALLENGING PHARMACEUTICAL manufacturers everywhere, every day are the myriad issues surrounding the acquisition, disposition and analysis of the huge amounts of data their operations create around the clock. Any Pharma producer worth its salt these days is likely investing a great deal of time, resources and effort to create or maintain a comprehensive information technology (IT) infrastructure to support compliant operations, process quality and efficiency, and ultimately assure product safety, effectiveness and affordability.

According to research firm Computer Economics, which provides benchmarking metrics to aid IT operations management, life science organizations have some unique attributes. In its study, "Comparative Analysis of IT Spending in the Life Sciences," Computer Economics compared high-level spending metrics for life science companies against a broad sample of organizations in all industries. The study delivered four key findings:

1. Life science companies have high IT intensity. They spend considerably more than the composite sample, as measured by total IT spending per user and spending as a percentage of revenue.

2. Life science companies spend a higher portion of their IT budgets on data center and network infrastructure than the average company, and they spend a correspondingly smaller portion on business application software.

3. The size of the application support staff and spending on application software per user is typical, indicating that high data center and network infrastructure costs are the factors that drive IT spending in this sector.

4. The staffing mix for life science companies is similar to other organizations. IT staffing headcount, therefore, can be benchmarked against similar-size organizations from all sectors.

Within the context of a typical drug manufacturing environment and its incumbent data volume, it makes sense that Pharma's spending may be proportionately higher than other industries to fund its high-capacity data handling needs. Recently, Gartner Benchmark Analytics released its "IT Metrics Data 2014" report which revealed that Pharmaceuticals, Life Sciences and Medical Products companies spend 3.2 percent of revenues on their IT infrastructure — a level higher than Industrial Electronics and Electrical Equipment (2.5 percent), Industrial Manufacturing (1.7 percent), and interestingly enough, Chemicals at 1.3 percent. What these figures seem to reflect is the reality on the ground; that is, Pharma is spending more (generally) now than peer counterparts because those industries are further along the curve when it comes to integrating a modern, enterprise-wide IT infrastructure to support operations and business goals.

SPENDING IN THE RIGHT DIRECTION

Where's IT spending heading for Pharma and Life Science companies? Analytics firm Informa Ovum forecasts global life sciences technology spending to reach $40.8 billion by the end of 2017. According to Ovum's research, spending will increase at a cumulative annual growth rate (CAGR) of 3.6 percent to reach the predicted figure. Ovum says its study reveals that "the increase in IT spending will be fueled in large part by the growth in data analysis and related technologies, the acquisition of systems to comply with new regulatory requirements, and increased spending on applications that advance operating efficiency and automation." Elsewhere, Ovum's findings show that "value chain fragmentation caused by new entities being spun out of Big Pharma and rapid growth in … emerging markets will see strong IT spending growth of 9.4 percent CAGR in the small pharma/biotech sub sector, totaling $10.5 billion in 2017."

"The factors driving IT spending in the life sciences industry continue to be complex, with payers of healthcare demanding greater value in the face of increasing costs, technological advances enabling new types of research that are changing societal expectations, and opportunities arising from the emerging markets," explains Andrew Brosnan, senior analyst, healthcare and life sciences at Ovum. "We expect much of this predicted growth to come from investment in business intelligence (BI) and analytics, as institutions look to collect, clean, manage and analyze the vast amount of data from sources such as social media, electronic medical records and genetic sequencing."

Ovum expects total IT spending as a percentage of total revenues to decrease to 3.4 percent in 2017, even though overall IT spending will be higher as total revenue increases, largely due to IT-related cost efficiencies and the increased use of generics, which are less IT-intensive to develop than novel medications. "The improvement of IT-related cost efficiencies will be achieved through systems simplification and infrastructure consolidation, further cloud adoption, falling component prices and increased external sourcing," explains Brosnan. "Greater externalization of what were once in-house resources and capabilities is occurring globally across all sub-sectors (biotech, small- to mid-sized pharma, and Big Pharma). The centralization of externalized services reduces the total cost of ownership by stripping out duplicate investments and realizing greater economies of scale."

IT INVESTMENT FOCUS

Pharma manufacturers and prominent members of the pharmaceutical supply chain are certainly looking to make sure their IT investments yield value. The efficient flow of process/machine data and information from production line to executive suite and back is dependent on a well-organized, modern data/informatics infrastructure. This is also unflinchingly true for the reams of data streaming from laboratory operations — especially those in support of cGMP manufacturing and its incumbent quality regimes.

WITNESSES, FIRST HAND

In discussions with customers trying to integrate more functionality and value into their existing IT infrastructure, information technology suppliers and integrators are witnessing first hand where customers are focusing their IT investments as well as the priorities they assign with their spend. Prominent Manufacturing Execution Systems (MES) supplier Werum IT Solutions' senior director Rolf Blumenthal explains, "Our customers are asking us to fill the gap between the business level and automation level. On this operational level, the first focus in pharma manufacturing is the replacement of paper batch recording with an electronic system." Of course, this doesn't just entail mere paper replacement, says Blumenthal, because customers are taking a broader approach to many business functions including material flow, quality control and process automation. Using this functionality across the complete lifecycle of a pharmaceutical product, from lab to market, he says, is positioning MES as a tool for process development, clinical trials production and commercial manufacturing. "During the last three years customers are looking more for strategic products in manufacturing than for customized [bespoke] software. Using an out-of-the-box product … with a strategic roadmap for the next decade, customers can achieve long-term investment protection and lower total cost of ownership."

The notion that Pharma customers are looking for a "transcendental" experience as they integrate new IT functionality and capacity is echoed by Thermo Fisher Scientific's Trish Meek, director of strategy – Informatics: "Our customers today are looking at how informatics can go beyond driving their processes to really transform their business," says Meek. "To push the boundaries of innovation, [companies] are monitoring their performance and quality and actively looking for opportunities they can capitalize on to improve their operations." This is due, in part, says Meek, to

macro-trends like big data and predictive analytics that are changing IT across all industries. "Gone are the days where we rely on statistics to take a sample of data that is believed to represent the whole because analysis of the entire data set is impossible. Today's modern in-memory computing platforms offer organizations the ability to look at their complete operation in real time or near real time." Customers, explains Meek, want to achieve a higher level of quality and efficiency and business agility, but that often isn't possible if that data is siloed and inaccessible. "Our customers are working with us to achieve a connected informatics infrastructure so that they can achieve these higher-level organizational goals."

> "At the end of the day, people are looking for solutions to eliminate paper, to become more compliant, and to increase efficiencies in and around [their] labs.
>
> —Gene Tetreault, *BIOVIA*

Citing the recent report, "Product Innovation Requires Laboratory Informatics Systems to Transcend Phases," Meek notes that Gartner analyst Michael Shanler recommends manufacturers "prioritize end-to-end informatics investments and align metrics for innovation, domain expertise, operational efficiencies and quality." "His recommendation," explains Meek, "is based on an observation that today's laboratories 'are, for the most part, disconnected.' By tightly integrating LIMS to other enterprise operation systems such as ERP, insights from the lab have the potential to be even more central to businesses seeking true enterprise-wide agility." Businesses aren't simply capturing and collecting data, Meek contends, they are making data actionable across the enterprise, putting management in the position to transform their businesses into agile organizations capable of responding quickly to market trends or new regulations and flexible enough to recognize and capitalize on cost-saving or margin-growing opportunities in the future.

Gene Tetreault, BIOVIA's senior director of enterprise laboratory management, also knows that besides test and development related data, informatics are key to managing lab operations effectively and holistically. BIOVIA's customers, says Tetreault, are seeking "a really good capability to manage inventories and managing all of the material flow in and out of the lab, as well as specialized things like environmental monitoring. That's a manufacturing application typically included in the LIMs, but it's all about managing the [potential for] microbial contamination in manufacturing. At the end of the day, people are looking for solutions to eliminate paper, to become more compliant, and to increase efficiencies in and around their labs. Once you get all of those systems [on a common electronic technology] platform, people are asking: 'How do I connect other systems together? How do I get the data out of them?'" Tetreault explains that once a comprehensive lab informatics system is in place, discoverable information becomes available and lab operations managers have tremendous opportunity to gather and aggregate data and then use it to look forward operationally — creating models and other visualizations to support quality regimes in manufacturing.

GAPS TO CLOSE

Indeed, priorities have to be ordered and pursued to close the gaps created by the complexities of Pharma manufacturing environments and their supply chains. Business leader Brian Vogel, for Rockwell Automation's Global Life Sciences business segment, finds Pharma needs to continue its efforts to organize IT to serve the enterprise holistically. "IT Infrastructure is a catch-all bucket that can include information and manufacturing software as well as hardware," says Vogel. "Most Life Science manufacturers are moving in two key areas. Beyond acquisition, there is a major movement to shift capacity to more profitable locations. This is paralleled with an emphasis on consolidating IT-related systems while improving and expanding access to shop-floor information."

As this unfolds, notes Vogel, Life Science manufacturers are coming to the realization that, while ERP is absolutely fundamental to driving the back end, there are considerable gaps at the shop floor. "As such, MES are now being deployed in the context of an enterprise solution. Rockwell Automation has a global customer base, so we see a wide variety of approaches to addressing this. Developing a common MES core to enforce quality, compliance and standard execution across all areas of manufacturing irrespective of what type or where a product is being manufactured is the leading trend."

There will still be areas of the world, says Vogel, where the cost of energy and personnel will drive an approach that is more centered on adding resources and lean processes. "However, most manufacturers are avoiding the "band-aid" approach and are working to develop a more systematic, global MES core deployment model."

Inarguably, says Jennifer Goldsmith, VP, Vault R&D, Veeva Systems, one the most data-driven areas in life sciences is manufacturing, which demands the ability to share information and collaborate quickly. Goldsmith contends raw data often exists in multiple systems and file formats, making it difficult for people to access and use. As a result, the data is often recreated in a document or structured report format to provide context and enable effective consumption. Content management systems (CMS) have become the home for many of these documents, and these systems typically lack the capability to incorporate new data as they are updated.

"Something as simple as a manufacturing specification may require manual update and confirmation of values as they change over time. Additionally, sharing this information across geographies and between organizations has also presented challenges. Cloud-based CMS allow easy, secure sharing of valuable information with other systems and a larger, relevant audience," says Goldsmith. "Users effortlessly collaborate with one another, while all communication, content and versions are tracked and stored. As cloud-based CMS evolve, they will challenge traditional definitions of documents, enabling the storing and updating of structured data with unstructured content — such as descriptions — in one document."

> "During the last three years customers are looking more for strategic products in manufacturing than for customized [bespoke] software. Using an out-of-the-box product … with a strategic roadmap for the next decade, customers can achieve long-term investment protection and lower total cost of ownership."
>
> — Rolf Blumenthal, *Werum IT Solutions*

OPEX OR CAPEX?

When it comes to expensing operational necessities like an IT infrastructure, controlling that spend can be challenging, especially because it is so critical to operational excellence and an efficient, compliant production environment. With Pharma's business models evolving quickly to meet the needs of the swiftly changing global marketplace, the industry is shifting how it invests and maintains its IT infrastructure. Some are looking for alternative ways to account for IT expenditures and shifting funding from the capital expense (CapEx) side of the balance sheet to the operating expense (OpEx) side in an attempt to better manage the rising and unavoidable cost of fielding a world-class IT infrastructure. When it comes to managing IT expenses, each company may take an approach biased in one direction or another depending on individual preferences and financial exigencies, but there's no clear "right" answer and Rockwell's Vogel agrees. "There is no right or wrong answer here; manufacturers of all sizes are managing expenditures as operating expenses and/or capital expenses at both the corporate and site levels," observes Vogel.

"Though most customers/partners who are developing the core model are treating the upfront design and build as a capital expense, and classifying the funding of the local extensions and roll-out as an operational expense."

Werum's Blumenthal offers this insight: "There is a trend on the radar that customers are expecting realistic solutions beyond the cloud technology discussion in the IT world. A new idea is to use a supplier-hosted MES and pay per batch record instead of purchasing complex IT infrastructure and an MES system." That is an interesting proposition and may offer very lean organizations an opportunity to stick to core competencies and leave the heavy lifting to companies whose core competency is in fact IT operations.

Speaking of heavy lifting, Veeva's Goldsmith points out that the emergence of cloud applications has provided a new alternative for financing projects, moving IT infrastructure spend away from capital expenditures and toward operating expenses. "New projects typically require a significant amount of upfront capital, and if the investment needed is too high, it may deter organizations from pursuing these opportunities at all," says Goldsmith. "The cloud lowers the barrier to entry and supports a pay-as-you-go model, enabling companies to try new ideas without long-term commitment and easily scale as projects grow."

BIOVIA's Tetreault says that customers usually don't include the company in the nitty-gritty of how they choose to fund IT investments, but that when making IT-related

capital purchases, "cost of ownership and time to value are two key metrics," that help customers valuate the potential return of their IT investment. "We are trying to deliver software at the lowest cost. We're trying to make it so they can basically get value [even if] it is from one mapped out goal. Cloud solutions, certificates of valuation, etc., all sorts of things to deliver tangible value and to lower both of those numbers. That opens up the world tremendously to thousands of labs, as opposed to hundreds of labs."

SOLUTIONS FOCUS

It's generally accepted that contemporary IT and informatics solutions must be adopted to effectively and profitably manage Pharma's operations or face the consequences. But just how are drug manufacturers working with vendors and integrators to apply and implement such necessary technologies? Rockwell's Vogel offers this insight: "A hybrid-regulated consumer goods manufacturer with over 100K SKUs needed to increase production throughput by 20 percent (without increasing personnel), and needed to meet increased market demand. After reviewing its manufacturing process, it was determined that the "First Time Pass" had to increase and the "Quality Hold Time" had to decrease by more than 60 percent. More work orders per shift also needed to be executed to meet the company's goals. After implementing a new MES solution, the number of work orders per shift doubled, First Time Pass increased by 85 percent, and quality hold decreased by more than 90 percent. Now, adoption of the solution is underway in four additional plants."

Another of Rockwell's customers, a global life sciences manufacturer was rolling out an ERP system to all its manufacturing facilities, Vogel says, explaining that the company needed to standardize its manufacturing intelligence interface with ERP and replace the myriad of existing MES site-level systems with an enterprise-wide solution. "The first challenge was the time frame, and the second was ensuring the MES system met existing functional and regulatory needs at each site — regardless of what or how a product or ingredient was being made. The system was rolled out in stages, focusing on core areas one at a time. Now, 17 plants are live, and five will go live in roughly 30 months since the program started." While each customer had different business drivers, says Vogel, the need to standardize their manufacturing process and improve time-to-results was achieved through Rockwell's platform.

Thermo Fisher Scientific's Meek notes that with her company's customer base, companies often take two distinct approaches: The first, one-stop shopping and the second, integrated laboratory systems. "Which approach makes the most sense is largely based on the existing systems investment and processes that are implemented in those systems," says Meek. "One major pharmaceutical manufacturer has implemented a global deployment of our LIMS and it is fully integrated with external LES and SDMS. By focusing on strong integration between these applications, they feel that they have optimized their deployment and have a continuous flow of information enabling them to make real-time decisions. They are currently looking at predictive analytics tools to drive to a more proactive environment."

> "Gone are the days where we rely on statistics to take a sample of data that is believed to represent the whole because analysis of the entire data set is impossible. Today's modern in-memory computing platforms offer organizations the ability to look at their complete operation in real time or near real time."
>
> — Trish Meek, *Thermo Fisher Scientific*

Customers who have not made a significant investment in LES and SDMS capabilities already, says Meek, see the value in a single solution that provides the functionality of a LIMS, LES and SDMS in one. "The customer was looking at Lab Execution and LIMS and when they realized that they could get both in a single solution, it made their decision for them. Their comment was that, 'We never thought we would find a solution for lab execution and management that is so tightly integrated, why would we go with anything else?'"

Veeva's Goldsmith notes good documentation is essential for manufacturing facilities to ensure activities are executed correctly and are in compliance. Most companies, she says, rely on content management systems that were built when companies were less impacted by globalization and had fewer regulatory requirements. "Today, customers are looking for solutions that enable greater visibility and flexibility, and collaboration across all parties. We have

customers that are in the early stages of adoption, having built a single source of truth for SOPs accessible by both document originators and consumers. Giving more parties visibility into document status accelerates edit, review and approval cycles. Built-in read and understood tasks also allow for real-time tracking of new SOPs as they are rolled out across departments and sites."

Goldsmith explains that her company's more mature customers understand that such systems deliver powerful insights into the health of processes, departments and partnerships. "Most metrics monitor output, only measuring what has happened. Tracking upstream metrics, by contrast, provides leading indicators into potential problems and can help identify bottlenecks before the damage is done," says Goldsmith. Companies that have developed a deeper understanding of their business processes are using metrics to gauge performance across the organization, and drive continuous process improvements and proactive decision-making.

Werum's Blumenthal provides a closer look outlining two solutions delivered to customers using their popular platform. "A customer is using our [platform] in process development to develop a stable, best-fitting process for solid dosage products," says Blumenthal. "The main business goal is to be faster to market with a new product. By using MES features like MBR and EBR for creating recipes and evaluating best fitting parameters via Design of Experiments, new processes will be continuously improved and stabilized. Development with such tools and the transfer of the gained knowledge to the next production phase is much faster and is the enabler to achieve expected business goals."

Another Werum customer is using the company's technologies in the commercial production of a biopharmaceutical product. The main business goal is to increase the yield of the factory, says Blumenthal. "Since production runs are very long, it is critical that the process is stable without any contamination. This can be achieved through our [platform] by controlling all process steps with additional checks of all material and all equipment that is used." Both business goals, he says, can be supported by the same system. The complete functionality supported by Werum's platform, says Blumenthal, is defined and controlled via recipes. The creation and change of recipes (MBRs) can be both flexible (process development) or highly controlled with access rights (commercial manufacturing).

A PATH TO IMPROVED OPERATIONS

"Many more parties are involved in the end-to-end production of a product adding another layer of complexity to the development process," explains Goldsmith. Supporting technologies are often deployed in a siloed model, limiting the ability for parties to collaborate directly, thus forcing the use of uncontrolled communication mechanisms, such as email, she says. "Mature companies are taking a strategic approach to technology, creating a strong foundation for information sharing and collaboration to achieve the biggest benefit. Companies that succeed in sharing information with all parties involved and between systems see significant improvements in all five areas."

> "Most Life Science manufacturers are moving in two key areas. Beyond acquisition, there is a major movement to shift capacity to more profitable locations. This is paralleled with an emphasis on consolidating IT-related systems while improving and expanding access to shop-floor information."
>
> — Brian Vogel, *Rockwell Automation*

Werum's approach, says Blumenthal, "is the implementation of a recipe-driven system that leads the operator through the business processes, enforcing the 'right first-time' principle and compliance with all pharma regulations. "Creating best practice recipes and following the guidance of the system along such recipes (like a navigation system) will always result in best product quality, reduced costs, safety, reduced risks and compliance," Blumenthal says.

Tetreault agrees that LES enforces right first time: "When you're following the process and doing QC testing on a particular batch — step one, prepare the agents and global phase samples and so forth. Step two, do this. Step three, do that. On step one, if you don't adhere to the process of running that analytical test, if you don't adhere to all the equipment being calibrated, all the materials being within tolerance and of course not expired, all of the training records — [the LES is] enforcing all of that at the time that you're doing the test." Tetreault notes test regimes, independent of the quality control provided by an integrated lab informatics platform can be problematic because any

issues or mistakes may only be revealed after a review. "… somebody comes along and reviews it and finds that there's a problem. Now there's a day's worth of effort into doing something that was wrong on the first step." Tetreault explains BIOVIA's platform (as with others) electronically enforces process rubrics at the time they are being done. "It reduces costs. It increases quality. It decreases safety risk."

Thermo Fisher Scientific's Meek knows that lab informatics platforms truly are the pointy end of the spear when it comes to assuring quality when it counts. "Ensuring product quality, risk reduction and regulatory compliance have always been among the top reasons to deploy a LIMS, she says. "Test results from suppliers are checked to ensure they are fit for use before time and energy is wasted, all sample results for the batch including environmental monitoring are collated before product can be released. Business processes are implemented in the LIMS and the users are [systematically] stepped through the organizations' SOPs to ensure compliance. Hazard warnings can be associated with any step in a workflow and, within the LES, users are reminded as they execute that step of the appropriate safety procedures including safety images and videos if appropriate."

It's important, says Meek, to remember that today's LIMS are far more than just lab information systems. "It is also a laboratory resource planning system. Method execution, scientific data visualization, instrument calibration and maintenance, and detailed resource planning and allocation can all be done through the LIMS." Typically, notes Meek, LIMS are on an upgrade cycle of around every five years, and the first thing Thermo Fisher Scientific does with its customers is demonstrate how much the functionality of its platforms have evolved since initial implementation and work with them to leverage the new capabilities of the system. The focus, she says, is to deliver on high-level organizational goals by leveraging their existing investments in laboratory instrumentation, informatics and enterprise systems. "And while the concept of a truly 'paperless lab' has been hotly debated for many years, it is really only now coming into its own. The latest Informatics solutions are capable of fully integrating the lab to the rest of the business, eliminating for the most part many of the paper-based processes that have caused bottlenecks in workflow or contributed to errors in transcribing results and generating reports."

Because LIMS are tightly integrated with other enterprise operation systems such as ERP, insights from the lab have the potential to be even more central to businesses seeking true enterprise-wide agility says Meek. "Businesses aren't simply capturing and collecting data; they are making data actionable across the enterprise, putting management in the position to transform their businesses into agile organizations capable of responding quickly to market trends or new regulations and flexible enough to recognize and capitalize on cost-saving or margin-growing opportunities in the future."

> "As cloud-based CMS evolve, they will challenge traditional definitions of documents, enabling the storing and updating of structured data with unstructured content — such as descriptions — in one document."
>
> — Jennifer Goldsmith, *Veeva Systems*

Rockwell's Life Science manufacturing customers, notes Vogel, are moving to maximize their operating options by standardizing the underlying recipe and execution process around five imperatives: product quality, cost control, safety, risk reduction and compliance. This will maximize quality adherence, reduce risk and minimize cost variations from plant to plant. "To ensure product quality, for example, enterprise MES coupled with advanced EMI software is being used by manufacturing and IT teams. Reports are produced throughout the day by aggregating data from machine, plant, enterprise and third-party applications to produce real-time dashboards with unique situational and historical context for different users."

To improve compliance, contends Vogel, "companies are selecting information technologies that go beyond collection and archiving of data. Today's manufacturers are looking to information technology to automatically gather required data, drive regulatory compliance, and enforce execution standards while having robust security capabilities. Deploying a Manufacturing Execution System (MES) with advanced information technologies such as these has been proving to be a "plus" to profitability. It greatly increases quality adherence coupled with the ability to shift the production of a single product or a group from under-performing plants to locations that are more advantageous to the bottom line."

Pharma's tech bench gets deeper with an All-Star lineup ready for the big leagues

BY STEVEN E. KUEHN, EDITOR-IN-CHIEF

HOME RUNS are getting harder to come by in the pharmaceutical industry and drug makers know it. Innovation writ large for Pharma used to mean funneling, stadium-filling amounts of money into research and development (R&D) efforts tied to finding the next blockbuster therapy and afterwards, reaping the rewards of its patent-protected profitability. For most of Pharma's history, those successes fueled even more profligate research spending, dollars which not only financed the development of new winners, but also plenty of losers as well. But in the wake of patent expiries (and an ever-shrinking pool of large-class disease categories), this "Blockbuster Quest" business model's being traded for a leaner, more cost-effective R&D and manufacturing strategy designed to focus drug discovery efforts and accelerate the time it takes to get a solid hit, take it around the bases and score a run.

Gaining such competitive agility is increasingly coming from the Pharma industry's technology and system suppliers. These companies are fielding some pretty impressive players to support big-league Pharma-style innovation. Fortunately, innovation is a competitive driver for Pharma technology providers as well, and their R&D efforts continue to deliver game-winning solutions ready to drive costs out and efficiencies in to drug manufacturing operations. These innovators deserve to be recognized. What follows are this year's All-Star Innovators: technologies and systems introduced within the last 12 months that, based on their relative applicational and technical merits, were selected by *Pharmaceutical Manufacturing*'s editors and reviewers to be on this year's All-Star Roster. Just like in the big leagues, each player, er, product is highlighted by its own card, complete with performance and other stats. What follows are excerpts from those cards, but to view them in their entirety visit PharmaManufacturing.com and click on the "All-Star Innovators" logo. For now, though, take your seat, grab some peanuts and find out which ones might have the potential to be on your team.

ANALYTICAL AND MONITORING DEVICES

Cobalt Light Systems' RapID developed its competitive edge via its patented Spatially Offset Raman Spectroscopy (SORS) technology, which permits a high-quality Raman spectrum to be measured through the thick, unopened layers of packaging. Most players know significant time and resources can be spent on verifying the identity of raw materials. Accurate ID of these materials is essential, but time consuming, expensive and resource intensive. RapID allows ID through unopened plastic containers for growth media and brown glass bottles for sterile liquids. According to Cobalt, sacks of lactose can now be identified through a multilayer paper sack in 20-30 seconds without needing to open or sample the sack.

Most understand that if you have a player who can execute on fundamentals a little bit faster and more accurately, it's likely it can make a winning contribution to an optimized process strategy. GE Power & Water's got one, the Sievers M9 Total Organic Carbon (TOC) Analyzer. Designed to measure TOC in a broad range of samples from ultrapure water to process waters, the M9 is able to measure TOC and conductivity simultaneously, and provide accurate results in only two minutes.

Prozess Technologie developed an interesting approach that drives a bit of complexity and a lot of cost out of spectroscopic measurement with its REVEAL Measurement Appliances. This in-process spectroscopic measurement tool confirms blend conformity in real time and is easily deployable at a price that is well below industry norms. The company refers to its devices as "appliances" because unlike other measurement platforms, the unit is a single measurement device, eliminating the need for labs and scientists while delivering an accurate measurement for batch-based and continuously processed compounds. REVEAL is designed to work in virtually any manufacturing environment including hazardous materials and provides data that is accessible anytime via wired and wireless methods.

Need a player who can deliver material ID wherever it's needed? Rigaku Raman Technologies has one ready to run the base line. Its Progeny Material ID Handheld system offers bench top analytical performance in a rugged, ergonomic and IP-68 sealed enclosure. Progeny's fully customizable workflow software is 21 CFR Part 11 compliant, and its fast quad-core processor manages demanding search and quantification algorithms without requiring remote desktop work routines. An innovative 512-pixel InGaAs detector delivers improved resolution, analytics and signal to noise, handling the most challenging mixture analyses.

Improving HPLC/UHPLC method development productivity is an optimal strategy to speed drug development operations. Shimadzu Scientific Instruments introduced its Nexera Method Scouting System at Pittcon 2014, where it was recognized as a stand-out performer. Equipped with two pumps — each with a quaternary valve — Shimadzu's system allows analysts to run binary gradients with 16 different solvent pairs. When combined with a robust, high-pressure resistant column selection valve, which holds up to six conventional or UHPLC columns, the system can investigate up to 96 unique separation conditions per sample. A transfer program allows ultra-high-speed conditions to be transferred to conventional conditions, making the system suitable for both R&D and QA/QC applications.

Waters ionKey/MS System integrates UPLC separation into the mass spectrometer for improved sensitivity and unparalleled compound separation and detection — something that reduces solvent consumption and costs and simplifies the user experience. Containing fluidic connections, electronics, ESI interface, a column heater, eCord Intelligent Chip Technology and 1.7 micron UPLC grade particles packed inside a 150 micron I.D. channel, the ionKey/MS System was Merck Beta tested revealing a >60-fold increase in sensitivity for GLP-1.

AUTOMATION CONTROL AND SENSING

Endress+Hauser continues to intervene at critical points in manufacturing and process control and data environments, and its CM44x Liquiline Multichannel Transmitter is a strong individual contributor to processing trains via EtherNet/IP. One CM44 transmitter in play allows access to many parameters and accepts inputs down to the sensor level, including sensor condition and diagnostics. Traditionally, devices measuring and controlling process variables rely on a process instrumentation network to transfer data, while other devices within the plant work on a completely different network. By improving this complex, multi-tier networking strategy with one standard network architecture — EtherNet/IP — users have better access to real-time information. This improves the ability to monitor overall performance, troubleshoot out-of-margin conditions and minimize downtime.

Diverse pH and ORP sensing applications across Pharma and chemical process system piping require a tough and smart player to get the job done. With its rugged Ryton body material, Georg Fischer Piping Systems' DryLoc Sensors deploy a positive connector

system to indicate a solid, water-tight connection and resist moisture/dirt intrusions. The sensors mount into standard Signet 0.50-inch to 4-inch fittings as well as into GF tees and reducing tees of ¾ inch or larger. The installation versatility makes virtually any manufacturer's sensor simple and easy to replace when coupled with the Signet 2760 DryLoc connector, which can hook up to other manufacturers' instruments.

BIO PROCESSING

Often innovation comes from understanding there's a gap and filling it. ASI Life Sciences engineers understood that without an available high-capacity, single-use heat exchanger, manufacturing engineers were being forced to choose one of two sub-optimal options: Insert a stainless-steel heat exchanger along with its incumbent CIP/SIP infrastructure or use a jacketed mixing tote or similar technology as a stop-gap solution. Certainly not ideal. ASI's DHX Single-Use Heat Exchanger now offers a purpose-built solution by combining the heat transfer properties of a high-capacity plate and frame heat exchangers with the advantages users can leverage from its single-use configuration. ASI's system offers advantages for cell culture at the manufacturing scale, allowing engineers to build temperature control into their process without having to sacrifice the benefits of single-use.

On deck last September and already bringing efficiencies to downstream single-stage clarification are EMD Millipore's Clarisolve Depth Filters. With higher titers coming from today's upstream bioreactors, conventional approaches have posed a challenge to clarification, that is, until now. Clarisolve depth filters eliminate the need for centrifugation, which enables implementation of a fully single-use process train and reduces pre-use flushing requirements. This technology was developed to address the shortcomings of traditional downstream clarification approaches when processing high cell density and high-product titer cell cultures.

Any process operation is likely well supported by automating manual tasks. Parker domnick hunter offers its SciLog SciFlex Filter and Dispense System, a downstream solution that automates final bulk filtration and container filling, a step previously performed in a manual fashion within a vertical laminar flow cabinet. The system can perform manual filtrations, constant pressure, constant flow rate or the company's R/P Stat Method, a hybrid method that maximizes filtration capacity. Playing for Fujifilm Diosynth Biotechnologies, the installation of the SciFlex Filter and Dispense System into the company's cGMP manufacturing was a critical success factor in achieving compliant, right-the-first time manufacture of biologic pharmaceuticals, according to the biotech firm.

Single-use systems rely most on the disposable vessels at their heart, and Sartorius Stedim Biotech has developed its Flexsafe Single-Use Family of scalable range bags to perform better. Flexsafe enables the implementation of single-use bioprocessing throughout all steps of drug manufacture using a single polyethylene film. The innovative concept addresses key industry requirements for future-proof single-use manufacturing of commercial vaccines and drugs. The optimization of the resin formulation, the complete control of raw materials, the extrusion process and the bag assembly guarantee lot-to-lot consistent cell growth performance. Furthermore, batch-to-batch consistent extractables and leachables profiles support drug manufacturers throughout the entire lifecycle of modern biological treatments.

PACKAGING AND HANDLING

Glass ampoules, vials and other vessels have been on Pharma's team a long time and possess many superior qualities. However, commercial-scale handling of glass in Pharma filling and handling operations is prone to create contamination issues from (relatively) rough handling. Garvey Corp.'s Infinity RX 36 Table Top Accumulator is a

potential trade for traditional rotary table or turntable accumulators in product-handling environments. The Infinity RX 36 can out-feed products faster than a traditional rotary table and with less pressure and no damage, says the company, and requires the same footprint as a traditional rotary table while greatly reducing the pressure and noise associated with rotary table accumulators.

Hamilton Storage Technologies' LabElite Benchtop Line offers users end-to-end, automated liquid sample processing, decapping, recapping and high-speed barcode reading. This innovator from Hamilton provides the market with the first system where users have the ability to positively identify the tube chosen for decapping/recapping and track it throughout the workflow. The LabElite I.D. capper enables labs to combine decapping/recapping and high-speed barcode reading within one device without additional user interaction. When sample tracking is not required, the LabElite DeCapper is ready for decapping and recapping tubes in 48-cryovial or 96-microtube racks. A new feature can automatically move the racks from portrait to landscape formats.

PROCESS HARDWARE

Process gas handling is often a critical control parameter, and the 544 Series IntelliSwitch IIv from CONCOA is designed to routinely switch between two gas sources without interruption. This team player offers reliable high-flow, high-pressure switching in the most demanding applications and environments. Economization software virtually eliminates liquid cylinder vent loss and substantially reduces residual return. Switching is actuated as inlet pressure falls below a user-defined point by means of a Web interface or a serial port. A server allows for remote monitoring and e-mail notification of events.

SOLIDS HANDLING

Conveying fragile, friable products to and from an operation along the line takes a player with a gentle touch. Flexicon Corp.'s Flexi-Disc Tubular Cable Conveyors have that touch able to move delicate pharmaceutical products gently, quietly and dust-free, horizontally, vertically or any angle with minimal space requirements. The conveyors are designed to integrate with upstream and/or downstream equipment that sources material from single or multiple locations and deliver it selectively to storage vessels, filling machines or other processing equipment. Flexi-Disc conveyor moves materials using high-strength polymer discs in 4- and 6-inch diameters affixed to a stainless-steel or galvanized cable. Systems can have single or multiple inlets and outlets, and convey over short distances or hundreds of feet/meters.

TABLETING

Attention to detail provides Bosch Packaging Technology's Manesty TPR 500 Tablet Press an innovative edge. Built for commercial, high-volume line duty, Bosch's press can produce more than 400,000 tablets per hour and features well-integrated components and an advanced HMI to deliver high throughput as well as reduced maintenance requirements. For instance, filling parameters can be reproduced to consistently support high-quality yields. To ensure the smooth delivery of tablets, its True Flow tablet discharge chute features a pneumatic gate mechanism and an optimized take-off angle, which

the company says reduces product damage and increases output, especially with shaped/friable tablets.

DRUG DELIVERY

Dosing compliance is an issue both Pharma and health care professionals are seeking answers for, and 3M is applying its vast materials and manufacturing experience to solve them. Its Hollow Microstructured Transdermal System is a patient-friendly intradermal delivery solution designed for difficult-to-deliver biologics and other therapies. Human factor refinements to the 3M hMTS include a textured grip and the capability for non-specific actuation. A cap protects the microneedle array, which patients simply remove, adhere to the skin of the thigh or abdomen, then press down to begin dosing. An audible click assures activation. The FDA-approved device is capable of delivering liquid formulations from 0.5 mL to 2 mL.

Achieving better performance per dose is something GlaxoSmithKline wanted for its FDA-approved type 2 diabetes drug and Novozymes' VELTIS Half Life Extension Platform provided via its Veltis albiglutide technology that helps diabetes therapies achieve an extended half-life; patients are only required to inject their medication once a week. Veltis' half-life extension platform is based on engineered albumins that enable manufacturers to define and optimize the therapeutic window of their drug candidate to help control dose frequency, dose quantity and improve drug tolerability. The platform also offers the ability to provide once-weekly, once two-weekly or once-monthly peptide or protein dosing.

West designed the SmartDose patch injector system technology to be a single-use system ready to deliver higher-dose volumes by injecting therapies slowly over a period of time. SmartDose can be pre-programmed and controlled to provide the optimal dosing rate because many injectable drugs currently on the market require repeated dosing and are intended for self-administration. West's system is delivered in a single package; patients insert the cartridge into the device's injector and adheres the system to the body. A push of a button inserts the needle and starts the injection, which is delivered over time, based on instructions entered by the drug company. Visible/audible indicators confirm operation of the system.

INFORMATION TECHNOLOGIES

Hitting the field at Pittcon, Bio-Rad Laboratories' KnowItAll ATR/IR and Raman ID Expert offer new technologies, says the company, that combine years of accumulated knowledge in the field of spectroscopy with advanced computational power to provide the fastest, most accurate answers possible to scientists identifying unknown infrared and Raman spectra. KnowItAll software offers users comprehensive solutions for spectral analysis, identification, search, data management and reporting. It supports multiple instrument vendor file formats and techniques including IR, Raman, NIR, NMR, MS, UV-Vis. Ready for cGMP and QbD-compliant operations, the spectral intelligence built into KnowItAll ATR/IR ID Expert, combined with the world's largest spectral reference collection, provides a high level of expertise to any scientist.

All-Star INNOVATORS 2014

Increasingly, mobile devices are bringing efficiencies to Pharma process and procedures, especially when it comes to paper-based SOPs in the lab. To help run down this issue and support mobile-device applications, BIOVIA, a brand of Dassault Systèmes (previously Accelrys) introduced Accelrys Capture at Pittcon 2014. Through a small mobile device, users can enter data quickly, find procedures and make instant procedural annotations at the bench without having to document changes outside the lab. BIOVIA's technology helps ensure that laboratory data meets prerequisite requirements before being recorded, thereby reducing review time and rework loops. Automated compliance solutions include validation-ready wireless infrastructure, validation-ready handheld devices for tracking/tracing process-linked data and numerous instrument-to-procedure integrations running on handheld devices in regulated laboratory environments.

A hit at Spring Training, Biopharm's BioSolve Process 5 process analysis and economic modeling platform provides insight that enables biopharma innovators to reduce manufacturing costs and make more informed process and operational decisions. Armed with data from a broad spectrum of sources, BioSolve Process can analyze a range of scenarios to support operations business planning, from building a business case for a fully integrated continuous biomanufacturing platform to the development of an integrated continuous purification process template for monoclonal antibodies.

Need a player who can deliver complete control over methods and SOPs from a single source, and one that combines SDMS, LIMS and LES into one integrated platform, and obsoletes paper-based systems? Thermo Fisher Scientific fielded its all-arounder Lab Execution System LES at Pittcon 2014 and is ready to play. The platform's functionality is built on the Thermo Fisher Scientific SampleManager platform and is fully integrated with the newest SampleManager LIMS. It combines all the functionality and integration capabilities necessary to move toward a truly paperless lab, and lets lab managers automate their SOPs and methods, but with much deeper integration.

SUPPLY CHAIN TRANSPARENCY

TruTag Technologies' TruTag microtags are inert, edible and can integrate into the fabric of a product, independent of packaging and labels, much like fingerprints. Millions of optical patterns can be embedded into a "TruTag," which is a dust-sized particle less than the width of a human hair. It can be used for the authentication of food, drugs and other commercial/consumer products. A security platform that will help prevent counterfeiting, TruTag's technology etches unique "spectral barcodes" into a porous silicon wafer. The codes can be measured via a portable spectrometer-based optical reader and can reference a label in a secure database, where more information about the item (including lot number, expiration date, date of manufacture, authorized customer, or country of authorized sale) can be stored as desired.

Imagine a labeling system that could provide seamless, wireless, near-field communications and data capture along with temperature and time sensing. Thin Film Electronics did, developing the Thinfilm Near Field Communication Smart Label. The platform is designed to handle a variety of sensing elements, both printed and conventional, and depending on the application, labels may be fully printed or feature a combination of printed and surface-mounted elements. Furthermore, Thinfilm's Printed-dopant polysilicon logic allows Thinfilm engineers to significantly compress the cycle time for new designs.

WASTE STREAM AND SUSTAINABILITY

A solution that simplifies both resource management and a necessary operational chore in an innovative way is sure to find a spot on any team, in this case near a clean control zone's locker room. CO_2Nexus' Tersus Cleanroom Laundering Solution enables simple, modular cleanroom laundry plants to be deployed virtually anywhere, liberating cleanroom garment end-users and service providers from the uncertainties associated with water availability, permitting, cost, validation and quality. Offering the world's first CO_2-based barrier (pass thru) system and the company's cleanroom-specific process and chemistry, Tersus uses liquid carbon dioxide in place of water, 40-45 pound cleaning capacity, 30-minute cycle times, and 90-pound throughput/hour via an advanced control system.

Vials vs. Dual-Chamber Systems

For freeze-dried drugs, packaging makes the difference

BY THOMAS OTTO, MANAGING DIRECTOR, VETTER

FREEZE-DRIED PRODUCTS are currently omnipresent and gaining more and more ground in the pharmaceutical market. If international pharmaceutical and biotech industries want to keep up, they are compelled to reconsider their strategies. In the past few years, no fewer than 30% of all FDA approvals for parenteral drugs were given for lyophilized products. Market research is even predicting that 50% of all parenteral drugs will be lyophilized in the future. For the manufacturers involved, the major change lies in the challenges affecting the choice of packaging.

Lyophilization is particularly advantageous for complex and highly sensitive substances. For instance, freeze-drying increases a drug's resistance to heat, light and other external influences. Development, manufacturing and delivery of such substances, however, demands different requirements than with liquid formulations. Galenic formulation, for example, requires other excipients, while manufacturing demands efficient freeze-drying cycles. Also, the drug has to be reconstituted completely and safely immediately prior to administration.

A STRATEGY FOR THE LONG TERM

Lyophilized drugs require manufacturers to think carefully about what kind of packaging their product will need; usually vials or dual-chamber systems, with the latter being either syringes or cartridges. These two systems involve different manufacturing processes and later delivery steps. Each offers specific opportunities that depend on the competitive situation. When determining the most adapted packaging for the chosen system, companies should take into consideration three critical factors:

- The market – What other drugs are available, and in what drug delivery system?
- The user – Who will be performing the injection, and will the user group be expanded to the homecare segment at a later date?
- Packaging know-how – Does the company itself or a contract development and manufacturing organization (CDMO) dispose of efficient production technologies and innovative injection systems?

INNOVATORS FAVOR VIALS

Vials are a good option if the product is a genuine innovation with no visible competition in the medium-term. They are less complex than other options, and the manufacturing processes are fairly standard. Choosing vials reduces time-to-market which, in turn, optimizes the duration of patent protection.

At the same time, vials require experience for the reconstitution of the drug and for producing an accurate dosage. If the user group includes not only doctors and nursing staff, but also patients and/or their relatives, then companies have the option of using auxiliary devices. For example, vials can be equipped with adapters that make reconstitution far easier to manage. Some CDMOs also have prefilled syringes with sterile water for injections (sWFI) in their portfolio.

FOR DRUG MANUFACTURERS, THE DUAL-CHAMBER SYSTEM OFFERS AN ALTERNATIVE FOR SENSITIVE SUBSTANCES

For users with little practice, these combinations provide an adequate and reliable solution. The systems are built to produce the precise dose of reconstituted substances, therefore, adapters and sWFI syringes are an option to support all user groups. When competitors appear on the market at a later stage, a company's product can then be differentiated by greater user-friendliness. Of course, this only applies if the competitor's drug has also been lyophilized and packaged in a vial.

PACKAGING FOR THE COMPETITIVE MARKET

The previously mentioned scenario applies solely to genuine innovations. These innovations are becoming rarer as the industry moves away from the remunerative blockbuster model. That is why companies must carefully scrutinize the competitive landscape that will be using their drug. IMS Health, a market research institute recently published a forecast report entitled:

IN A NUTSHELL:
LYOPHILIZED VIALS

For manufacturers

- Less complex manufacturing process
- Fast time-to-market

"The Global Use of Medicines: Outlook Through 2016." The report states that in the next three years about one-third of all new molecular entities will be in the follower therapies category. The IMS report also predicts an increase in the share of generics to 35 percent of the entire market. Thus, it is critical that manufacturers use every possible opportunity to differentiate themselves from the competition.

The choice of packaging is one such opportunity. Defining a proper packaging strategy early in the process is one way to stave off competition both in the present and the future. If lyophilized drugs are also available in similar delivery systems, using a dual-chamber system like those offered by some CDMOs could be a recipe for success. They allow reconstitution directly inside the system be it a syringe or a cartridge. The lyophilized substance is located in one chamber and the diluent in the other. The drug is reconstituted just before administration. It is a simple and controllable process completed in a few easy steps.

And it eliminates the more complex vial solution which requires a needle and enough experience to draw up the exact amount required.

USER-FRIENDLINESS – A REAL USP

Innovative syringes and cartridges also represent product differentiation vis-à-vis vials. For the professionals, they simplify the process and save time. Regarding the number of applications, doctors and caregivers save valuable time in the treatment and care of patients. In addition, the all-in-one-system reduces the risk of needle stick injuries which can represent a problem with vials.

The dual-chamber systems also open the way to entirely new segments such as the homecare market. Thanks to the injection systems, patients and their relatives can perform the injections themselves if need be, without fear of erroneous dosage. This is a genuine relief, particularly for patients who have to take medication themselves over longer periods. Of course, this particular segment includes unpracticed users with chronic illnesses. Such users often have the necessary experience, but their illness means they are less able to inject themselves due to declining motor skills. All-in-one systems will then mean safer self-medication.

The dual-chamber systems can also be made even more user-friendly if extended with auxiliary devices. For example, for multi-doses there is the dual-chamber cartridge in a pen system. These devices are especially suited for medication destined for children and older people while having the additional advantage of reducing the users' possible fear of the needle.

IN A NUTSHELL: **DUAL-CHAMBER SYSTEMS**

For manufacturers

- Product differentiation
- Less overfill
- Product lifecycle management option

For patients

- All-in-one system
- Simple administration
- Precise dosing
- User-friendly system

THE FUTURE IN LIFECYCLE MANAGEMENT

For drug manufacturers, the dual-chamber system offers a competitive alternative for sensitive substances. They do, however, have another advantage as they allow a company to design a coherent lifecycle management strategy based on the competitive situation. For instance, innovators can put a lyophilized drug on the market in a vial at the start of a lifecycle and profit well from it. If the competition introduces the same product, the company can then focus on the user perspective. Additional value can be obtained by the use of adapters and sWFI syringes. If the market situation requires standalone features for the drug, then switching to a dual-chamber system will be an option. With pens, this solution can be further improved to enable continuing gain of market share.

KNOW YOUR PACKAGING

When choosing the packaging, comprehensive knowledge of the systems and its processes is a key factor. While the dual-chamber systems offer many competitive advantages, they also demand a high level of skill and knowledge in developing and manufacturing. For instance, the dual-chamber system has both an end and middle stopper. Construction and assembly of the syringes and cartridges must be adapted to allow for appropriate break loose and glide forces in order to make the injection process smoother.

Special technologies and processes are also necessary to enable efficient manufacturing of freeze-dried drugs. To avoid losses of the active substance, the preferred option is in-situ lyophilization. But that option demands special knowledge of both formulation and process know-how. For example, because the substance is filled into the front chamber, the distance between the API and the freeze dryer shelf is greater as compared to a vial. This difference in heat transfer and the narrower glass barrel dimension result typically in lower sublimation rates, and the composition and concentration of the excipients must be also sometimes adapted accordingly. The lyophilization cycle will be different and might be only slightly longer. However, the loss of active substance is minimized because the dual-chamber system requires up to 20% less overfill depending on the filling volumes.

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COMPLIANCE MANAGEMENT

Implementing a continued process verification program for bioprocess manufacturing

By Marco Arocha, manager information systems, Baxter International Inc.

IMPLEMENTING A Continued Process Verification (CPV) program requires overcoming obstacles manufacturing companies typically face when they evolve their traditional systems. Leveraging technology solutions can help break through such barriers to ultimately make it easier to access and use process data for trending, automated alerts and improved process understanding and business benefits.

For the past few years since the FDA updated its guidance for process validation, many life sciences manufacturers have been adopting new programs. Process validation is defined as the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products.

Process validation involves a series of activities taking place over the lifecycle of the product and process. The FDA describes the process validation activities in three stages: process design, process qualification and CPV, which is the "ongoing assurance (that) is gained during routine production that the process remains in a state of control." The FDA emphasized in its document that process validation should not be thought of as a singular event, but as a program requiring ongoing demonstration that a process remains in control.(1)

The products and processes of Baxter International Inc.'s BioScience business are varied, but they share the common connection of improving the lives of patients with rare conditions, chronic diseases or limited treatment options. Commissioning its Global Information Technology team to lead the charge, Baxter knew it could capitalize on the following business benefits through an automated CPV program:

- **Improved Data Access** – Access to data is generally achieved through a few subject matter experts (SMEs)

who know where and what the data is and how it relates to a process. CPV programs formalize this knowledge so that more people have self-service access to the data with a common "data dictionary" used for reference and to guide access to the data.

- **Better Control** – Data is frequently extracted into multiple spreadsheets or data and sources. A CPV program can reduce the number of data sources and formalize control processes by creating a single point of self-service access to data that provides a single version of the truth.
- **More Integrated Data** – Data must be integrated with its context (e.g., data type, genealogy, lot number, date, batch number, process step, etc.) to be understood as information that drives action. Most frequently this context is provided personally from the knowledge of SMEs. CPV can formalize and automate this data contextualization so that scarce and expensive SME time can be allocated to more value-adding activities. Additionally, there is a desire to relate the information from different sites and systems, and CPV can optimize this type of integration through one point of access.
- **Automation of Routine Process and Product Monitoring** – In-process and final product parameters can be monitored automatically rather than manually. This provides a high assurance of product safety with evidence from every batch that all parameters are operated within their desired manufacturing limits, not just the final product specifications.
- **Automated Alerts for Review-by-exception** – Monitoring by exception through an automated CPV program provides operating staff and support teams with automated out-of-trend (OOT) alerts, so they can take action before batches begin to fail. This allows technical experts to spend their time only on those process parameters that are trending outside of pre-set limits rather than reviewing hundreds of trend charts to catch just those few that require immediate attention.
- **Validated Environment** – Baxter's CPV program included systems that conformed to the FDA's 21 CFR Part 11 requirements and Good Automated Manufacturing Practices (GAMP) to ensure its electronic record data capture, as well as the rest of the software systems, are validated and, therefore, trustworthy and reliable for decision-making without the need for the additional expense and risks of second person verification tasks.
- **Data More Easily Re-used** – Data is frequently extracted for a single use, and each time the data is needed by different people it is extracted again and calculations/derivations are made repeatedly. Through CPV programs, data and key calculations/derivations can be stored for more efficient re-use.

Baxter wanted to implement a global management approach across multiple sites, to improve process understanding and control process variability across its entire network of manufacturing assets. With its new automated CPV program in place, the company expected to identify yield improvement opportunities through process comparison within a site and/or across different

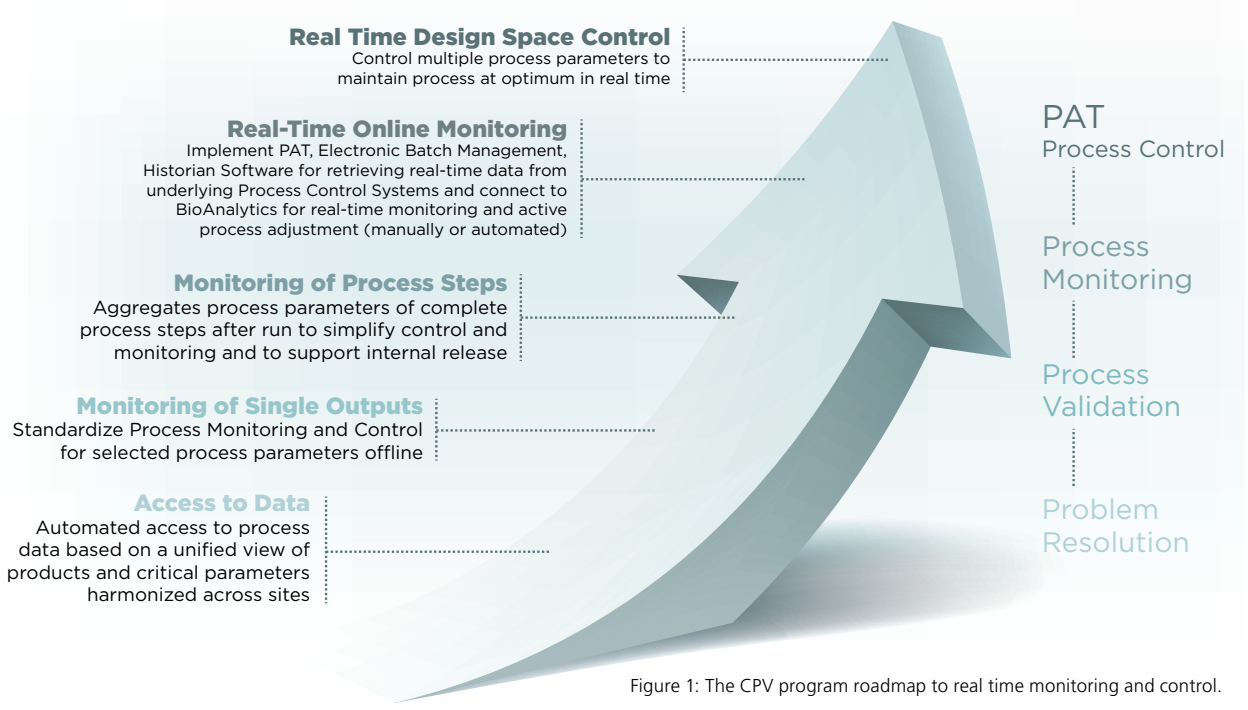

Figure 1: The CPV program roadmap to real time monitoring and control.

manufacturing sites. It wanted to better understand the correlation between process parameter and quality indicating outputs, especially the Critical Process Parameters (CPP) and Critical Quality Attributes (CQA). This would allow trending of parameters, so teams could take action before a specific factor became a problem, thereby avoiding costly deviations and product discards.

Ultimately, Baxter could switch from a data collection and reconciliation mode to an analyzing and decision mode of operation. For the future, Baxter knew its CPV program could enable real time process monitoring and control as Figure 1 illustrates.

OVERCOMING BARRIERS

Baxter's CPV program is known internally as BioAnalytics, and it consists of integrating Operations Intelligence (OI) and guided input from Manufacturing Operations and Quality departments. The vision is to establish efficient manufacturing processes and enable the production of high quality products for patients. The company set out to create an automated analytical capability based on a unified view of products and critical parameters harmonized across its global manufacturing network sites to improve process knowledge and control.

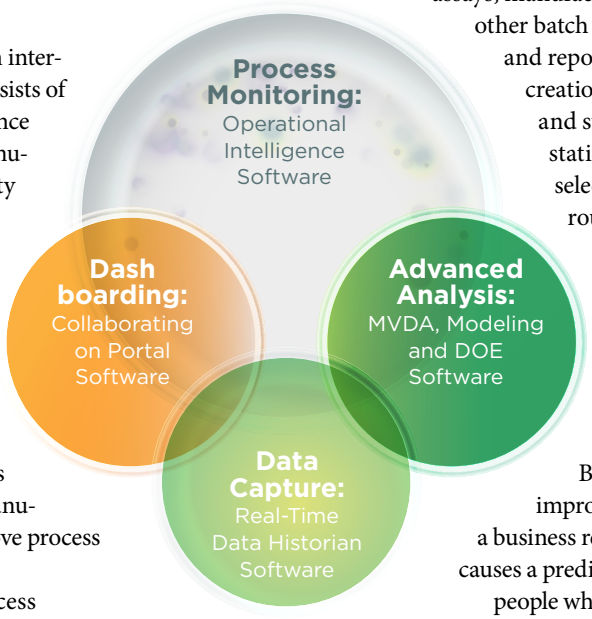

Figure 2: BaxterBioAnalytics tools portfolio is harmonized throughout its global BioScience manufacturing network.

Baxter defines OI as the process of bringing together operations data from many sources to generate process knowledge that will drive improved results. OI elements include automated transfer of data from the shop floor, aggregation of data from multiple sources, providing context and structure to the data and providing capabilities for standard and ad hoc analysis and reporting. All of these elements were considered essential for a collaborative CQV program.

Like other life sciences companies, the nature of Baxter's business presented inherent barriers and special considerations for implementing a CPV program, including:

- Accessing process and quality data stored in both electronic and paper systems
- Improving data analysis/understanding process variability
- Making comparisons across global manufacturing network
- Changing the culture/adapting participants to new habits.

When Baxter began its CPV implementation program and related technology enablers, the team used an incremental approach for each product and manufacturing site to overcome short-term challenges while working toward long-term goals. It defined how technology enablers mapped to each of the three process validation lifecycle stages.

The BioAnalytics program team is responsible for implementing the global harmonization of the tools shown in Figure 2. Baxter wanted to implement a global software system that could provide access to all manufacturing data, including, but not limited to, process control systems, in-line device recordings, results of laboratory quality assays, manufacturing execution data and other batch record data. It needed analysis and reporting capabilities including the creation of control charts, product and stability trending, and other statistical analysis based upon selected data and automation or routine updates and alerts. And, last but not least, it wanted the ability to compare results across all plants and at the overall divisional level.

The team borrowed change management methodology from author Brien Palmer who said, "All improvements to how we operate as a business require change, and all change causes a predictable resistance by those people who are affected by the change. Unfortunately, this tendency — the lack of acceptance of the change — often causes a project to fail, even if the desired change is perfectly logical and necessary."(2)

To help overcome this "human" barrier, the team outlined organizational requirements, assigning each department's role in the CPV transition and program across Quality Operations, Manufacturing Operations, Global Information Technology and Technical Services and Process experts. Individual sites were prepared for the BioAnalytics implementation by assessing the current readiness and defining actions to sustain and utilize the accompanying systems and processes.

The implementation of BioAnalytics relied on the availability of validated underlying systems that contain the data, such as online data/historians, ERP software, process control systems, electronic batch management (EBM) batch release workflow and in-process and final product quality record management software.

Among its lessons learned, Baxter's team recommends identifying process champions to drive the project, and ensuring early on that the team is well defined and utilizes change management tools and assessments to make necessary corrections and support the implementation. Gauging realistic time commitments from SMEs helps focus resources on the project without distractions from competing priorities. SMEs who can make a difference — and who are often the key beneficiaries of the use of the product — can rally the team and follow up with consistent messages to ensure the overall vision and common goals are always present.

Integrating Baxter's global and local teams was an important step. Local site resources were increased to ensure continuity and accommodate related, increased demands. They increased local flexibility by having a local Six Sigma Black Belt on site and an IT representative, who was empowered to support local change management activities, develop changes and adjust configurations, for example. At the global level, the team established peer reviews for configurations and directed changes through an operational steering committee on a quarterly basis.

To date, Baxter's BioScience business has mapped thousands of parameters for product development, process monitoring or investigational purposes. It has implemented its BioAnalytics program for three of its products. Eight sites have started implementations, with three using the program for product manufacturing.

Time savings across projects and routine production have been mapped to easily available process monitoring data. Opportunities to reveal previously unknown processing elements and new CPPs, along with early trend detection that helps avoid out-of-spec (OOS) results have positively affected yields. These benefits, together with a better availability of data, time spent on investigations has been reduced by 80%, encourages Baxter to move forward along its path toward real time monitoring and control.

REFERENCES

(1) FDA Guidance for Industry, Process Validation: General Principles and Practices, January 2011, CGMP, Revision 1.

(2) Palmer, Brien, "Making Change Work: Practical Tools for Overcoming Human Resistance to Change," ASQ Quality Press, 2003.