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VOLUME 12, ISSUE 7

Pharmaceutical MANUFACTURING

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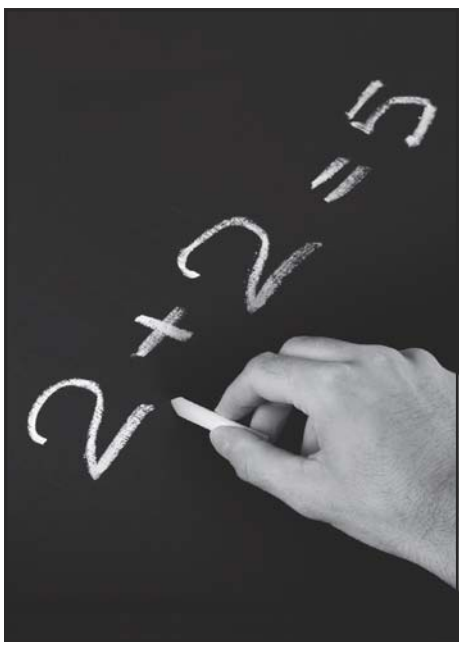

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USPS number (023-188)

from the editor

Pharma Manufacturing in the Information Age

Welcome to PM's Information Technology Almanac 2013

IF YOU hadn't guessed by now, this issue of *Pharmaceutical Manufacturing* departs from its usual format. Our Information Technology Almanac 2013 offers a compendium of general interest information on the critical role information technologies play in creating safer, more effective medicines and therapies. Published annually, traditional almanacs like *Farmers'* provided farmers with statistical weather and other data so they could better plan their growing season. This almanac has similar intent, but it's edited to be a guide to help operations executives and managers farm better data from their processes, technologies and procedures and use this information to get better cost-effective yields from their operations.

Right up front we have "What's Trending in IT," which delivers a virtual panel of leading IT industry experts discussing how data/informatics can deliver great benefit to pharma operations from the development stage on out to high volume production. Compliance in the pharma processing environment is predicated on collecting high-quality data from key points along the process continuum. QbD and cGMPs are proven to regulators via this data — unfortunately, much of the recent regulatory action against producers stems first from poor data-collection processes (some still paper based) compounded by organizational/internal barriers that suppress and divert information before it can be turned into relevant, actionable business knowledge.

Progressive and aggressive pharma companies recognize the absolutely critical need to extract and use enterprise and process data to achieve business results. According to Uri Hillel, Head of R&D Quality and Compliance for Teva, information technologies are deployed to support operations at many levels: "Data driven decisions are an integrated part and one of the main benefits of QBD development. Statistical software is currently being utilized for data-mining techniques and design of experiments at the R&D stage. Moving into post submission development, validation and continuous monitoring and improvement, the goal is to leverage from data and knowledge gained at the R&D stage and keep building this database, utilizing additional statistical tools like SPC and process capability assessment. "

Data analytics and informatics efficacy is dependent on channeling and integrating streams of data from SCADA, LIMs, MES, EBR and ERP systems and more. The issue isn't that there isn't enough data; it's traditionally been the inability to process such data effectively and leverage it to serve the enterprise. With the help of IT, automation and data analytical solutions providers as well as consultants, robust tools to farm the rich data fields of pharmaceutical process are available — solutions proven in other manufacturing-intensive industries. Backing this trend is the inexorable movement in the attitudes of executives and operational managers who understand that there is little room in today's competitive and regulatory environment for them not to accelerate the integration of knowledge systems, data analytical platforms across their businesses. Organizations have to commit to introducing standards and procedures as well as rigorous training of their people to tap continuous improvement if they are to achieve the agility to succeed.

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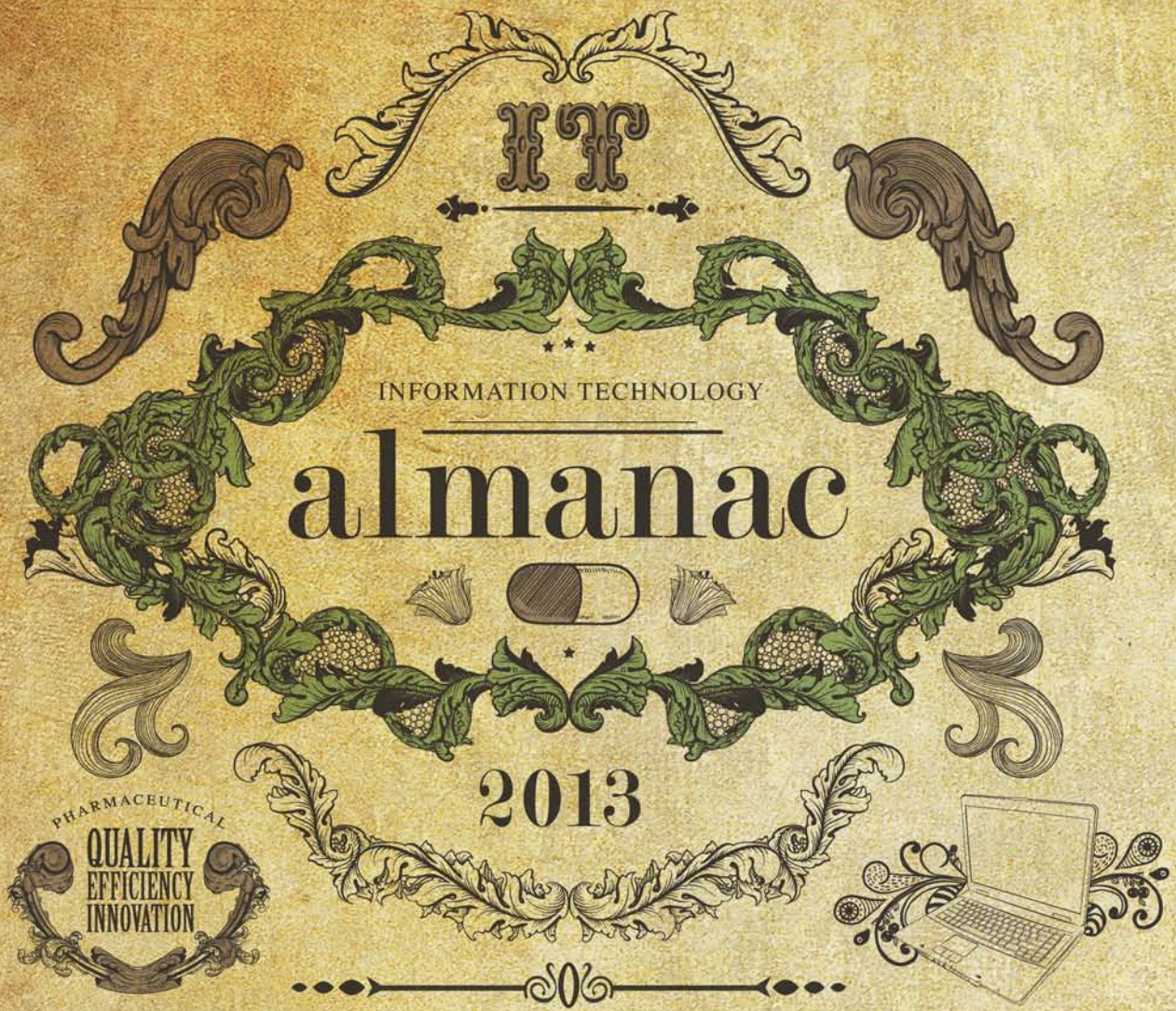

PHM'S VIRTUAL PANEL WEIGHS IN ON

INFORMATION TECHNOLOGY TRENDS

IN PHARMACEUTICAL MANUFACTURING

BY STEVEN E. KUEHN, EDITOR IN CHIEF

What's Trending in IT

At the heart of successful cGMP and QBD-based pharma manufacturing is real time operational data generated by highly networked control, sensing and analytical technologies across the process continuum. The volume of data generated by pharma enterprise information and manufacturing technologies is immense, but the availability of data is not the issue—what is at issue is the ability to generate high-quality data then extracting and shaping meaningful, relevant information from it, then delivering it to the organization in forms that serve business and process decisions.

The efficient flow of data and information from process to executive suite and back is dependent on a well-organized, modern data/informatics infrastructure. But for many organizations basic data input and information handling remains haphazard and antiquated, relying on paper records, subject to human-induced error. Similarly, access to decision-supporting information continues to be problematic, with knowledge kept in silos and behind other artificial barriers that ultimately impinge on efficient, cost-effective operations.

To gain clarity on IT-related issues facing the industry today, Pharmaceutical Manufacturing sought input from leading IT suppliers and consultants; convening a virtual panel to discuss trends in Pharma information technologies and reveal insight into how companies can better manage this aspect of their operations in pursuit of operational excellence and business success.

Pharmaceutical Manufacturing: In spite of commercial realities prompting closer alignment between functional executive ranks (i.e. facility/manufacturing managers) and higher order business intelligence IT operations, it's perceived a gap still exists. In your experience, what has been effective at closing this gap and creating the alignment pharma enterprise needs to be successful?

K.R. Karu, industry solution director, Sparta Systems Inc.: "Closing the gap and aligning information within the pharmaceutical enterprise is best accomplished by globally harmonizing processes and identifying which systems will manage which subset of data. These systems should then be integrated so master data can be stored in one system and consumed by all. When global data is harmonized in a strategic group of systems, the data can be used by many for their particular function within the company."

Ken Rapp, managing director for Analytical, Development, Quality and Manufacturing, Accelrys: "During the course of our work with Pharma industry leaders, Accelrys has identified two specific pain-points — the independence and isolation of standalone vendors / applications and the inability to connect the data from separate application to separate application. This hinders new product innovation and decreases efficiencies because information valuable to new product development cannot be accessed and shared up and down the value chain. Information never becomes knowledge. We think addressing these two problems is the core to closing this gap in Pharma. Technology that effectively connects data and provides valuable knowledge up and downstream from product development through commercial applications is needed. We believe applying technologies that provide the 'scientific platform' to allow communication between disparate applications is the most effective way to close the gap in the Pharma industry."

THE REALITY IS THAT THE COST OF MAINTAINING **PAPER PROCESSES FAR EXCEEDS THE COST** OF INTEGRATING SYSTEMS. — **TRISH MEEK**, *Thermo Fisher Scientific*

Dino Busalachi, practice director, Unified Manaufacturing, Applied Group: "The gap exists and unfortunately, in our experience it is all too often the 'norm.' For many years, the executive suite dictated its information priorities for the overall organization and IT served those interests: hoever, corporate IT and manufacturing have generally not possessed an intimate understanding of each other's needs and concerns, leaving the operations/facility leadership to their own devices to collect, deliver and leverage valuable operational intelligence.

However, the need for alignment between IT and manufacturing IT, supported by an integrated IT and analytics infrastructure, is critical - especially when it comes to the FDA and compliance. Owning and implementing an enterprise-wide intelligence solution has historically been capital intensive and challenging; it requires a close, ongoing relationship between corporate IT and manufacturing to deploy and sustain the solution. Given the often tenable relationship btween corporate IT and manufacturing, many executive boards have chosen not to invest the significant capital necessary to build the required infrastructure and implement manufacturing intelligence solutions.

PhM: Most will agree that process data and record keeping is not managed as well as it could be in the Pharma space. Paper-based systems remain pervasive and record-keeping lapses have been identified as a major factor in compliance issues with regulators. But in spite of the obvious risk, it is feared that change will lead to tremendous expense associated with process revalidation and fresh exposure to regulatory scrutiny. Are these fears justified? And how might they be overcome?

Trish Meek, product strategist, Informatics Business, Thermo Fisher Scientific: "No, those fears are not justified. I think these fears are born out of experiences that happened in the past, but the technology has improved greatly over the past five years. The reality is that the cost of maintaining paper processes far exceeds the cost of integrating systems. The other fact to consider is the potential cost to quality [that stems from] not removing manual, paper based processes. The best a human being can achieve is four sigma for transcription activities. That means that for every 1000 results someone transcribes from an instrument they will make 3-6 mistakes. This error increases drastically to 3 per 100 if there is math or stress involved.

results in a batch being approved and then later recalled, or a failed FDA audit, the cost of this one mistake would far exceed the cost of the IT system that would have prevented it.

Forrest Rudnick, vice president, Vendor Management and Compliance, Datalynx-U.S.: "First and foremost, patient safety is the primary concern. This, above all other elements, cannot be sacrificed. I would have to include risk management to be addressed through business impact assessments audit and remediation efforts to improve the compliance aspect, which would be accomplished by a mindset alteration and effective and continual training. Removing the human element with validated systems and processes that provide repeatable and consistent output will yield a tremendous amount of data, either correct or incorrect, but consistent. So if incorrect, the fix would be relatively easy versus the human input and paper-chase system.

Implementing an IT mindset and moving from paper to an integrated infrastructure will be met with mixed emotions depending upon which group within the company you address. Finance will not see it the same as data managers or process and operations personnel. Of course Senior Management will always demand more and one way to do so is through consistent process applications and a strong founded infrastructure inclusive of electronic signature, repository storage, data back-up and recovery and disaster recover plans. Each of these comes with a price but the performance far outweighs the paper systems and human interaction to maintain said systems.

K.R. Karu, Sparta Systems Inc.: The fears of expense and regulatory scrutiny are unfounded and the opposite is actually the case. Managing processes and the related data from auditing, deviation management, CAPAs, lab investigations, change management and complaints in a harmonized global system creates efficiencies and opportunities for savings rather than an expense. Instead of managing disparate processes in siloed systems or paper records, these process records are easily shared and visible to all who are involved in the process.

Root causes of issues and the corrective actions can be shared across other functional areas that

may have the same conditions, and preventive measures for future problems can be addressed. Companies that cling to paper systems because of perceived cost savings and perceived protection from regulators eventually find that they are actually exposing their company to expensive manual processes that require excessive head count and create systemic quality issues that regulators can easily uncover with little effort. Once regulators find — let alone continuous improvement, or increased process understanding on paper.

Documentation is a big deal. Applied Group was born in the manufacturing space as a consultant, so documentation and change management processes are in our DNA. Part of the isuue is they're afraid ... and this is true for all highly regulated industries — whether that's gaming, health care, financial services or manufacturing. They're afraid of what

IMPLEMENTING AN IT MINDSET AND MOVING FROM PAPER TO AN INTEGRATED INFRASTRUCTURE WILL BE MET WITH MIXED EMOTIONS DEPENDING UPON WHICH GROUP WITHIN THE COMPANY YOU ADDRESS. — FORREST RUDNICK, *Datalynx-U.S.*

inconsistent adherence to SOPs, different methodology, and record quality between sites/functional areas will find themselves exposed to expensive regulatory actions.

Ken Rapp, Accelrys: The fear of change and expense associated with integrating to a paperless system is historic in the pharma space. However, transitioning to a paperless system is ultimately essential for companies to thrive — reducing total cost of ownership and time to value while increasing quality and compliance standards. The efficiency of the new paperless systems is unparalleled compared with the old fashioned paper-based systems, and eventually the ROI will be too great for companies to ignore.

Dino Busalachi, Applied Group: "Applied Group provided consulting for a pharmaceutical company that recently acquired the assets of another company and found that the acquired company's data capture was entirely paper based because the organization said it was concerned about data storage. But from our perspective their concerns were less about data storage and more about compliance change management, operations and the introduction to new technologies and applications. So to this client, having paper in their manufacturing operations was deemed the least risky way of managing data. But frankly, if you are paper-based, the information provided is very stale. Managers are getting information weeks or months too late to do anything meaningful with it.

Also, data can walk off your floor any time when it's on paper, not to mention the fact that it's hard to do trending on paper. In all practicality, it is impossible to do trending the regulators are going to say to them if they change. But if the process is documented, logical and thorough, it's less risky. A lot of the recent 483s and other issues that manufacturers have been called out on are really because of a lack of rigor in their data and record keeping and their inability to back claims with high-quality process data.

PhM: Improvements in the Pharma industry tend to revolve around five key areas:

- ***Assuring product quality/patient safety***
- ***Driving out cost***
- ***Accelerating time to market***
- ***Reducing risk***
- ***Improving compliance***

How can information technologies best be deployed to improve on these imperatives?

K.R. Karu, Sparta Systems Inc.: "Progressive companies that have implemented enterprise-wide harmonized systems for managing quality processes have found measurable improvements in all five areas listed above. When global processes and data capture are in place for auditing, issue investigation and resolution, CAPA management and change management; problems are discovered and remediated earlier in the manufacturing process which makes for a better and safer product released to market. The earlier a problem is discovered and resolved, the less it costs, which ultimately reduces all manufacturing costs and reduces shortages. If lessons learned in one area can be applied to many, this creates

further efficiencies and helps produce more 'first time right' which reduces risk and accelerates time to market. Having global systems in place that are proven to produce these results always improves compliance with regulations."

Ken Rapp, Accelrys: "We believe the key to improving these five areas is standardization. By employing the best practices of the industry — the 'tried and true' automated processes that have proved they provide value — the cost of ownership decreases dramatically while the time to value increases dramatically. We like to think of these automated solutions are to IT what Betty Crocker cake mix was to baking. Just add eggs and water, and you're guaranteed an excellent cake every time without the fuss of the gathering and measuring various ingredients and going through tedious preparations. In the same way, the best practices of lab automation make experimentation more efficient, driving costs down, improving product quality, accelerating time to market, reducing risk and improving compliance."

Dino Busalachi, Applied Group: "Concerns around product quality, cost reductions, improved profitability, risk reduction and compliance improvements — those frankly are what drive our conversations with our customers. Within the manufacturing side of our business, that is, our automation practice, we have a heavy focus on OEE [overall equipment effectiveness]. There's the famous quote from management consultant and author Dr. H.J. Herrington, 'Measurement is the first step that leads to control and eventually to improvement. If you can't measure something, you can't understand it. If you don't understand it, you can't control it. If you can't control it, you can't improve it.' From our perspective, it's all about OEE and it's all about improvement and it's all about real time contextual intelligence.

Trending is a big piece of OEE; for example, we can measure output from sensors on specific devices in a manufacturing operation, and look at how that particular sensor performs for given a period of time, enabling preventative maintenance on a cell line. But the possibilities are limitless. People can do a lot of things with information that leads to improved quality and operational efficiency — decision support in real time. You can't pursue your business goals if you don't manage your assets effectively and understand what's happening in real-time. With access to real-time manufacturing/operational intelligence, you gain the ability to manage forward, versus managing from a rear-view mirror."

Trish Meek, Thermo Fisher Scientific: "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. 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.

Today's LIMS is far more than just a lab information system. It is also a laboratory resource planning system. 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 capabilities of the latest Informatics solutions are capable of fully integrating the laboratory, 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.

In addition to taking advantage of the latest LIMS functionality, we also find that integration and data visualization are key components in our customers' paperless lab strategies. Data visualization takes integration to the next level. The ability to see not just the final result number, but the actual chromatographic or spectral data gives scientists the ability to quickly identify if a result is a bad sample or a bad run. This enables them to quickly escalate problems with a batch or an environmental contaminant or retest the sample as a priority sample and approve the batch."

PhM: What, in your opinion, are the key elements of an effective data/informatics infrastructure?

Ken Rapp, Accelrys: "For a data/informatics infrastructure to be effective, it must be flexible enough to meet the needs of a very dynamic customer environment. Customers should have the ability to use barcoding, connected computing or mobile technologies. Everything should be accessible whether on the premise or in the cloud, and it should have the ability to migrate from what is currently in place today to a new environment tomorrow. It's also essential for customers to have the ability to work with their partners, and this partner ecosystem is constantly changing and evolving, so the infrastructure must also have the ability and flexibility to change too.

Another key component is standardization. In addition to the benefits mentioned above, standardization accommodates the flexibility use personnel. With personnel shifting from department to department frequently, the ability to provide them consistent tools regardless of their current setting is essential to ensuring data informatics solutions are effective."

COMPANIES THAT FAIL TO LEVERAGE THE INFORMATION **THEY CAN RECEIVE USING TECHNOLOGY ARE DESTINED** TO HAVE LIMITED OR DECLINING GROWTH. — **K.R. KARU**, *Sparta Systems Inc.*

Forrest Rudnick, Datalynx-U.S.: "Key obstacles for achieving an effective data/informatics infrastructure facing pharmaceutical manufacturers today include an unstable economy, rising costs and fierce competition. Constant pressure from leadership to improve operational costs while embracing quality and long term output, cost reduction and quality/productivity improvement is always the fore front of executive meetings. With growing Global competitiveness undue pressure on cost, quality and customer demands, people cannot measure, monitor, and control performance for all personnel during the process time. It is important to track and leverage information technologies/systems and automation and satisfy management.

Measures can be taken to meet all the immediate needs through automation of monitoring inputs and outputs, trend analysis reports and by making simple processes repeatable. Review documentation each month to ensure adherence or improvement. Invoke an incentive program to catch problems early. This accomplishes two areas of concern, gets your employees involved with solution management and helps with reduced operating costs. Every company is good at putting together task forces to identify the cost problems, but no companies put together a task force to close the cost gaps identified."

K.R. Karu, Sparta Systems Inc.: "The first step is to identify your core strategic systems for data, including ERP as the foundational system, and then Enterprise Quality Management Software (EQMS), LIMS, Document Management, CRM and any others that may be necessary to run your business. Then define which systems are responsible for which processes, and make sure systems can share data and hand off results to each other. Embrace technology advances: for example, using i-Pads during audit processes and mobile devices to report events as they are discovered.

Finally, collecting data is not enough. Identify how data is analyzed. Having an analytics tool to slice and dice the data for each individual business area allows for discovery of trends and better and quicker fact based decision making."

PhM: What do you think are the consequences to the Pharma industry if it fails to effectively leverage information technologies to tackle industry challenges?

Forrest Rudnick, Datalynx-U.S.: "A key area of misunderstanding [stems from the fact that] many of today's executives did not come up through the ranks of the blue collar environment so they do not grasp the far reaching effects and impact to all the processes and systems involved when demanding greater output or higher efficiency at a lower cost. The FDA Warning Letters and notification of violations repeatedly identifies the same issues regardless of what facility is inspected primarily due to humans not performing consistently as machines. Where a machine can run 24 x 7, be shut down for preventive maintenance or calibration and then be up and running again with consistent output, people cannot. Even on their best day, humans will always introduce errors into the process.

IT automation has the ability and capacity to outperform a human in so many areas to make those FDA 483s become a thing of the past. Without the intervention of a mechanism that has repeatability with consistency, the FDA will continue to find the same problems over and over. Reducing time to market, lowering costs and providing a consistent product will remain a pipedream unless IT automation is introduced into the process. IT automation still requires human interaction, continual training, mentoring, and adapting to new technology. Without this progression, elements that have haunted the pharma industry will live on indefinitely."

Ken Rapp, Accelrys: "I don't think it possible for the pharma industry to fail here, and it is [our] mission to ensure that they don't. There are already too many pharma companies on the path of effectively leveraging information technologies and succeeding for the entire industry to turn back. While some companies may not adopt these technologies, they will be the ones falling behind; not the industry. We're at the tipping point with lab automation — the more companies that successfully implement the systems, the more others will need to follow suit."

Trish Meek, Thermo Fisher Scientific: "To push the boundaries of innovation, companies across the life sciences spectrum must assiduously monitor performance and quality and be ready to capitalize on opportunities to transform and grow. The good news is that many established pharmaceutical companies have spent more than two decades methodically adding technology in preparation for these challenges. But all this investment could be for naught unless these companies take deliberate and strategic steps to align non-integrated, often disparate resources in ways that enable maximum agility for their businesses. And for a lab of any size, new technologies go well beyond instrument advancements alone; cloud and mobile computing, for example, are driving major changes that not only affect business velocity, but also lower entry barriers to increasing competition. In this way, technology is an equal-opportunity catalyst that puts even more pressure on CIOs to stay ahead.

The real risk to today's pharmaceutical companies is that their competitors will discover how to more effectively leverage information technology. There is great focus in the industry on improving pipelines and optimizing manufacturing operations. Our customers are working with us to determine how to leverage their existing investments. Companies that aren't thinking this way may fall behind in the market."

K.R. Karu, Sparta Systems Inc.: "Companies that fail to leverage the information they can receive using technology are destined to have limited or declining growth. Being nimble and making decisions based on all of the facts can help assure a company will provide the market with safe and effective products that are trusted by doctors and patients, while creating manufacturing efficiencies that will allow faster time to market in a highly compliant manner."

SECONDARY SOLUTIONS

Where The Real Work Happens

ERP IS KING, BUT DATA MANAGEMENT "SECONDARY SYSTEMS" ARE THE POWER BEHIND THE THRONE

By John P. Helfrich, Sr. Director, Analytical, Development, Quality and Manufacturing Solutions, Accelrys Inc.

THERE ARE few industries that have as many regulatory challenges involving how to process and control its products as the life science industry — pharmaceuticals, biotechnology, medical devices and the contract companies that support them. Some companies may be able to remediate their existing legacy Enterprise Resource Planning (ERP) systems to meet compliance mandates; however, most "IT systems" simply will not support new compliance or global business mandates without significant total cost of ownership challenges. This has led many life science organizations to implement new purpose-built, commercially available software or "secondary solutions" and integrate them into existing ERP technologies. This approach, as opposed to costly development of custom-coding ERP software into operational systems, provides a "best-in-breed" holistic IT system for operational excellence on a global scale. Typical "secondary solutions" include Laboratory Information Management Systems (LIMS), Electronic Notebook Systems (ELN), Lab Execution Systems (LES) and/or Electronic Batch Record (EBR) systems for quality and manufacturing operations.

The controlling system with respect to final product manufacturing and release to the marketplace is the ERP system; however, this system must be data-fed by other workflow automation systems to capture, catalog, specify, track/trace and approve data through the entire raw materials to in-process to final product manufacturing process. In fact, this product lifecycle management process starts at the development stage of the formulation, synthesis or bioprocess and analytical methods creation stages and has an increasing importance with respect to downstream Quality by Design (QbD) operational needs of the industry.

OPERATIONAL EXCELLENCE REQUIRES OPERATIONAL DATA

The mantra in the C-suite for life science companies is "Operational Excellence" from all segments of the supply chain, both internal and external. As companies initiate "lean" or "six-sigma" programs and begin the now-popular externalization of processes that previously were performed in-house — from R&D through pilot operations and now into full CMO-based API production and packaging — executive managers are becoming increasingly aware that their information/data management infrastructure requires updating. Past practices of patching custom-coded business practices into years-old existing ERP and LIMS systems are fast becoming a bottleneck with respect to both the time and costs necessary to complete the task and the compliance overload it creates for validating any custom programming effort.

A key strategic element to a successful Operational Excellence effort is capturing and cataloging the experimental and operational data streams as the

product transitions from early phase development through pilot and into commercial operations. These data constitute the foundation for true data management transformation to operational wisdom (see Figure 1).

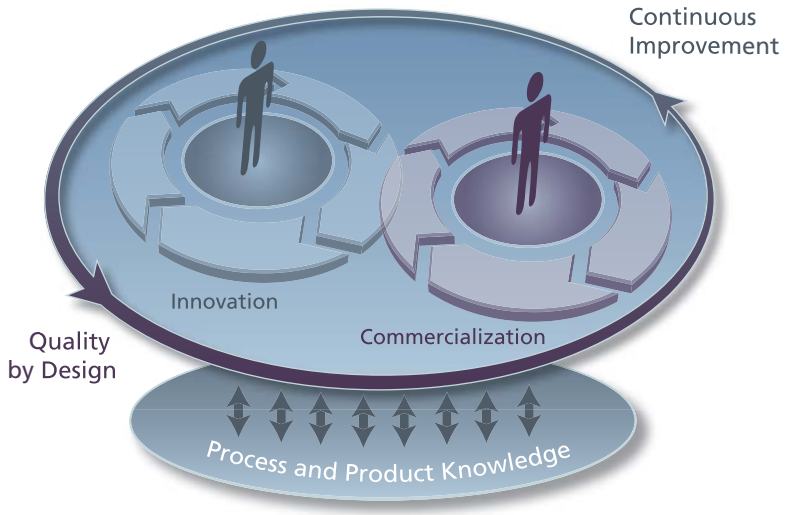

Figure 1 – The data management requirements for global operational excellence begin at the early stages of a product's lifecycle and continue through full commercial operations.

CUSTOM-CODING VS. PURPOSE-BUILT SOLUTIONS

The data feeds for operations and the source for operational excellence programs, generally come from a master ERP system and a LIMS, as well as from a large array of paper-based "systems," be they in Microsoft Word, Excel, lab notebooks or point-workflow logbooks. The data can be difficult to access and generally does not correlate with any true context of daily workflows. Often there is a lot of manual approvals and manual transcription of data/information into other electronic systems. In the life science industry, this translates into a host of compliance risks for data accuracy and integrity and is often the cause of deviations to cGMP guidance. In fact, the majority of FDA-related 483 observations occur because personnel do not accurately follow written procedures.

Often, IT management initiates a large investment in customizations or configurations of existing systems (ERP, LIMS etc.) in an attempt to automate the data capture processes. Again, these customizations require specialists, often from outside the organization as consultants, to define, custom-code and implement solutions that will automate the workflows and data capturing processes and define the compliance and validation tasks required by cGMP regulations. The bottom line is these customizations are difficult to implement and are often too costly in the long run to maintain.

The solution is to seek out purpose-built "secondary" IT systems that are already complete and are installed and validated in a few months versus the year or so needed for customized "solutions." These secondary solutions include process development ELNs, QC/QA LES, LIMS applications designed for the life science industry, and EBR systems. These product-based solutions versus project-based customizations are the key to short-term success for any operational excellence initiative (see Figure 2).

QUALITY BY DESIGN PROVIDES AGILITY

A recent operational efficiency initiative, endorsed by regulatory agencies, is Quality by Design (QbD). Under the QbD process, an operational "design space" is developed by using the development data to support an operational window, allowing production to modify or adjust process conditions (i.e., temperature, pressure, pH, etc.) to account for variations in raw materials or process conditions that fall within the operating guidelines of the design space. This provides

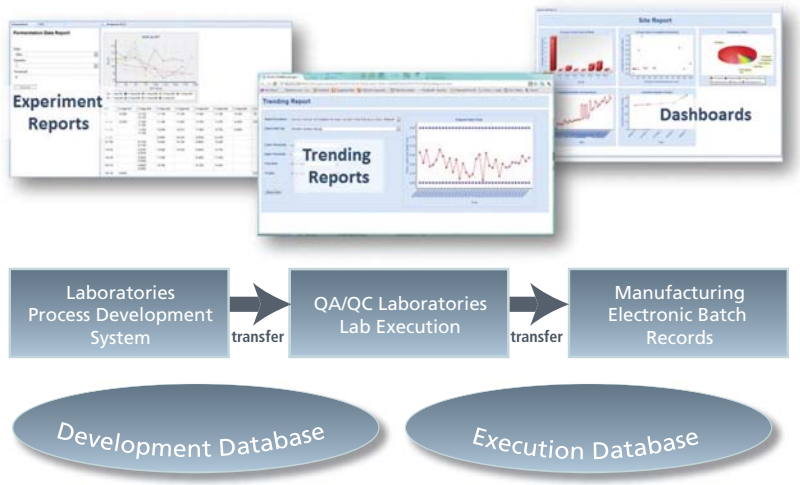

Figure 2 –Product-based IT solutions outline data capture and databases across the process development and execution environment and search tools to access and report information across the continuum. Product and lot releases from ERP are governed by these "secondary IT systems."

the ability to adjust manufacturing processes, as close to real-time as needed, to bring product-critical quality attributes (CQAs) into alignment without notifying the agency for approvals. This alone provides operational excellence conditions that did not exist a decade ago. The key IT component for QbD is the development data containing cause and effect relationships useful for QbD correlations during plant operations and events.

Critical to the QbD process are the relationships between Critical Process Parameters (CPPs) and Critical Quality Attributes (CQAs) that are developed during the product development stages in process and formulations R&D. The development database and the execution database need specific correlations for manufacturing to operate at 100% efficiency. Developing the IT informatics system to obtain these contextual correlations is key to implementing best practices for operational excellence.

SECONDARY SYSTEMS' ROLE

There is growing consensus that new product development is increasingly ineffective — especially for science-driven innovation. Currently, only 25% of projects in industries ranging from pharmaceuticals to aerospace result in the commercialization of new products, according to IDC Manufacturing Insights. Of the 25% of products that make it to market, 66% fail to meet original design or consumer expectations.

For science-driven organizations, there is a productivity gap that spans the entire innovation-to-commercialization cycle. This productivity gap exists because traditional information technology solutions have proved incapable of adequately managing the complexity of scientific data and processes and the volumes of unstructured data characteristic of scientific R&D. Scientific processes, for example, are difficult to automate and track, and therefore information is hard to access and reuse during the scientific and product innovation and commercialization cycles. Critical scientific insights and context from the late discovery and development stages are never transferred to the commercialization operations (i.e., QbD needs) of a business because downstream enterprise software can't handle the unstructured data generated in the R&D cycle. Key parts of the innovation process are consequently lost, along with actionable insights that could bring novel products to market more quickly and cost effectively.

To close the productivity gap and better manage the scientific innovation lifecycle, many life sciences companies are taking a "systems" approach that encompasses a scientifically aware, service-oriented architecture (SOA) for enabling the integration and deployment of broad scientific

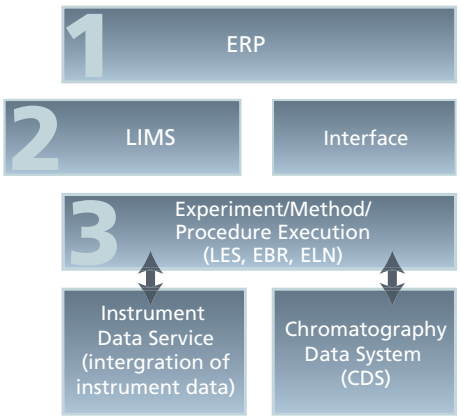

Figure 3 – A tiered IT infrastructure to enable SILM strategic operations for global harmonization and standardization leading to true production operational excellence.

solutions (versus custom coded "projects") spanning data management and informatics, enterprise lab management, event modeling and simulation, and workflow automation from lab to plant. Foundational elements are seen in Fig. 3.

The key elements of this tiered approach include ERP, LIMS, an e-Notebook type workflow execution system (for R&D, QC and Production), and an instrument/equipment and CDS interface for full data capture from procedure development through final product production and process QC execution.

CLOSING THE GAP BETWEEN INNOVATION AND COMMERCIALIZATION

A critical driver of the implementation of secondary systems is the need for compliant operational excellence. For decades, most data has been paper-based, requiring numerous non-value-added checks to ensure end-to-end data integrity and quality from product development through product commercialization. These paper-based systems combined with local ERP and LIMS systems are even more problematic as life science companies increasingly externalize operations. After all, the lab and production floor is where the real work happens.

Today's technology can eliminate these paper systems and replace them with efficient electronic environments supporting science to compliance. Within any pharmaceutical company there are three key informatics design issues depending on where scientists or operators are working within the lab-to-plant continuum. Research scientists require an open-ended, free-form ELN for experimental design, results capture and IP protection. QA/QC scientists and process operators in cGMP environments need just the opposite — a highly structured, procedure- and method-centric operation with full instrument integration and data exchange capabilities with other IT systems (LIMS, ERP, MES, etc.). Between discovery R&D and manufacturing QA/QC are the unique needs of the development groups. Here, flexible experiment design coupled with parameter variations are the key informatics documentation needs. This development informatics/ELN environment enables quick technology transfer of ruggedized, automated test methods to quality operations as well as process parameters to pilot plants and manufacturing facilities. When the molecule goes into full commercial production, the informatics platform enables recursive data access supporting QbD efforts and continuous product/process improvements.

Companies can adopt an informatics approach that effectively connects the innovation and commercialization cycles with high fidelity data that retains contextual information as a project moves through R&D through pilot and into manufacturing. Scientific Innovation Lifecycle Management (SILM) supports this approach with a comprehensive, scientifically aware, informatics framework for capturing and harmonizing data along the product R&D and manufacturing/quality continuum.

Combining best-in-breed ELNs, LES, EBR and instrument integration with LIMS functionality and an interchange based on international industry standards to ERP systems, bridges the innovation productivity gap between development and commercialization, enabling successful, end-to-end tech transfer across new product development and production/QA/QC operations. Companies adopting this novel informatics IT solution will experience:

- Better decisions through optimized experimentation and sample processing with real-time results;
- Enhanced productivity through better understanding of the design space critical to Quality by Design;
- Faster time to market through shorter cycle times and reduced latencies between cycles;
- Improved compliance through automated execution and reporting;
- Effective externalization through enhanced collaboration within globalized R&D and across dispersed internal and partner-based teams.

ABOUT THE AUTHOR

John P. Helfrich is the Senior Director in the ADQM solutions group at Accelrys Inc. At Accelrys, Helfrich is involved in the method and process translation of R&D and QC lab test methods/SOPs to the software conventions used in the Accelrys ELN (formerly Symyx Notebook) and Accelrys Lab Execution System (formerly SmartLab ELN).

DOE Improves Throughput in Manufacturing of Key Intermediate

SOFTWARE OPTIMIZES EXPERIMENT DESIGN AND ANALYSIS IN PURSUIT OF PROCESS VARIABLES

By Steve Collier, Ph.D. (former) Director of R&D at Codexis Laboratories, Singapore

A KEY intermediate, (2S, 3R)-Epoxide (1) is used in the production of Atazanavir (marketed as Reyataz), an antiretroviral drug used to treat human immunodeficiency virus (HIV). Existing methods of producing epoxide 1 involve the diastereoselective reduction of the amino acid derived ketone 2 followed by cyclization of the intermediate chiral alcohol 3. However, the reported approaches (see Figure 1) suffer from either low selectivity or low throughput and most also utilize hazardous reagents or catalysts. Codexis felt there was potential to improve on these methods by using an isolated ketoreductase (KRED) enzyme to enable a biocatalytic reduction of ketone 2.

Codexis researchers screened its extensive KRED library and found hits with near perfect chiral selectivity. However, throughput of the initial screen was too low for commercial applicability. The researchers improved the performance of the enzyme using directed evolution, and also performed two stages of design of experiments (DOE) to identify and optimize key process variables. The final process conditions provided 99%+ selectivity and throughput 50% above the target level without requiring any hazardous reagents.

THE FIRST

Atazanavir was the first protease inhibitor approved for daily dosing and also has lesser effects on the patient's lipid profile. More recent research has found that the drug can inhibit the growth of brain tumor cells, so the drug is being investigated for anti-

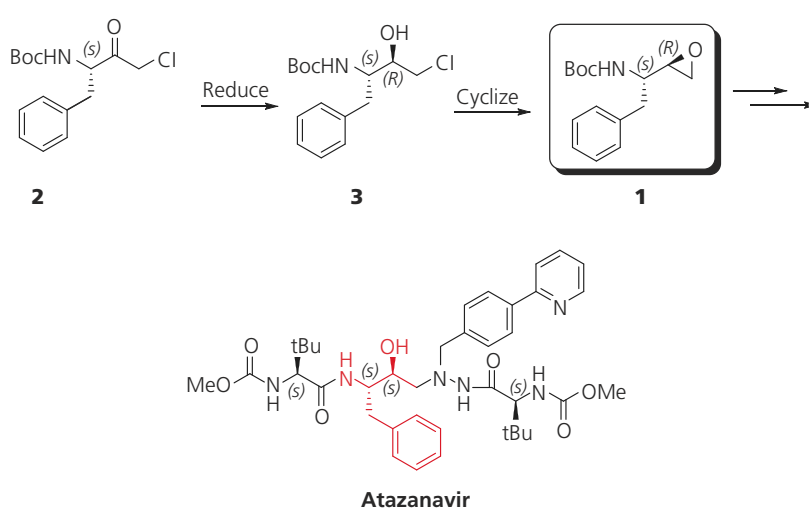

Figure 1: Approach to Epoxide 1

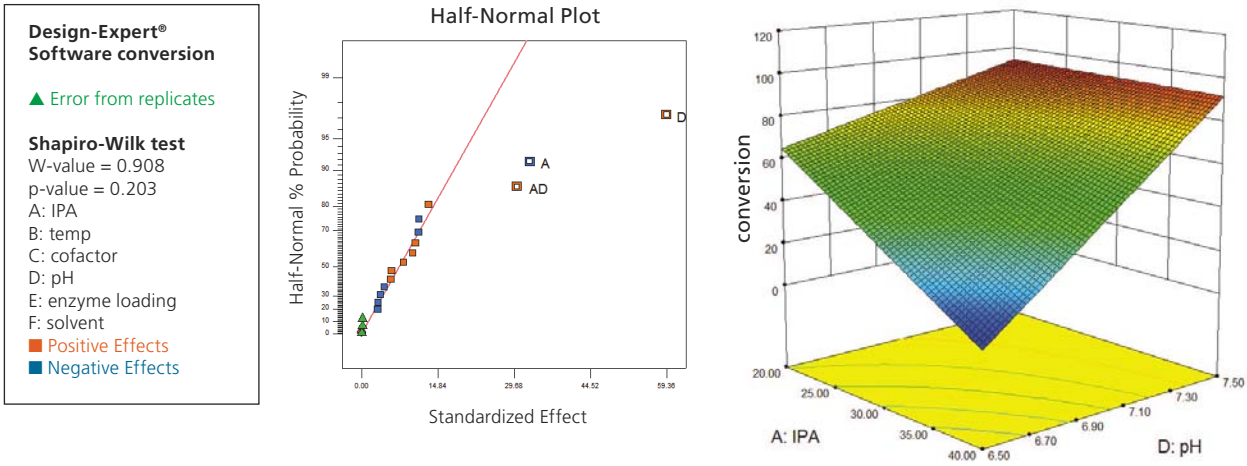

Figure 2: The initial DOE showed pH and IPA concentration were the most important factors

Variable	Low	High
A: IPA aqueous	20%	40%
B: Temperature	20%	40%
C: Cofactor (NAD+)	0.25 g/L	0.75 g/L
D: pH	6.5	7.5
E: Enzyme load	2 g/L	4 g/L
F: Solvent volume	8 vol	12 vol

Table 1: Factors used in the first DOE experiment

Variable	Low	High
A: IPA	10%	20%
B: Temperature	25C	35C
C: pH	7.0	9.0
D: Enzyme load	1 g/L	3 g/L

Table 2: Factors in second DOE experiment

cancer applications. Epoxide 1 is a key intermediate in the chemical synthesis of Atazanavir. The diastereoselective reduction of chloroketone is the most challenging step in the production of the epoxide.

One reported approach involves reduction of ketone 2 with hindered hydride reagents. However the chiral selectivity of this approach is suboptimal and upgrade of the diastereomeric purity via recrystallization is required, resulting in significant yield loss. An alternative approach, whole cell bioreduction using a Rhodococcus species, provides good chiral selectivity but with very low substrate loading — which translates to unacceptably low throughput.

The use of KRED-catalyzed reduction is now an established strategy to manufacture chiral secondary alcohols in very high chiral purity. However, with some substrates natural enzymes are not sufficiently active or capable of delivering the product in high enough chiral purity. In such cases, the product requires upgrading, resulting in low yield. Directed evolution technologies have been used to deliver superior enzyme catalysts, including KREDs. The enzyme is optimized to provide high activity and outstanding selectivity for products that previously were produced with poor selectivity or were even inaccessible with natural enzymes. Simultaneously, the catalysts can be engineered to withstand the rigors of a commercial manufacturing environment, allowing them to withstand conditions intolerable for many natural KREDs.

CODEXIS INVESTIGATES

Codexis researchers investigated the potential for achieving both high selectivity and high throughput by producing alcohol 2 using an isolated KRED. They screened the company's extensive KRED library for activity and found 18 hits with 100% selectivity for the desired stereoisomer. However, the initial performance of the screened enzymes suffered from low substrate loading of 3 g/L, high catalyst loading of 5 g/L and conversion of only 30%. The goal was to achieve substrate loading of 100 g/L, catalyst loading of 1 g/L and conversion above 99%. Improvements were made to the enzyme using directed evolution technologies, and the

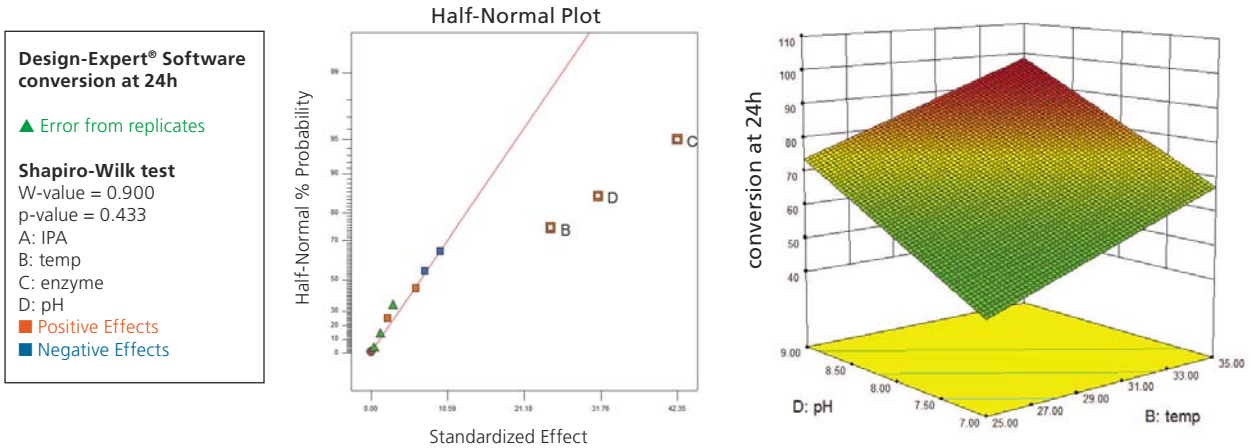

Figure 3: The second DOE showed pH was still key and temperature was also important

Factor	Initial performance	Target performance	Final process
Substrate loading	3 g/L	100 g/L	150 g/L
Catalyst loading	5 g/L	1 g/L	1 g/L
Reaction time	24 h	24 h	10 h
Conversion	30%	>99%	>99%
Diastereoselectivity	>99%	>99%	>99%

Table 3: Results exceed initial goals

process was developed in conjunction with these efforts.

Trying to improve the process using traditional one-factor-at-a-time (OFAT) experiments would have been expensive and time consuming. The researchers turned to DOE because it is specifically intended to identify interactions between process variables that play a critical role in pharmaceutical manufacturing. This powerful approach makes it possible to identify ideal combinations of factors in far fewer experimental runs than the OFAT approach. DOE varies the values of chosen factors in parallel so it uncovers not just the main effects of each factor but also the interactions between factors.

DOE enables chemists to efficiently define, better understand and optimize factors that are important to yield and robustness, particularly where multiple parameter interactions are involved. The Codexis team uses Design-Expert software from Stat-Ease, to design and analyze DOE experiments. They originally selected the software because it is designed for use by subject matter experts who are not necessarily experts in statistical methods. The software walks users through the process of designing and running the experiment and evaluating the results.

In this case, the team picked the most promising catalyst candidate and performed DOE with the goal of rapidly optimizing the process to achieve these goals. Codexis used Design-Expert software to create a fractional factorial experiment with six factors as shown in Table 1 and four center points for a total of 20 experimental runs. The conversion and chiral selectivity of each run was measured.

The results showed that conversion was strongly dependent on pH and amount of IPA in the aqueous buffer. There was also a significant interaction between these two variables. Changing both variables simultaneously increased conversion more than would be expected from the single variable effects alone. The diastereoselective of the enzyme was unaffected by the variables studied.

A second DOE was used to optimize key factors in the process as determined by the initial DOE (see Figure 3). The second DOE was a fractional factorial experiment with four factors and four center points and a total of

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SampleManager 11 at a glance:

- Configurable workflow and extended lifecycle features
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- Flexibility in splitting and merging aliquots and sub-samples
- User-Friendly Search Syntax, new Internet Explorer features and improved support for Windows 7 and 8
- Files, web links and attachments for any entity available for inclusion in reports

12 runs (see Table 2). The cofactor was set at 0.5 g/L and the concentration at 10 volumes because the initial DOE showed these two factors did not have a significant impact on the results. The reaction was sampled at 24 hours and the conversion and chiral selectivity were measured. The results showed that conversion was still strongly dependent on pH, and temperature also showed an influence. As expected, the conversion was also dependent upon the amount of enzyme charged.

Additional refinements to the process included a further increase of substrate loading, a reduction in IPA loading, and an increase in reaction temperature. The final process conditions were a pH of nine and the use of 10% IPA solvent in buffered water at 45 C. The product was extracted into an organic solvent and clarified to remove any traces of the enzyme.

Codexis researchers also optimized the remainder of the process for producing epoxide 1. They sought a solvent for chloroalcohol extraction that provides telescoped ring closure while being immiscible with water and providing a clean phase split. Rapid and clean conversion is required and the epoxide product should be crystallized from the reaction solvent or in an easy solvent swap. A focused screen of base/solvent combinations was performed. Methyl tertiary butyl ether (MTBE) gave excellent performance so it was selected as the preferred extraction/reaction solvent. Potassium hydroxide (KOH) was found to be a suitable base and given its low cost and ready availability was chosen as the base. The metrics for the final process are shown in Table 3.

The final process begins with reduction of chloroketone with KRED biocatalyst in a mixture of 10% IPA in aqueous buffer at pH of 9 at 45 C. The product is extracted into MTBE and undergoes clarifying filtration. KOH is added and the resulting mixture is cyclized to epoxide. The organic phase is washed with water and undergoes a solvent swap to heptane. Crystallization and filtration yields pure epoxide.

Codexis researchers rapidly developed an efficient catalytic manufacturing process for manufacturing epoxide 1. The catalyst was initially identified from Codexis' panels of evolved KRED variants and was engineered to increase activity. Optimization of the process using DOE and reaction screening allowed development of an efficient process from the chloroketone to the target epoxide. Epoxide 1 was obtained in high throughput yield with excellent chiral selectivity and purity.

How Not to Improve Manufacturing Productivity

THREE COMMON MISTAKES PHARMA EXECUTIVES MAKE WHEN ATTEMPTING TO BOOST MANUFACTURING PERFORMANCE

By Scott Klages, Vice President-Sr. Manufacturing Consultant, Parsec Automation Group

PHARMACEUTICAL MANUFACTURING may be tougher than it has ever been before. It seems like once one has tackled everything, integrated best practices, purchased state-of-the art equipment, and hired consultants to help wring every last bit of profit out of the process, reduced margins throw a monkey wrench into the equation and the company's leadership demands staff cuts, then slashes the capital investment budget.

FINDING THE MONEY

Where can one look to for better profitability? Plenty of people are looking in some pretty strange places and doing some pretty unusual things. In pursuit of better margins, some are making colossal mistakes as they attempt to improve profits in today's tough pharma environment. One thing's for certain: No one can continue to do the same thing over and over again and expect different results — otherwise known as the definition of insanity. Like many people, trying one approach after another to lower costs is not an effective strategy. If that sounds familiar, it could be time to find new, more resourceful ways to get the job done, and discover more control over one's destiny.

Pharmaceutical manufacturing and packaging has changed. Could it be time to make those adjustments one's been putting off? Because in all this change there is opportunity, but such opportunity brings with it the inherent risk of failure. But failure is instructive and one can learn from the mistakes of others, so in that spirit, following are three common mistakes pharma executives make when attempting to increase manufacturing productivity.

mistake #1

THINKING THERE IS AN ACCURATE PICTURE OF DOWNTIME

Convincing someone that they "don't know what they don't know" can be extremely difficult. While speaking with plant operations people, GMs, VPs, etc., they often tell me how much they've spent on state-of-the-art equipment, how well they've adopted Six Sigma, how they've squeezed every last drop of cost out of their manufacturing process, etc., but remain frustrated because their lines aren't living up to expectations.

Most of the executives running plants that I've encountered claim they track it, document it, analyze and minimize it — and that seems like so much "hogwash." It's not that executive managers don't try, it's because the process in which measuring and documenting downtime in most facilities is extremely inaccurate — and in many cases — not uniformly defined, or practiced from plant-to-plant or even line-to-line.

A lot of bonuses, ratings, and pats-on-the-back are tied to reporting good key performance indicators, and there is a deeply ingrained cultural bias against making downtime look too big or too bad. Over time, many plant operators have come up with methods for measuring efficiencies that

omit the biggest losses. For instance, one can inflate one's efficiency numbers if time related to clean-up, changeover, start-up, preventative maintenance, material shortages, breaks, meetings, training, etc. is omitted. In essence, if one only measures efficiency when lines are running successfully, one can report pretty good looking efficiency numbers. Everybody gets their bonus, but the company loses because this "look the other way" or "minimizing" approach conceals the underlying problems, that once fixed, could kick efficiency into high gear.

Many plants that are routinely reporting a line efficiency of 80-85% find that when implementing a more rigorous measurement criteria, such as Overall Equipment Effectiveness (OEE), that their true OEE is in the 50% range — or less. This can be a shocking discovery for middle managers who likely fear repercussions from management, so it's critical that top management be involved in establishing a reward system based on accurate measurement of manufacturing productivity and foster a culture of improvement, rather than a culture of reporting the highest number. A lower starting number represents more potential for improvement. For example, if a line that is running at an OEE of 50% improves to 55% by developing rapid changeover methods, this correlates to a 10% boost in output.

Another common problem of human management is the under-reporting of downtimes. A situation that took the manager a reported five minutes to resolve may have actually have taken 20 minutes. What do you think gets reported? And here's something else to ponder: Doesn't it seem strange that all problems start at times like 10:10, 8:45, or 2:30, and are resolved in round numbers like 5, 10, or 45 minutes?

A REVEALING PHENOMENON

A very revealing phenomenon is to observe a line that implements a system with fully automated recording of downtime incidents. What do you think happens? Under these circumstances it is common for downtime incidents to increase ten-fold. Did the automatic reporting introduce problems? No! But it now faithfully reports every incident, in a very precise way: No emotion, no fudging. For instance, a typical pharmaceutical packaging line may have 1,000 short stop failures per week, averaging just 1-2 minutes in length, but each eats away at the line's productivity. At first, this thought terrifies, but in time you have so much more feedback about your line, you can see and correct a whole series of problems that may have been hiding in the background. Conclusion? Systems that don't automatically collect logged data significantly under report downtime. This makes it much more difficult to identify the real root causes.

> Real-time knowledge is the key to uncovering the elements of any line that are impeding its productivity and manual data-collection methods.

mistake #2

THINKING THE WALL'S BEEN HIT ON ASSET UTILIZATION

A manager has struggled through every asset utilization scheme he or she could find. That person's optimized, been consulted, and Six Sigma'd until they were blue in the face. No matter what was tried, they just were not able to squeeze any more asset utilization out of the lines. Everything that can be done has been done, right? Research shows probably not. Most lines have an entire "new" layer of growth in asset utilization, hidden in full view. This layer lives in the following list; can you spot the areas that may need work?

The six major sources of lost productivity, per a TPM methodology, are:

1. Major breakdowns.
2. Setup and adjustments.
3. Short stops (idling).
4. Reduced speed.
5. Startup rejects.
6. Production rejects.

Do any these seem familiar? They happen on every production line, and can be minimized with the proper combination of accurate PLC (Programmable Logic Controller) data, good human oversight, and a tool that makes sense out of the mountain of data the line is generating.

Here's an example: Sales are up: Good news — the wallet packaging line is at capacity. Bad news: It costs more than $4 million to add a new line. Interestingly, the secret to getting more production out of the existing line resides in the PLCs running the line. Most line managers see them as valuable tools in automating a line, but just as critically important — they generate heaps of data that if properly collected in a database and analyzed on-the-fly — will point the way to more savings.

Many lines are swarmed over by an army of clipboard-toting functionaries, obtaining the occasional error condition or fault report, but these folks and others fail to realize that the key to squeezing more productivity out of the line is to look at all the data the entire line produces. Manual process will always be inherently expensive and replete with human error, opinion and sleight of hand to insure conditions appear better than what they really are. Real-time knowledge is the key to uncovering the elements of any line that are impeding its productivity and manual data-collection methods — or even automated ones that result in reports days later — are a sure sign that the line is not performing optimally and not living up to its potential.

When business is good, real-time analysis of production can unleash the unused capacity of assets without a big investment in equipment and training. The growth that the board of directors and stockholders want is right there for the taking — and without the growing pains. And, when business is tough, this kind of real-time analysis can help scale back your production to only the necessary shifts, reducing overtime, waste, and help identify and eliminate underperforming assets in pursuit of lower depreciation and maintenance costs — especially on mature production lines where the easy gains have already been made. Finding ways to improve are much more subtle.

In real time, managers can immediately know what the real problem is, and walk (or run) out on the line and see how to solve the problem, perhaps fixing it just enough to get the line moving again.

Conclusion? Most lines inherently have substantial opportunity for improvement. In many cases, the expense of a new line can be pushed off into the future by practical analysis of current downtime, and focusing on major loss contributors.

> It's time to change with the market instead of waiting for the market to change.

mistake #3

THINKING THAT IMPROVING OEE REQUIRES EXTENSIVE INVESTMENT

Overall Equipment Effectiveness is music to most all pharmaceutical executives' ears — the idea of having production lines producing at their peak — or at least close to it for hours on end. There are five essential components of a program to successfully optimize OEE, but if they are missing, productivity gains won't stand a chance:

1. Management involvement to set the business objectives related to an improvement program and to maintain program focus.
2. Ability to accurately measure productivity in real time.
3. Ability to accurately capture detailed reasons for efficiency losses (so corrective actions can be taken), including non-operating conditions like cleanup, changeover, breaks, meetings and preventative maintenance.
4. Ability to selectively involve the operators in key downtime events.
5. Web reporting and graphical Web dashboards for easy visualization of current performance information by Operations, Maintenance, Engineering and Quality teams.

MORE THAN THREE

Unfortunately, there are a lot more than three mistakes executive managers can make. Instead of putting the energy, effort and money into fixing any fatal mistake after the fact, it may be time to take a more careful look at how to intelligently and safely remove those impediments to high performance. Take advantage of the tools offered; learn and conquer the latest technology (it's easier than you might think), and benefit from its promise.

The marketplace has changed — more changes are yet to come. All we know for sure is that it's time to change with the market instead of waiting for the market to change. Those executives who make the investment now to improve their asset utilization and operational effectiveness — bringing them up to world-class levels — will assure that their companies are prepared for whatever the future brings.

ABOUT THE AUTHOR

Scott Klages is a vice president and senior manufacturing consultant at Parsec Automation Corporation. Klages began his adventures in manufacturing over 30 years ago as a struggling "jack-of-all-trades" in a small but energetic family-owned machine design and fabrication company based in Pittsburgh.

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DATA SECURITY

Toward Better Sterilization Control System EDS Compliance

ELECTRONIC DATA SECURITY ASSURANCE IS REQUIRED FOR STERILIZATION AND WASHING EQUIPMENT; STERIS BUILDS IN AN INTEGRATED SOLUTION

By Robert Ziemba, Siemens Industry Inc.

STERIS CORP.'S Life Sciences division engineers technologies and systems that prevent contamination at virtually every critical point in the pharmaceutical manufacturing process. The company's systems are designed to answer the contamination challenges associated with highly regulated pharmaceutical environments including research laboratories, aseptic processing and bulk biopharmaceutical manufacturing.

Products provided by the Life Sciences division include steam sterilizers, washers, vaporized hydrogen peroxide systems, distillation systems and steam generators. Most of these systems are sold in a skid-mounted configuration, and all require some degree of automated operation and connectivity to facility informatics and system data networks.

Although Electronic Data Security (EDS) regulations are more than a decade old, only in the last few years has the FDA moved to boost compliance throughout the pharmaceutical industry. In 2009, STERIS began to understand from its pharma users that their organizations were looking for capital equipment to include EDS features enabling them to comply with Audit Trail, eSignature, Data Storage and other data security requirements.

The company also realized there was confusion about 21CRF Part 11 and how it should be applied to GMP sterilization and washing equipment in particular. The company set out to define robust, standard Electronic Data Security options, which would address the relevant aspects of data security regulations and provide pharmaceutical manufacturers the features to automate and integrate compliance data reporting.

To deliver this functionality, STERIS turned to automation and services supplier Siemens. Following Gamp 5 methodology, both companies' managers collaborated during a week-long workshop, studying the details of European and U.S. EDS regulations as they applied to decontamination and washing equipment. The collective team produced a gap

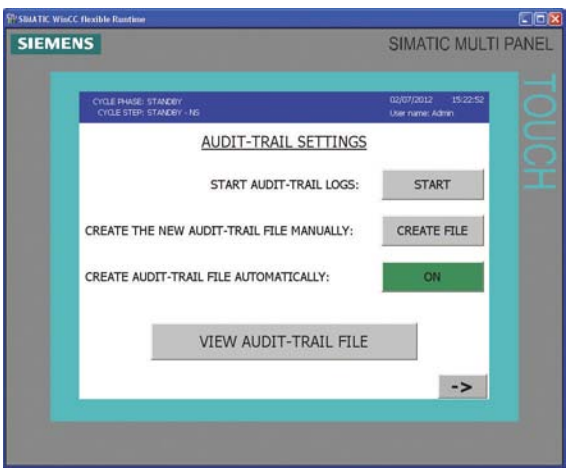

Figure 1. Steris users need electronic records, which include production data and audit trail information; its EDS solution delivers this functionality at the HMI.

Steris, understanding that its customers needed EDS to be well integrated into its offerings, turned to automation supplier Siemens to deliver the solution.

analysis, white paper and risk assessments that eventually fed the creation of functional and technical specifications. After carefully defining the functionality requirements, the teams began work on developing the hardware and software to support the solution.

EDS FUNCTIONALITY

The specific EDS functionality required by STERIS customers is in compliance with regulation 21 CFR Part 11 "Electronic Records; Electronic Signatures" of the U.S. regulatory agency Food and Drug Administration (FDA). 21 CFR Part 11 defines the FDA acceptance criteria for the use of electronic records and electronic signatures in place of records in paper form and handwritten signatures on paper.

The European Commission defines requirements for the use of computerized systems in Annex 11 to the EU GMP Guideline. In contrast to 21 CFR Part 11 of FDA, the European guideline covers all topics related to computerized systems, but in some cases lacks the in-depth details with regard to electronic records and electronic signatures as provided in 21 CFR Part 11.

In addition to electronic signatures, users typically need electronic records that include production data and audit trails to track changes, along with extensive password protection features.

With the power and programming flexibility of most modern automation systems, it's possible to develop almost any required functionality using products from any major supplier, including EDS. However, Siemens' EDS solution is built into the automation systems via its Simatic WinCC Human Machine Interface (HMI) software product — with thorough documentation already developed, proven in use and accepted by customers and regulators.

Implementing EDS with built-in functionality, as opposed to an automation system that requires a great deal of custom programming and additional hardware, offers cost-efficient benefits. First, custom programming effort is minimized,

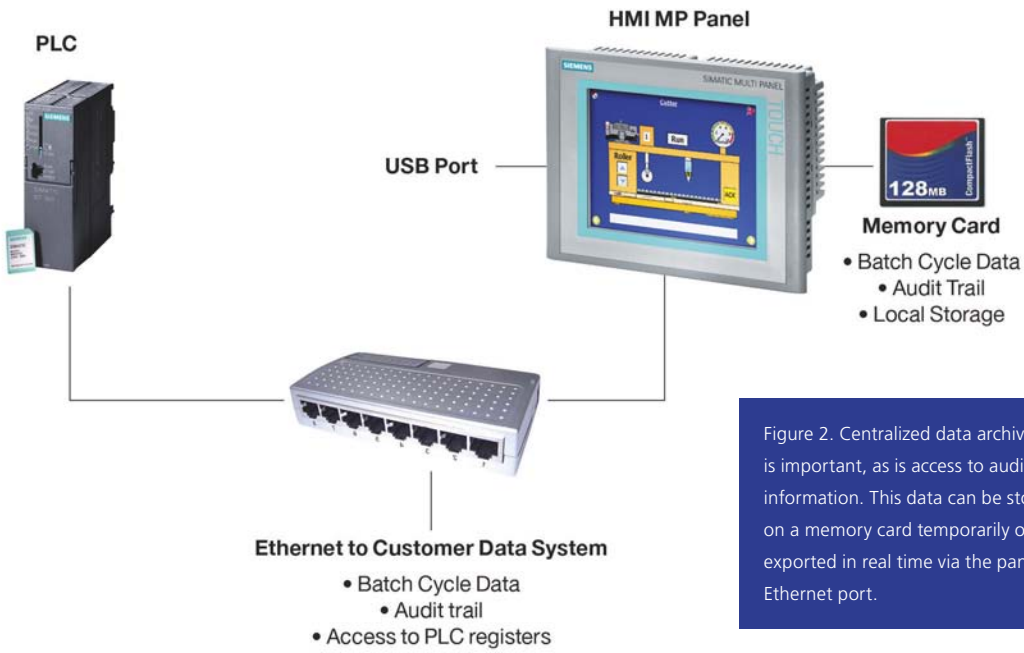

Figure 2. Centralized data archiving is important, as is access to audit trail information. This data can be stored on a memory card temporarily or exported in real time via the panel's Ethernet port.

and in many cases eliminated, and less complexity makes it easier to create standard systems. According to STERIS, its pharma customers prefer standard, as opposed to custom solutions, as it's easier to maintain HMI programs with a minimal amount of complex custom code. By creating a well documented, well tested standard solution with features that enable their customers to comply with regulations, the company provides an effective means to assure data security reporting compliance.

EDS IMPLEMENTATIONS

For customers with centralized data archiving and reporting capability, STERIS provides an S7-315 PLC and an HMI MP OIT as depicted in Figure 1. The operator interface panel runs the software with audit trail capability including user identification, time and date for initiation of cycle, cycle abort, cycle parameter changes, alarm acknowledgements, unsuccessful login/access attempts, etc. All audit trail information is reviewable from the operator interface panel.

A local memory card installed in the operator interface panel provides temporary data storage of audit trail, batch cycle and other data. The panel's Ethernet port allows export of all relevant information to the customer's data system.

Specifically, the Ethernet data export function is typically used to send data from the PLC data registers in real time to the customer's database system. Batch cycle, audit trail and other data are exported in a user-specified format such as CSV or TXT. This data can then be used to generate and print reports using customer-supplied reporting tools.

The operator interface panel includes extensive password protection functionality including but not limited to unique access levels, aging, alpha numeric requirements and automatic log-out. E-signature is also provided, typically used for final batch acceptance and other instances where verification is required.

For system users that don't have centralized data archiving and reporting capability, STERIS provides a complete, flexible PC-based EDS solution.

The company also offers a higher-order solution that provides centralized data archiving and reporting capability in a self-contained package. This configuration provides all of the capabilities of the simpler solution but includes an upgraded operator interface.

The main difference is that local data storage is now provided via the PC's hard drive. Batch reporting is also included, typically in a PDF format. Batch reports may be exported to a customer's printer, or STERIS can provide an optional printer. As with the simpler system, an Ethernet port is included for connection to customer computing systems.

In today's highly regulated Life Sciences environment, it's critical to provide required EDS functionality and to document that this functionality complies with all existing codes and regulations. With built-in EDS functionality at the HMI level, STERIS is able configure two cost-effective, off-the-shelf EDS Option Packages and provide its pharmaceutical customers the ability to comply and integrate system data into an overall plant-wide compliance strategy.

Reviewing the Basics of Stats

A QUICK CHECK OF THE FUNDAMENTALS WILL HELP YOU APPROACH MANUFACTURING ANALYTICS WITH THE RIGHT STATISTICAL MINDSET

By Kate DeRoche Lusczakoski, Ph.D., and Aaron Spence, M.A., Aegis Analytical

PHARMACEUTICAL MANUFACTURERS today rely on process-related statistics for sound decision making related to Quality by Design (QbD), process improvement initiatives and investigations. They pull data from disparate sources across manufacturing networks to populate graphs, charts and predictive models designed to alert teams to potential problems and prevent unwanted batch outcomes.

Valuable insights help determine whether a particular process change or preventative action is worth the required time and cost. Useful as they are, statistics overwhelm most non-statisticians in manufacturing, especially when teams are thrown into the process analysis fray with limited background (this may resonate with any of you who say, or know people who say that they "took a stats class in college").

Large life sciences companies often have upward of 100 statisticians employed on the clinical side, but only a handful of trained statisticians in manufacturing. With so few experts, more manufacturing and quality team members need to become better "data scientists," armed with a high-level, conceptual understanding that helps gather and analyze the right elements to make better-informed business decisions.

Without returning to a university classroom, you can improve your understanding of statistics to avoid common pitfalls, ask the right questions, and make sound conclusions when statistical results are presented — helping to provide an appropriate check-and-balance for your organization. We provide the following recommendations using simplified examples with an important disclaimer: In practice, some situations can be much more complex and require consulting with a statistician. However, these examples may help you approach experts with the right mindset.

UNDERSTAND STATISTICAL ERRORS

Statistical inferences are based on probabilities. What is the chance of a right-handed baseball player hitting a pitch from a lefty? What is the likelihood that you have a car accident on your way home or win the lottery? Statistics allow you to work with probabilities and draw educated conclusions for informed choices. The science of statistics relies on analysis, which encompasses data gathering, organizing, filtering, visualizing and summarizing.

The difference between "inferential" and "descriptive" statistics is a useful starting place. The latter (also known as "summary statistics") is used for process monitoring (statistical process control) in manufacturing.

Inferential statistics is the science of drawing statistical conclusions from specific data using a knowledge of probability. Typically, inferential stats help answer investigational questions and cover statistical analysis such as t-tests, Analysis of Variance (ANOVAs),

multiple regressions and correlations. Insurance companies, for example, use inferential statistics to charge young males with red sports cars a premium over older soccer moms who drive minivans.

In manufacturing, we use a combination of inferential and descriptive statistics for process monitoring and investigations. Have you ever heard someone say they can make statistics look any way they want to support conclusions? This is somewhat true, because there is a degree of error in all statistics. The important goal when using statistics for science-based knowledge is minimizing errors that occur when statistical results differ from what is truly happening on the manufacturing floor.

There are two types of statistical errors to understand. A Type 1 Error, or false positive, incorrectly concludes that there is a difference in yield between sites even though there is no true difference in the manufacturing process.

Conversely, a Type II Error is a false negative, incorrectly concluding there is no difference in yield between sites while a true difference really does exist in the process. Basically, because inferential statistics rely on probabilities to reach conclusions, there is a chance that the results of a statistical test are incorrect. The following describes how you can ask critical questions to help reduce the chance of committing statistical errors, and/or the misinterpretation of statistical results, to improve manufacturing analytics.

EXAMINE STATISTICAL DIFFERENCES

While you may never strive to be a full-time statistician, as a statistics user presented with a "statistically significant difference or relationship" you should ask the following questions to gain a better understanding of the statistics used to drive decision making.

1. What is the confidence level (alpha level)? What was the sample size?

To evaluate statistical errors, we look to a "magic number" called a confidence level, or alpha (α) level. Typically, an alpha level of .05 is used, meaning there is a 95 percent confidence level that the statistical results were not obtained merely by chance. You can change the confidence level, however, if you are willing to take more or less risk. For example, huge sample sizes increase the likelihood of obtaining statistically significant results. Therefore, you might decrease the alpha level (i.e., increase the confidence level) because you are more likely to find statistically significant differences just by chance with a large sample size.

INFERENTIAL STATISTIC GUIDANCE CHART

	Dependent Variable	Independent Variable	Example Use Case
Difference in	One numeric parameter	One categorical parameter with two unrelated levels	Is there a significant difference in the average batch yields in the 10 batches produced with the old equipment and the 10 batches produced with the new equipment?
Difference in	One numeric parameter	One categorical parameter with two related levels	Is there a significant difference in the effects of drug A before and after the treatment on the same person?
Difference in	One numeric parameter	One categoricalparameter with two or more unrelated levels	Is there a significant difference in yield among the three different raw material vendors?
Relationship among	One numeric parameter	One numeric parameter	Is there a significant relationship between a process parameter and the amount of protein produced in a fermentor?
Relationship among (to predict or explain)	One numeric parameter	Two or more numeric parameters	Do the five critical process parameters significantly predictor or explain the moisture content in aspirin tablets?

Table 1 illustrates how, with this guidance, you might choose appropriately from tests including independent t-tests, paired t-tests, one-way ANOVA, multifactor ANOVA, correlation, simple regression and multiple regression.

Ignoring large sample sizes and maintaining a high alpha level is a common mistake that sends investigation teams off and running in "fire drill fashion" to determine root causes of problems that do not really exist (reflected in the Type I Error shown in Figure 1). In Figure 1 (next page), where the manufacturer incorrectly concluded a difference in yield between sites, a higher confidence level would lower the chance of finding group differences or relationships. Conversely, small sample sizes can result in overlooking significant differences or relationships that actually exist (reflected in the Type II Error in Figure 1). This occurs because there are not enough observations for the statistical tests to conclude that there are group differences or relationships.

To summarize, the bigger your sample size, the more likely you are to find statistically significant results, and the smaller your sample size, the less likely you are to find statistically significantly findings. As a quick rule of thumb, a sample size should be somewhere between 30 and 500 observations. In manufacturing you often can't change sample size; however, you can change your alpha level and interpret your results in light of the sample size that you have. In the statistical world, the topic of reviewing confidence levels and sample size to interpret your results in light of the conditions is referred to as statistical power.

2. What sampling method was used?

Sampling techniques are a critical component of manufacturing analytics. There are two general categories of sampling methods: (1) random sampling (representative sampling) and (2) nonrandom sampling (purposeful sampling). Determining what type of sampling technique to use is dependent on what you are examining and how you would like to generalize your statistical inferences. As a good consumer of statistics, you should inquire about the sampling method — was it random or non-random? If random sampling was used, how did you select the samples at random? Watch out for answers like "the operator randomly selected them," because this may or may not be a "truly random" sample. If non-random sampling was used, then ask about the rationale for how the sample was collected. For example, was it collected from the end of the process because that was the focus of an investigation or because that is the only data you had access to? Also, does the non-random sampling method fit the purpose of the analysis?

	Statistic	Statistical Assumptions	Notes
	Independent t-test	Normality- examine with Normality Tests; Equal variance - examine with Variance Tests; Independent observations	Wilcoxon Rank Sum Test is a non-parametric statistical test to use when assumptions are violated or with extreme outliers. Typically display results with a Bar Chart or Box & Whiskers Plot.
	Paired t-test Also called a dependent t-test	Normality- examine with Normality Tests; Equal variance - examine with Variance Tests; Dependent observations	Typically display results with a Bar Chart or Box & Whiskers Plot.
	One-way ANOVA	Normality- examine with Normality Tests; Equal variance - examine with Variance Tests; Independent observations	Typically display results with a Bar Chart, Box & Whiskers Plot, and/or Pair-wise Plot.
	Correlation	Normality- examine with Normality Tests Linear relationship between the parameters; Independent observations; Residual Assumptions– examine with Residual Output Options	Select Pearson Correlation with true numeric parameters. Select Spearman correlation with ordinal parameters, non-normal or outliers. Correlation does NOT imply causation. Typically display with Fitted Model Plot/Scatter Plot or Correlation Plot Matrix.
	Multiple Regression	Normality- examine with Normality Tests; Linear relationship between the parameters; Independent observations; Residual Assumptions– examine with Residual Output Options	Forward, Backward and Stepwise variable selection methods are available.

Regardless of what type of sampling method is applied, the sample used dictates the frame for the interpretation of the statistical analysis. If data was gathered in 2012, then the statistical interpretation should be restricted to only 2012. If data was only gathered from a single site, then the interpretation of the statistical results should be restricted to that site. While sampling methods can become extremely complex, understanding the rationale for the sampling method selection is critical to the proper use of statistics.

3. What statistical test did you use?
Determining the most appropriate inferential statistical test typically depends on three elements related to what you are asking the data to explain or predict. Before diving into the three elements, however, it is important to grasp the concepts of independent and dependent variables. An independent variable is one that affects an outcome (i.e., changes the dependent variable). A dependent variable is an outcome variable whose value depends on other variables. For example, if you believe large amounts of chocolate pudding increase happiness, the amount of chocolate pudding is your independent variable and happiness is your dependent variable. After identifying your independent and dependent variables, you can go through these three steps to determine the most appropriate statistical test:

		Statistical Results	
		Statistics report a difference (p< .05)	Statistics report NO difference (p> .05)
Truly happening in manufacturing/PD	There is a difference in yield between sites	Correct	Type II Error
	There is NO difference in yield between sites	Type I Error	Correct

Figure 1. Type I and Type II errors within the manufacturing process

- Are you interested in looking at a difference in parameters or a relationship among parameters?
- What type of parameter is your dependent variable(s)? (numeric or categorical)
- What type of parameter is your independent variable(s)? (numeric or categorical)

4. Did you check the statistical assumptions?
Statistics rely on assumptions, and making incorrect assumptions about your data can lead to errors in conclusions due to incorrect interpretation of the statistics. Linearity, independent observations, normality and equal variance (LINE) are assumptions of commonly applied statistical tests (parametric statistics), and ignoring these assumptions can lead to misinterpretation of results.

Comparing yield across three manufacturing sites with an ANOVA test, for example, we assume yield is normally distributed, the observations are independent, and there is similar variance in yield between all of the sites. If any of these ANOVA assumptions are violated, then results may be incorrect.

Statistical errors will continue to run rampant in life sciences manufacturing with today's point-and-click, data-rich environments making access to statistics much easier. Having a sound working knowledge of statistical best practices and understanding commonly misapplied areas of statistics (sampling, process capability, statistical process control and ANOVA) will better inform your organization's decisions. Proper interpretation by a trained statistician is always most valuable, but — as a minimum standard — a smart data scientist offers a check-and-balance by asking important questions that help avoid inaccurate conclusions.

Editor's note: This article originally ran in Nov/Dec issue of Pharmaceutical Manufacturing.

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Harnessing IT to Strengthen Relationships

CONNECTING KEY INFORMATION SYSTEMS ASSURES YOUR SUPPLIERS ALL PULL IN THE RIGHT DIRECTION

By Doug Bartholomew

IT'S 2013. Do you know where your drugs are on that other guy's plant floor? You should. Unfortunately, pharmaceutical companies often lack the visibility they need to carefully manage their contract manufacturers and contract development organizations' performance.

That's surprising, considering the benefits pharma manufacturers can reap by connecting key IT systems enabling the sharing of critical information about product quality and manufacturing efficiency. First and foremost, meshing quality, manufacturing, laboratory, and other business information systems can help accelerate understanding of potential quality problems and support a faster resolution of plant floor issues. In other words, by expanding the flow of information between pharmaceutical companies and their contract drug manufacturers, both entities stand to gain. The payoff is greater visibility into operations, better information on which to make business decisions and easier tracking of manufacturing exceptions.

As pharmaceutical firms' dependence on contract manufacturers has increased, the need to expand and speed up connections with suppliers has intensified. While many of the most prominent pharmaceutical companies have connected business systems such as enterprise resource planning systems (ERP) with those of their outsourcing partners for supply-chain purposes, those that have connected other pharma-related IT systems — CAPA, LIMS, QMS, MES and enotebook systems — tend to be far fewer.

MINORITY REPORT

Of the 173 pharma industry professionals who responded to a *Pharmaceutical Manufacturing* magazine survey last year, only a minority reported that their firms had connected their various internal quality systems with those of their outsourced manufacturers.

For example, about one-fourth (24%) said they had integrated their corrective and preventive action (CAPA) systems with those of their suppliers. Only a limited number of respondents (13%) said they were using technology to connect their quality management systems (QMS) or similar IT platforms with those of their contract suppliers. Finally, one-fifth indicated that they had set up dashboards to electronically monitor key performance indicators (KPIs) for their contract partners.

Clearly, by strengthening connections with their contract suppliers through better, more extensive integration and application of various IT systems, pharmaceutical manufacturers stand to reap a host of benefits. One of the most obvious places to start is automating the workflows supporting various processes.

"The more you use technology, the better off you are in terms of efficiencies," says Tee Noland, chairman of Pharma-Tech Industries, a pharmaceutical contract manufacturer in Royston, Ga. "Connecting our ERP system with our customer Johnson & Johnson saves a lot of time for them, because we do a lot of the supply planning for them. For

instance, with Johnson & Johnson, we manage our inventory in their distribution centers," Noland says. "It saves a lot of time for them, because we do a lot of the planning. And of course, if they have a promotion, we have to boost our inventory to meet the increased demand."

Pharma-Tech, which uses an ERP system from Syspro, depends on it for a variety of information essential to the company's successful providing of services to its customers. "Our ERP system gives us information on inventory, scheduling, production, production efficiencies, and materials ordering, as well as financial information," Noland explains. "We also have our own homegrown databases to track quality issues and any non-conformances."

Each shipment from Pharma-Tech to Johnson & Johnson is accompanied by an electronic notification that the shipment is en route. In a similar fashion, once each week, Johnson & Johnson sends Pharma-Tech an XML-formatted file containing a forecast for the products the contract firm needs to provide. "I take their forecast and import it into our system, and we use that to schedule our production," says Kristin Brown, customer service and planning manager at Pharma-Tech. In the next step, Brown uses the electronic forecast to do the materials planning for the customer. "We receive the forecast file and then go in and do the planning for them," she says. She connects with the Johnson & Johnson SAP system through the pharmaceutical company's SAP portal. "We see their inventory and sales, and then we do the planning and supply chain work for them," Brown adds.

> Another factor driving the increased use of technology for information sharing is the need to provide serialization.

Still, many of Pharma-Tech's customers are smaller drug makers that continue to use purchase orders, sales forecasts, and other non-electronic means of communicating with the contract firm. For quality-related issues, Pharma-Tech's quality department sends the appropriate forms to the customer's website or portal.

"For the most part, with our smaller customers," Brown says, "they email us their purchase orders, and we manually type them into our system. For a broad supply chain view, it's better to have all the information imported directly into our system.

"Overall," she adds, "If we had more electronic connections with our customers, it would bring improvements, including better planning, better decision making— for our own company and for the customers as well — greater visibility, and the ability to order in bigger chunks. And it gives us better flexibility in scheduling the workload."

Pharma-Tech also is able to share certain financial information with customers. For instance, the company shares pricing data for raw materials used to manufacture their products. If the cost of raw materials goes up during the year, Pharma-Tech is able to recover the variance in the purchase price by pulling the purchase information out of its database into a spreadsheet that displays the variances. "If there are price changes during the year, we want to get the money back if the cost of goods went up, or we may have to reimburse them if the costs were lower," Brown explains.

Another factor driving the increased use of technology for information sharing between pharma companies and contract manufacturers is the need to provide serialization of products to facilitate tracking and tracing. For instance, some larger pharma companies are using their ERP systems to provide the serial numbers to be used by CMOs, which in turn, communicate back to the pharma OEM a status report.

"The CMO will provide an overall 'statusing' of which codes were used, which were not used, and which were for products that were pulled for quality sampling, or where the labels did not come out right and the product was scrapped," says John Danese, Senior Director of Life Sciences at Oracle Corp., one of the leading ERP vendors.

Despite the apparent benefits, many pharmaceutical companies have been somewhat slow on the uptake to embrace the sharing of various kinds of information with contract suppliers. "I think the bus is about half full, with some pharmaceutical companies yet to get on board," Danese observes. "For some CMOs, their idea of advanced communications is a fax. There is a broad spectrum of maturity among companies in the way they deal with their partners."

Looking ahead, Danese believes that in the next few years, the industry will more fully embrace the electronic sharing of product quality information between pharma companies and their outsourcing partners. "The exchanging of quality information electronically is a bit down the road," he says. "I think we'll see a larger uptake in the next three to five years."

In fact, the sharing of quality data has historically been an area where pharma firms have lagged. While most pharmaceutical firms have a CAPA system in place, those systems' lack of connectedness or integration to larger systems such as ERP has been a serious stumbling block to information-sharing between drug manufacturers and outsourcers. One reason is that CAPA systems often are not connected with other plants or with systems that can measure overall process effectiveness.

Nonetheless, connecting CAPA with ERP promises huge potential benefits. The chief goal is to ensure that everyone who needs to know about — or act upon — production miscue or quality problems, has easy and immediate access to the necessary data. The ability to both trace a batch of material to the source as well as to access all documents associated with it through the production journey can be very helpful in correcting and preventing future occurrences of similar problems.

Compared to the pharmaceutical industry, the high-tech industry is light years ahead in terms of information sharing with contract partners. Of course, outsourcing has long been a way of life for electronics firms, which often have little or no manufacturing of their own, but instead depend on an entire ecosystem of semiconductor foundries, assembly makers, and test providers to handle production. Many high-tech companies outsource logistics and warehousing as well, and some even outsource every aspect of their business.

But in a highly regulated industry like pharmaceuticals, there is an even greater need for information sharing and stronger ties between manufacturer and CMO. "We see pharmaceutical companies sharing quality data both ways, manually and electronically," says Elaine Schroeder, vice president of sales at Pilgrim Software, a provider of quality and compliance management systems.

From a quality standpoint, OEMs must first certify the supplier through an audit to determine that the contract firm adheres to standard operating procedures and GMPs. For instance, if a packaging non-conformity has been identified at the CMO, the pharmaceutical company may require the outsourcer to report on the problem electronically. "Pharma companies that have a quality management system may require the packager to respond through their supplier portal," Schroeder says. "But some respond through faxes or other means," she adds.

"Usually if the pharma company issues a change in supplier materials, they will communicate this through a supplier portal," Schroeder points out. On the sharing of CAPA data, Schroeder says, "It's not all that complex to have one CAPA system feed another CAPA system."

Yet another challenge facing many pharmaceutical firms is, ironically, an internal one — too many versions of the

same ERP system that have yet to be consolidated into one. This lack of consistency within an organization inhibits the smooth sharing of data with outsourcers. "We have a well-known medical device company with three versions of SAP that don't communicate with each other," Schroeder says. "Another client has more than 60 versions of their call-center software, so they are not even treating their customer complaints in any homogenous way."

Companies that have a manufacturing execution system (MES) in place have a leg up when it comes to collaborating with contract suppliers, Schroeder explains, because they have more detailed production data already on tap. Certainly in the high-tech industry the use of an MES with web-based access at both the electronics manufacturer and the contract outsourcer provides:

- Demand signs to the contract partner
- A view of current production status at key points
- Quality data
- Data for measuring supplier performance

Much of the impetus to adopt these technologies in the pharmaceutical business can be attributed to action on the part of regulatory agencies. "I think the regulatory bodies are providing the push in certain sectors of the industry, such as in the medical device area," Schroeder says. Device makers are required to do electronic submission of product deficiencies or non-conformances to a regulatory agency, she adds.

"There is a great deal of interest in expanding connections between pharma companies and their contract manufacturers," Schroeder adds. "But the contract manufacturers look at it as a way to get a competitive advantage by having a QMS in place."

Still another stumbling block preventing the industry from fully embracing more IT systems for collaborative purposes is a widespread concern among pharma companies over exposing their proprietary information to others. "The pharma industry still has a real fear of exposing their quality systems to suppliers," says KR Karu, pharmaceutical industry solution director at Sparta Systems, a provider of quality management systems.

"When it comes to the business systems, there is a back-and-forth of data sharing between systems," he says. He cites just-in-time ordering data utilizing shared inventory information, shared purchasing information and other supply-chain data that is routinely provided by pharma companies to their outsourcers, and vice-versa. Not so, however, with product quality data, which often is kept within the manufacturer's systems.

By contrast, Karu points out, "In the high-tech world, the electronics firms' partners are in their systems as if they work there." Although most pharma companies adopted quality management systems years ago for use inside their own firms, few were willing to share that data with their contract suppliers. The result has been that many drug companies now find themselves handling quality issues the old-fashioned way. "Now that the industry is moving to more of a real supplier base, pharma companies are dealing with quality problems through phone calls, faxes and emails," he says. "There are quality issues falling between the cracks, I am sure, as a result."

The gains to be had by sharing quality data, however, far outweigh any concerns over data security, asserts Sparta's Karu. "For example, when you have a manufacturing deviation, you are not sure what the cause is, and having all hands on deck throughout the supply chain is important," he says. "You need visibility and transparency across the organization. If you have a supplier that fails, you need to know right away, so you can find another supplier somewhere in the world who can provide this service."

Standardization of data is another key area for collaboration between the pharma firm and the contract provider. "One of the top life sciences companies is working with us to take standard procedures and standardized data so that everyone is doing things the same way," explains Ken Rapp, managing director and senior vice president at Accelrys, a provider of lab execution and management systems. "As a result, we are now getting real transfer of process data between systems."

This kind of connectivity between systems at different partner companies has been extremely difficult up until now, Rapp asserts. "It's been nearly impossible to get the job done in the past, but I think there is change afoot," he says. "Today we have tremendous pull between the supply side and the partner side to get this done."

As an example, Rapp cites a pharmaceutical client that depends on Accelrys to keep close tabs on what's happening at its suppliers' labs. "We have a customer with three contract suppliers that they monitor closely. They run a dashboard every day to see what's going on with the manufacturing process at their three partners," he says.

"It's become a critical need for our customers to know what's going on," Rapp adds. "They want systems that include process informatics, and they want them faster, easier to deploy, and with shorter times to get to the benefit. We need to broaden the number of companies that can take advantage of these systems."

Editor's note: This article originally ran in the Feb. issue of Pharmaceutical Manufacturing.

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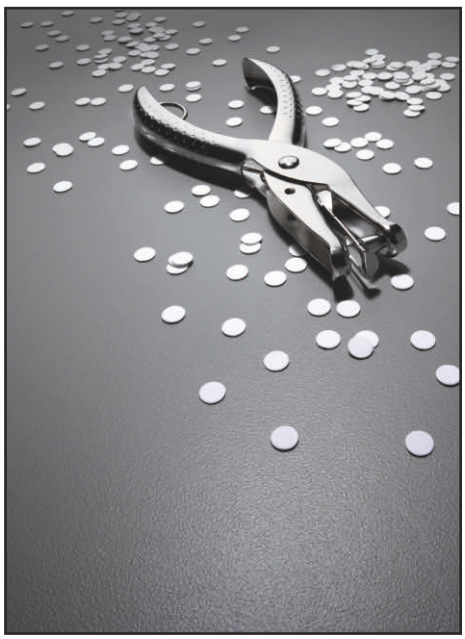

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