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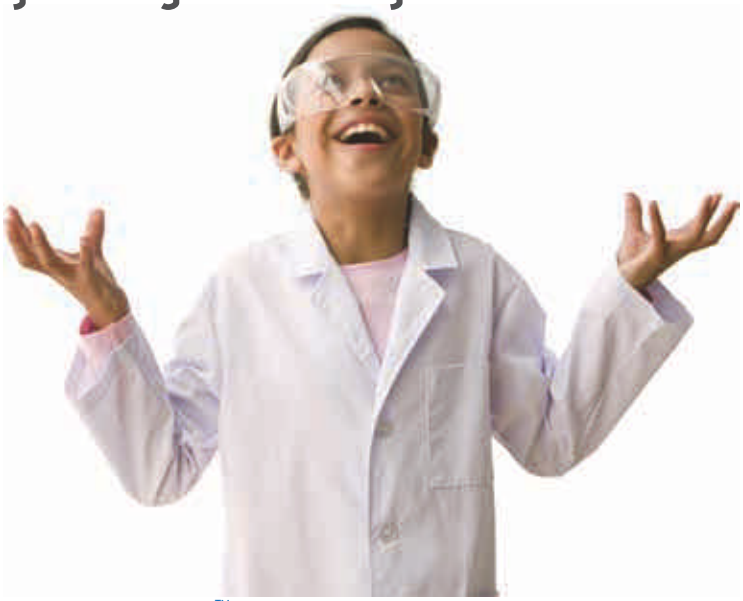

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First, Do No Harm

Modern control is the best way to ensure patient safety (and corporate survival).

THE PAST few weeks have brought more news of expensive pharmaceutical manufacturing failures. Not only Ranbaxy's Consent Decree, which will cost over $500 million, but a mixup that drove Novartis to recall some bottles of over-the-counter medicines, which may have contained opioid prescription painkillers.

We also learned that a couple in Washington is suing Johnson & Johnson, alleging that their toddler died after taking Children's Tylenol that contained 100 times the appropriate level of API. The product was part of a batch that had triggered a "phantom recall," in which J&J hired people to buy back lots of questionable products.

Is it possible that distraught parents accidentally overdosed the child? Administering acetaminophen in its various liquid forms, especially to young children, can be problematic, as FDA disclosed in an April report and safety communications throughout last year. But 100 times the API?

One hopes that the battery of QC tests routinely used today would detect superdosing of that level. Could contaminants have triggered allergic reactions? We may never know what really happened, but the story did make me wonder: How often do drug manufacturing problems result in patient reactions that we never hear about, that are attributed to something else?

You deal with huge levels of risk every day. There's always a chance that ingredients might interact with one another, or that even a tiny change in their manufacture, or an issue with some piece of equipment and its operation and maintenance, at your or a supplier's plant, might affect final product quality. Are you using the best approaches and technologies to handle all this risk?

One regulator minced no words at the International Forum on Process Analytical Chemistry (IFPAC) meeting in Baltimore last month, "It's an indictment that this industry has not forced itself to form clinical connections with assays, and measurements such as dissolution, impurities, content uniformity . . . every company should be able to prove that every dose in every batch is as good as clinical testing batches."

Such direct connections to the patient may remain years away, but at least a foundation of process understanding and risk assessment is being established to allow them to be made. More evidence? A double digit increase in attendance at IFPAC this year. At the conference, less was heard about three-letter acronyms and more about how to apply them, with PAT living on as smarter validation and QbD as process understanding and smart drug development.

More drug companies are using statistical process control (SPC) and process capability analysis in their everyday operations. Some are also applying Raman and NIR in new ways to to ensure consistent ingredient and product safety and quality.

LISTEN FOR THE VOICE OF THE CUSTOMER AND YOU'LL HEAR YOUR OWN.

People within the industry are also openly discussing the need for new QC test sampling and quality standards (p. 14), to bring everyday practice closer to the original spirit of cGMP mandates for "statistically significant" testing and process control.

More attention is being paid to out of trend data, as authors from Noven Pharmaceuticals outline on p. 24. All of these efforts are bringing science to bear on drug manufacturing uncertainty.

Driving the science is the voice of the customer. Patients are demanding low prices, improved dosage forms and convenience. But even before that, they and those who speak for them are demanding consistent safety.

The next time someone suggests that you cut a corner or use an outdated technique, even during these times when everyone is doing more with at least 10% less, listen for your customer's voice and you may hear your own. Is that good enough? Would it be good enough for you or for your own child? Don't you, and all of us, deserve better? PM

AGNES SHANLEY, EDITOR IN CHIEF
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Scientists and Twitter

Twitter's influence on what research gets read and cited is significant.

MICHELE VACCARELLO WAGNER, SENIOR EDITOR, DIGITAL MEDIA

I HAVE been speculating on the many uses for Twitter since it was first introduced in 2008. What started as a venue for broadcasting what you had for dinner or how you have to do laundry has morphed into a vehicle for well, still that, but also for knowledge sharing, public service announcements and now, apparently, for science.

There is an increasing impact of social media on most everything, but its impact on the scientific community and scientific literature citations in particular is growing at a rapid rate. Alexis Madrigal, a writer for *The Atlantic*, citing research done by the *Journal of Medical Internet Research*, has noted that articles which are frequently tweeted about are roughly 11 times more likely to be cited in scientific publications than those few people tweeted about.

WHERE AN ARTICLE MAY ONCE HAVE TAKEN MONTHS FOR REVIEW, IT CAN NOW TAKE JUST A MATTER OF DAYS.

He writes, "Its implications are even more interesting. It generally takes months and years for papers to be cited by other scientific publications. Thus, on the day an article comes out, it would seem to be difficult to tell whether it will have a real impact on a given field. However, because the majority of tweets about journal articles occur within the first two days of publication, we now have an early signal about which research is likely to be significant."

However, there is much debate on the validity of the sources tweeting and retweeting scientific articles (and most everything in general) with many "twit-bots" serving information automatically and without review. But, one thing remains true in regard to twitter and science . . . where an article or topic may have once taken months for review and opinion, it now can be accessed by thousands in a matter of days.

A recent article in *Forbes* points out three social media take-aways for those in scientific industries:

1. We are creating knowledge in new ways but have a philosophy of science modeled on a pre-web way of working; we still tend to think of science and any rigorous thinking as an object that we collectively cultivate and grow.
2. The *Journal*'s research may be a useful early indicator of how social is changing science publishing but also a lesson for the wider community of opinion formers that opinion forming is itself changing and we need to understand its more fluid nature.
3. What we know will change. For decades it has mattered where you publish and peer review has been a brake on some innovative perspectives. It has tended to defend established viewpoints. The possibility is that new interpretations of experience can evolve and evolve rapidly. It needs a new philosophy of knowledge.

Do you think Twitter is a good venue for scientific research, citations and collaborations? Let us know: mvaccarello@putman.net.

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Can Harmonization Be More Equitable?

A new not-for-profit aims to correct what it views as failures by the established regulatory community.

BY PAUL THOMAS, SENIOR EDITOR

IN JANUARY, the not-for-profit Regulatory Harmonization Institute was launched, with the mission of being a regulatory body to better represent the interests of emerging countries and "non-regulatory stakeholders." Founding members include BIO, the Generic Pharmaceutical Association (GPhA), and other notable global organizations, as well as representatives of AstraZeneca, Bausch & Lomb, and other drug and device manufacturers. (See PharmaQbD.com for more, including a list of RHI's leadership.)

The organization is rooted in the belief that global harmonization efforts to date, says RHI president Dean Erhardt, have failed to:

- Include significant and meaningful input from non-regulators (especially industry)
- Adequately represent the interests of emerging nations
- Better balance drug regulation with business interests
- Successfully build global "regulatory capacity"

These are strong assertions. To find out more, we sought out Erhardt, who is also principal of D2 Pharma Consulting, LLC:

PhM: What's the impetus for RHI? What is it going to do that other bodies (namely, ICH) are not doing?

D.E.: RHI differs from the ICH efforts in variety of ways—however, most notably:

a. The ICH efforts are very regionally based in that they are focused on the EU, the US and Japan, effectively excluding other countries, particularly emerging markets.
b. RHI is working to address key issues that are outside of the scope of ICH—namely, issues such as: a) administrative issues; b) compliance; and d) global consistencies around manufacturing implementation.

Further, while various organizations engage in regulatory capacity building with some success, results are extremely limited because:

a. industry (multi-national corporations nor local companies) is neither a participant nor a target of those efforts. RHI is working to include industry, particularly in the emerging markets;
b. there is a complete failure by regulatory authorities and other regulatory stakeholders to properly educate non-regulatory stakeholders; and
c. as a consequence of this lack of education, poorly understood regulatory practices are made subservient to other priorities by these non-regulatory stakeholders.

RHI is focused on addressing each of the above factors by enabling strategic capacity building among BOTH regulatory authorities and regulated industries. This capacity building is effectively acting as the vehicle to leverage regulatory harmonization efforts already underway, and empower them through dialog, training, and external communications to non-regulatory stakeholders.

In doing so, RHI is focused on the efforts that are driven by the best available scientific underpinnings, rather that directing efforts toward mitigation of any nation's specific rules or regulations that, when viewed from a global perspective, seem redundant or unnecessary, but in fact are established under very different economic, knowledge and other constraints affecting any single nation.

PhM: What are the various ways that drug manufacturers can work with and use the institute's services?

FUNNY PHARM

"We can only sell those items with secure and documented supply chains." – Michael Brown

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

D.E.: RHI is a membership organization that is working with manufacturers across multiple fronts to assist in the educational process related to regulatory issues. RHI is currently working with multiple international companies to assist in their understanding of the U.S. market. In addition, RHI is working with working with various government agencies to support educational programs for companies looking to expand from local to multi-national status. Specifically, RHI has provided educational programs for Japanese and Korean entities.

PhM: Part of your mission is to "identify divergent regulatory practices." Once identified, will RHI seek to influence regulators to bring the divergent practices more in line with each other?

D.E.: Simplistically, yes. RHI will work to educate industry on both the "identified divergent regulatory practices" and solicit feedback from industry, going beyond just the regulatory to create practices that are both sound from a regulatory perspective but also sound business policy.

PhM: Finally, does RHI plan to be more behind-the-scenes in working with regulators and industry, or will it be out front seeking to shape public opinions and media perceptions?

D.E.: RHI will be working on both sides of this issue, working with regulators and industry to create a communication link that facilitates and expedites key issues. In addition, RHI will be working in conjunction with various regulatory and industry associations to address regulatory issues and to help shape the public dialogue.

PHARMA REPLAY

"Sadly, this will result in more retirements from the agency."
– A leading consultant, John Avellanet, believes Congress will tighten the screws on FDA in 2012.

"2012 "will also contain its share of setbacks and people who continue to act as if it was still 1994 or even 1984."
– The Philadelphia Inquirer's Daniel Hoffman, waxing pessimistic on the year ahead.

"Abbott quit their pharmaceuticals business. J&J abandoned the cardiovascular stent category. And, big drug companies shelved R&D categories they have invested billions in over the past decade."
– Beaker's Blog on "The Great Slimdown" in pharma that will accelerate in 2012.

"Gators appear when you drain the swamp."
– Hospira CEO Michael Ball on finding additional quality problems after reassessing its manufacturing practices.

For a monthly review of pharma's best quips and quotes, sign up for the Pharma Replay enewsletter on PharmaManufacturing.com.

FDA Releases Case Study on Modified Release Dosages

FDA HAS made available a major (159-page) case study to aid manufacturers in applying QbD to modified-release drugs: Quality by Design for ANDAs: An Example for Modified Release Dosage Forms. Earlier drafts of this and another case study on immediate release products had previously been posted by the Generic Pharmaceutical Association, but not in this longer final form.

Here's a brief descriptor of the product: "Example MR Tablets contain drug substance Z, a chemically stable BCS Class I compound. To match the RLD, Example MR Tablets were designed to have immediate release (IR) granules and extended release (ER) coated beads with extragranular cushioning agents and other excipients all compressed into scored tablets. ANDA aaaaaa documents the approved formulation and manufacturing process for the IR granules. Kollicoat SR 30 D was selected as the release rate controlling polymer and the formulation was optimized using design of experiments (DOE). Two grades of microcrystalline cellulose (MCC) were used in an optimized ratio to prevent segregation of the IR granules and ER coated beads. The appropriate levels of disintegrant (sodium starch glycolate) and lubricant (magnesium stearate) were also identified to produce a robust formulation."

The following paragraph on "Dissolution Method Development and Bioequivalence Studies" provides an example of just how complex this challenge is:

"It was important to understand the relationship between in vitro drug release and in vivo performance in order to: 1) evaluate the impact of formulation and process variable changes on drug product

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quality during development; 2) predict the performance of the commercial batches based on the BE data from the exhibit batch manufactured at the pilot scale; and 3) facilitate the evaluation of post-approval changes. Therefore, we decided to develop a predictive dissolution method and establish an *in vitro-in vivo* relationship (IVIVR) between *in vitro* drug release and *in vivo* performance of the drug product. A predictive dissolution method should be able to predict *in vivo* performance of the drug product reasonably well and also discriminate between the formulations that perform differently." See PharmaQbD.com for more. *–Paul Thomas*

Largest OpEx Benchmarking Survey: 2012 Version

THE INSTITUTE of Technology Management (ITEM-HSG) and the Transfer Center for Technology Management at the University of St.Gallen (TECTEM), Switzerland, are conducting their seventh international Opeational Excellence benchmarking study, under supervision of Professor Thomas Friedli. The survey has been conducted since 2004, with 181 pharmaceutical manufacturing sites of more than 80 different companies included in the database. Participants receive a personal report (including 50 operational KPIs) to help establish improvement priorities for future competitiveness. For further information please visit www.opexbenchmarking.com. Dr. Friedli will share results and analysis later this year.

Sampling: Will Pharma Move to Large N?

AT IFPAC last month, Sonja Sekulic of Pfizer and Merck's Lori Pfahler and Gert Thurau, all of whom are on a PQRI committee dedicated to this issue, discussed QC sampling issues. Currently, Europe uses content uniformity for release, but USP does not offer specific standards for testing larger samples of tablets for content uniformity. Sekulic noted, the question now is: "How much tighter should the standard be," especially as more drug companies implement at-line or online/inline analytical systems allowing them to test many more than the 10-30 samples allowed by conventional methods? A lively debate explored some of these issues (for a longer report, visit PharmaQbD.com). As Sekulic said, there should be no disincentives for companies to use the larger data sets.

Merck's Pfahler discussed her company's experience and some of the statistical issues involved. At PQRI's Fall conference devoted to this topic, she and her colleague Thurau had presented results based on five years of real-time release work. Merck used tablet weight and automated sampling, testing 240-690 tablets, collecting NIR data on average concentration by batch, mg/g and plotting operating characteristic curves. "We spent a lot of time looking at OC curves, with y axis indicating the probability of passing the batch, and x, the percent relative standard deviation(RSD) of product." As RSD goes up, she said, p, the probability of passing the batch, goes down. Steepness of curve indicates the discrimination capability of the batch. Several methods have been proposed so far, she noted.

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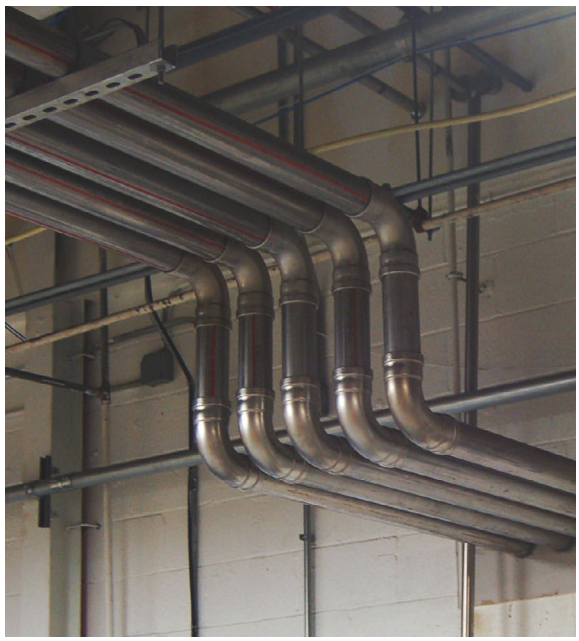

> *"The Viega ProPress system allowed us to pre-run all the pipe, except for the connections at each end, parallel to the existing lines while production still ran. Viega can be installed so fast—we were able to do the final cut-ins during lunches, so they had very little downtime."*

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

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

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

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

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

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

Compendial tests are often multistage, making them difficult to do, so tests that PQRI has proposed so far are single-stage tests. In addition, she noted, the committee is trying to avoid zero-tolerance criteria and is working with both Large N and modified Large N. Ultimatly, PQRI's committee opted for a quadrant approach.

"Release tests are just an audit of our system," Pfahler noted. "We ensure quality by assuring that processes and products are well designed from the start."

Later, FDA's Rick Friedman noted the industry's dichotomy between business (producer) risk vs. consumer risk. "The producer risk is that you fail a good product, the consumer risk is that you release a bad product," he said. The industry is currently between the two. Instead, why can't it get them to converge? he asked.

–Agnes Shanley

COMPLIANCE QUIZ

Welcome to Compliance Quiz. (Find each month's full quiz, and more details on answers, on PharmaManufacturing.com.) February's quiz focuses on 21 CFR Part 11. For answers, see below, right.

1. CFR Title 21 Part 11 breaks down into 3 sections:
a. General Revisions (Changes to Guidances), Electronic Records, and Hybrid Signatures
b. General Provisions (Scope and Definitions),Electronic Records, and Electronic Signatures
c. General Recommendations (Scope and Requirements), Implementation, and Controls

2. Part 11 requires companies to use electronic records and signatures. True or False?

3. Under Definitions, sec. 11.3, (3), Part 11 states: "Biometrics means a method of verifying an individual's identity based on measurement of the individual's physical feature(s) or repeatable action(s) where those features and/or actions are both unique to that individual and measurable." Currently, a common biometric security used on laptops is:
a. Facial recognition
b. Retinal and iris recognition
c. Fingerprint scan
d. Palm print

4. Electronic records must have at least three elements of accompanying metadata:
a. The printed name of the signer, the date and time of signature, and the meaning of the signature.
b. Comments and event details, year and month, electronic signature.
c. The printed name of the signer, an email address or contact information, and year and month signed.

5. What is the difference between "Closed" and "Open" systems?
a. Closed systems shut down at the end of each event or process. Open systems operate 24/7 except during power outages and network downtime.
b. Closed systems are not controlled by persons who are responsible for the content of the system's records. Open systems are controlled by persons responsible for the content of records on the system.
c. Closed systems are environments in which system access is controlled by persons who are responsible for the content of electronic records that are on the system. Open systems are environments in which system access is not controlled by persons who are responsible for the content of electronic records that are on the system.

6. Subpart C requires that persons using electronic signatures must certify in writing to the FDA that their electronic signature is:
a. the legal equivalent of their written signature
b. a close approximation of their written signature
c. written with their dominant hand

Answers
1.B 2.False 3.C 4.A 5.C 6.A

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Pfizer: Towards Holistic Supply Chain Security

When it comes to patient safety, says Brian Johnson, there should be no "competitive advantage."

BY PAUL THOMAS, SENIOR EDITOR

ONE COULD say that supply chain security is the most pressing problem facing the drug industry and perhaps facing our health care system as well. Supply chain is at the heart of health care's greatest problems: drug counterfeiting, shortages of key medicines, and of course, escalating medical costs. To solve these problems and ensure a truly secure supply chain, a holistic approach is necessary.

How to achieve such an approach was the subject of a recent PharmaManufacturing.com webcast—"Supply Chain Security: Threats, Strategies and Successes"—featuring Brian Johnson, Pfizer's senior director of Supply Chain Security. (Please visit the Webcast library on PharmaManufacturing.com to view.)

Johnson began his talk by reminding the audience that there is no one-size-fits-all or optimal approach to securing drug supply chains. "This is one company's view," he said. "It's not necessarily the best view. It's our approach."

"We believe that supply chain security is something that we're all in together," he continued. "And by sharing our approach, our thinking, we're really hoping that it's going to promote collaboration and partnership in our united effort to fight criminals."

Indeed, Pfizer must be credited with being proactive in sharing its lessons learned from various supply chain pilots—Viagra and other Pfizer medications have been favorite targets of counterfeiters, and the company was, for example, a pioneer in testing item-level RFID tagging of products.

Pfizer's approach to its supply chain has greatly evolved over the years, Johnson said. "When we started talking about the threats that we were faced with, we really talked about these three buckets of threats: cargo theft and diversion, counterfeiting, and economically motivated adulteration," he said. "These are all crimes against our industry, and they all represent significant risk to patient safety."

Yet it quickly realized that supply chain security is bigger and more complex than that. The context has changed in particular. "A lot of companies are dealing with significant patent expirations," he noted. "A lot of companies are dealing with lack of R&D productivity. A lot of companies are starting to work in parts of the world where they have not historically worked . . . And there's increasing pressure to control health care spending, and at the end of the day, provide affordable medicines to those who need it."

TABLE 1. PFIZER SUPPLY CHAIN SECURITY: DEVELOPING A STRATEGY

Understanding the Threats
- What are the supply chain security threats and how big is the problem?
- What are the key components of the strategy?
- How will we define the supply chain?
- What regions around the world are impacted?

Current / Future State Mapping
- What organizations are involved?
- What are the key processes?
- How do we attack the problem holistically?
- How do our processes integrate?

Developing the Strategy
- What is our future state vision?
- What are our opportunities for improvement?
- How do our processes need to change?
- How can we best deliver safe, authentic, and effective medicines to the consumer?

Pfizer Supply Chain Security

These drivers are changing the pharma business model, he stated. "I've been in the industry for 28 years," he said, "and ten years ago, we were not looking at a global, complex situation like we are today, where raw materials will come from one part of the world, maybe processed in another part of the world, the finished product is moved into another part of the world, where it's repackaged, and now we're selling our products in markets where it's quite complex."

"Given the increasing threats and these changes, we as a company said it's time to step back and really make sure that we have a good, consolidated, 'One Pfizer' strategy around supply chain security." Developing this strategy took multiple steps, as shown in Table 1.

Said Johnson: "That process drove our strategy in terms of what our end state looks like, what opportunities we have to improve, and what processes really need to change to address the increasing threats that we are faced with."

From raw materials to finished products received by consumers, Pfizer identified more than 100 business

processes in 15 organizations that were critical to its supply chain security program. Some of these processes are familiar, such as GMP processes, Johnson said, but some are more obscure business, logistic, and security processes. Together these hundred-plus processes create a picture of supply chain security.

The picture is one that acknowledges that Pfizer's responsibility does not end when it sells products to wholesalers and distributors. Just the opposite, in fact: Selling the product marks the beginning of successive steps to engage and support trading partners, monitor and measure what's happening in the market, and even working directly with consumers on their experiences.

It's a holistic approach, noted Johnson, that is managed via a sophisticated matrix—comprised of disciplines as diverse as procurement, quality, security, communications and media, external supply, and commercial teams. "The matrix approach was really the only viable way to handle this," Johnson stated. "We did not feel it was appropriate or viable to try to create a big centralized organization around this."

On the whole, Pfizer's supply chain security program is "a combination of preventative processes, processes to detect issues, and processes to respond to issues out in the marketplace."

"And nothing that we have or that we're doing provides us a competitive advantage," Johnson summarized. "We're happy to talk and share and work with many supply chain partners."

OUTSOURCING NEWS AND NOTES

Bristol-Myers Squibb will take over **Inhibitex**, which is developing a promising oral hepatitis C compound.

Patheon and **Procaps S.A.** will work together to provide "P-Gels," a new line of prescription soft gel product development and manufacturing services.

Fleming Pharmaceuticals sold rights to many of its core products to **Valeant Pharma**. Fleming has retained rights to Thyro-Shield (which blocks radioactive iodine absorption during nuclear emergencies), and will continue to operate its contract manufacturing site in St. Louis, Missouri.

BioVigilant Systems, provider of Instantaneous Microbial Detection, has changed its name to **Azbil BioVigilant**, reflecting its alignment with Japan's Azbil Group.

Sartorius Stedim Biotech and **G-Con** will partner on biopharma production platforms. A new product line will leverage G-Con's cleanroom "pods" and SSB's single-use and reusable product portfolio.

Abbott announced that select FDA laboratories will begin using its STARLIMS laboratory information management system.

Sigma-Aldrich recently purchased **BioReliance Holdings**, a specialist in testing services for drug development and manufacturing.

AAIPharma has purchased testing and lab service company **Celsis Analytical Services** to expand its portfolio.

Lonza has fired CEO Stefan Borgas following disappointing 2011 earnings.

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Patient Safety

ARE YOU IN CONTROL?

Analytics, certification and data analysis can help ensure consistent ingredient and product quality

By Agnes Shanley

THE PHARMACEUTICAL industry today faces more competitive pressures than ever before, not only patent expirations but a growing number of quality and compliance failures. The past few years have seen a number of pharmaceutical product recalls motivated by improper API loading, particulate contamination in finished product, API contamination and sterility failures in injectibles. A large number of inconsistencies have occurred in over-the-counter (OTC) products and tablets.

Proactive manufacturers are responding by going back to risk-management basics and looking more closely at data, particularly manufacturing data. They are also creating closer connections between manufacturing and development teams, in the true spirit of pharmaceutical Quality by Design.

In our special feature on "Outliers," following this introduction, the QC team from Noven Pharmaceuticals shares best practices on analyzing the process and analytical information on ingredients and finished drug products in Annual Product Review reports. Often, they say, such data is just sitting there, waiting to be mined for continuous improvement efforts that can help ensure consistent ingredient and product quality.

Of particular interest is "out-of-trend" data for products and processes that are still performing within spec, yet indicate future potential risk. Other efforts are converging:

- the movement to independent third-party auditors to certify ingredient manufacturers' GMP compliance
- establishment of ANSI standards for auditing ingredient suppliers for GMP compliance
- efforts within the industry, and at individual companies, to apply risk-management principles to ensure a better understanding of material properties and the safety of ingredients
- increased use of analytics, including NIR, Raman and NMR, to develop a better understanding of the factors that can lead to inconsistent quality
- progress by regulators to harmonize efforts and by USP to articulate requirements and modernize testing methods, and to set best practices for overall supply chain management.

This brief summary will touch on some highlights (for more in-depth coverage, please check our special report on PharmaManufacturing.com this month).

One of the biggest stumbling blocks to product quality assurance has been excipients, frequently natural materials that exhibit high variability between batches and suppliers. Rather than functioning as mere fillers, their interactions among each other and with API can lead to adverse responses in patients.

Pharmaceutical companies are taking action on the individual level to better understand, characterize and use these materials. At the recent IFPAC conference in Baltimore, Bruno Hancock, research fellow with Pfizer (Groton, Conn.), described efforts that his company is taking to develop a risk-based framework for evaluating excipients. "Most formulations contain four or more excipients, each with more than 10 attributes that could potentially affect formulation performance," he explained.

At Groton, Pfizer has assembled a group of subject matter experts from research, manufacturing, regulatory affairs, and procurement, both internal and external to the company to study issues. Efforts generally occur, Hancock says, once Phase III formulation and process have been defined. Risk assessment principles are used

to collect data, and team members refer to the target product profile, for instance, accounting for special considerations for pediatric formulas or products bound for specific geographical regions.

SCORING EXCIPIENT RISK

Together they identify control properties and potential risk factors, scoring them from 1 to 10 in key areas such as particle properties (size distribution and aspect ratio), chemical properties, bulk (tapped density, moisture content), solution properties such as viscosity, and powder flow and compaction.

On a much broader scale, academic researchers are working to optimize a comprehensive database of excipient properties, in efforts headed by Professor Steven Hoag at the University of Maryland (Baltimore), who also spoke at IFPAC.

The effort, important enough to have received $35 million in funding from FDA last year, aims to clarify the connection between properties, such as crystal size and particle size distribution and critical final product quality attributes, such as dissolution, hardness and disintegration time. Vendors, including Malvern, Glatt, Insitec and Innopharma Labs, are involved in various aspects of this project.

The goal is to develop process flowsheets such as those used in the petrochemical industries, to account for different configurations.

Carl Wassgren, a professor from Purdue University (West Lafayette, Ind.), one of several who is working on data collection for this project, gave a progress report, discussing relevant factors for milled alpha lactose monohydrate as an example. They include apparent density, PSD, tapped bulk density, shear cell flowability, elastic modulus, tensile strength, and critical stress intensity factor, which indicates how difficult the particles are to fracture. Future work will consider other properties, he said, concluding his talk by stating the need for industry to form an independent organization to measure, compile and report on excipient properties. To visit the database, and comment, visit www.pharmahub.org/excipientexplore.

Analytics are being used in novel ways to study not only excipients but API's and the interactions between the two. At IFPAC, Justin Prichard from Vertex Pharmaceuticals (Cambridge, Mass.) discussed how his team was using particle characterization to better understand difference in granule quality.

Focusing on undergranulated API, the group compared engineering batches vs. in-house development lots and used G3D Raman imaging and Raman mapping, as well as NIR to study the chemical heterogeneity and API-excipient interaction within the granules.

As Prichard explained, it is relatively common to examine particle size distribution (PSD) by using pressure bed dispersion and light scattering. However, his team has been examining changes in PSD relative to changes in dispersion pressure to better describe the attributes of material being developed. "Changes in PSD can be as important as absolute distribution," he said. Other analytical tools the team is using include NIR screening, and Raman, mercury porosimetry on sieved samples. "We look at the same size cuts from different runs," he explained. Starting this work during preformulation helps guide development work, ensuring that there is sufficient process understanding of how granules affect process parameters, he said.

> Manufacturers may overlook critical supplier data in a search for "validation data."

Other efforts are focusing on vetting suppliers of excipients. As David Schoneker, regulatory affairs director at Colorcon (Harleysville, Penn.) and member of IPEC has explained, drug manufacturers may often overlook critical supplier data such as process capability analysis data, in a search for "validation data." In essence, this is the data required for validation, he said in a presentation at IPEC's 20th anniversary meeting last year.

IPEC has developed a "Total Excipient Control" platform designed to help manufacturers optimize ingredient quality throughout the supply chain, and last month, was scheduled to complete review and comments on ANSI NSF 363, a new ANSI standard for excipient GMP's.

Its affiliate, IPEA, has been certified by ANSI to conduct GMP conformance certification of excipient manufacturers, providing assurance that any ingredient supplier meets regulations without their having to perform site audits. Registering a manufacturing site costs $22,000 for a single site manufacturing a single excipients. Users can receive a Certification Audit Report. So far five pharmaceutical excipient suppliers, including Johann Halermann Ltd. (Houston), Dow Chemical Co. (Plaquemine, La. and Freeport, Tex.) and Grace Davison in Sorocaba, Brazil, have been certified as GMP compliant. In Europe, EXCIPACT, a similar global excipients certification program, was launched last month, to offer GMP and good distribution practices auditing. Participating as a third party auditor is SGS SA.

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Studying Outliers

TO ENSURE PRODUCT QUALITY

Out-of-trend results from APRs offer unique insights into ingredients and finished products

By Bir (Barry) Gujral and Peter Amanatides, Noven Pharmaceuticals

WHEN THE U.S. FDA rewrote its current good manufacturing practices (cGMP's) for drug products back in 1976, it added the requirement that manufacturers review the quality standards for each drug product every year, and that they write up results in an Annual Product Review (APR). After some manufacturers commented on the proposed regulation, objecting to FDA's initial report requirements, the Agency revised the proposal to allow each manufacturer to establish its own procedures for evaluating product quality standards. They were to base the final report on records required by cGMPs. The final requirement became law in 1979, as 21 CFR 211.180(e) [1].

Conducted for each commercial product, the APR provides the basis for deciding on steps needed to improve quality. The APR must include all batches of product, whether they were accepted or rejected and/or stability testing performed during the last 12-month period. The APR must cover a one-year period, but does not necessarily have to coincide with the calendar year. A report for the APR addresses the assessment of data, documents and electronic records reviewed.

The data generated from the batch or product are trended using appropriate statistical techniques such as time series plots, control charts and process capability studies. Control limits are established through trending, and specs for both starting materials and finished products are revisited. If any process is found to be out of control, or to have low capability indices, improvement plans and corrective and/or preventive actions must be taken.

Out-of-specification (OOS) regulatory issues have been well understood and documented in the literature [2]. However, out-of-trend (OOT) issues, for product stability, raw materials (RM) and finished products (FP) data identification and investigation are less well understood, but rapidly gaining regulatory interest.

An OOT result in stability, RM or FP is a result that may be within specifications but does not follow the expected trend, either in comparison with historical data of other stability, RM or FP batches respectively, or with respect to previous results collected during a stability study.

The result is not necessarily OOS but does not look like a typical data point. Identifying OOT results is a complicated issue and further research and discussion are helpful.

Table 1. Potency in mg/unit versus Lots Produced in 12 Months

Lot	Potency (mg/unit)	Mean	Mean + σ	Mean - σ	Mean + 2σ	Mean - 2σ	Mean + 3σ	Mean - 3σ
A 46062*	54.2	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 46065	54.6	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 46266	54.5	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 46269	55.5	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 46272	56.5	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 46120	54.8	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 46121	54.3	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 46678	55.2	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 47311	55.1	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 47313	56.3	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 47526	55.6	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 47527	55.4	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 47937	55.6	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 47941	55.3	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 47952	54.4	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 47952-2	54.8	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 47955	54.6	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 47955-2	54.1	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 47958	54.2	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 47958-2	54.5	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 49235	53.9	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 49203	54.2	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 49638	55.4	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 49724	55.8	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 50796	54.5	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 50797	54.7	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 50260	55.2	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 50261	55.4	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 50265	54.6	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 50297	54.6	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 50301	55.2	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 50304	54.4	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 50319	54.9	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 50322	54.3	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 52320	54.3	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 52702	55.3	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 52927	55.4	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 52931	53.7	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 52999	54.3	54.9	55.6	54.2	56.3	53.5	57.0	52.8
A 53999	56.9	54.9	55.6	54.2	56.3	53.5	57.0	52.8
Mean	54.9							
SD	0.7							
Mean + 3σ	57.0							
Mean - 3σ	52.8							

The lot numbers and ranges shown above in the table are not related to any product or company specific. The table has been built up to make use of all the statistical tools in the paper.

REGULATORY AND BUSINESS BASIS

A review of recent Establishment Inspection Reports (EIRs), FDA Form 483s, and FDA Warning Letters suggests that identifying OOT data is becoming a regulatory issue for marketed products. Several recent recipients of 483's were asked to develop procedures documenting how OOT data will be identified and investigated.

It is important to distinguish between OOS and OOT results criteria. The FDA issued draft OOS guidance [3] following a 1993 legal ruling from United States v. Barr Laboratories [4]. Much has since been written and presented on the topic of OOS results.

Though FDA's draft guidance indicates that much of the guidance presented for OOS can be used to examine OOT results, there is no clearly established legal or regulatory basis for requiring the consideration of data that is within specification but does not follow expected trends.

United States v. Barr Laboratories stated that the history of the product must be considered when evaluating the analytical result and deciding on the disposition of the batch. It seems obvious that trend analysis could predict the likelihood of future OOS results.

Avoiding potential issues with marketed product, as well as potential regulatory issues, is a sufficient basis to apply OOT analysis as a best practice in the industry [5]. The extrapolation of OOT should be limited and scientifically justified, just as the use of extrapolation of analytical data is limited in regulatory guidance (ICH, FDA). The identification of an OOT data point only notes that the observation is atypical.

This article discusses the possible statistical approaches and implementation challenges to the identification of OOT results. It is not a detailed proposal but is meant to start a dialogue on this topic, with the aim of achieving more clarity about how to address the identification of out-of-trend results.

This article will focus on studying the OOT trends in finished products and raw materials only. A different approach would be necessary to identify and control OOT in stability, and will be discussed in subsequent articles.

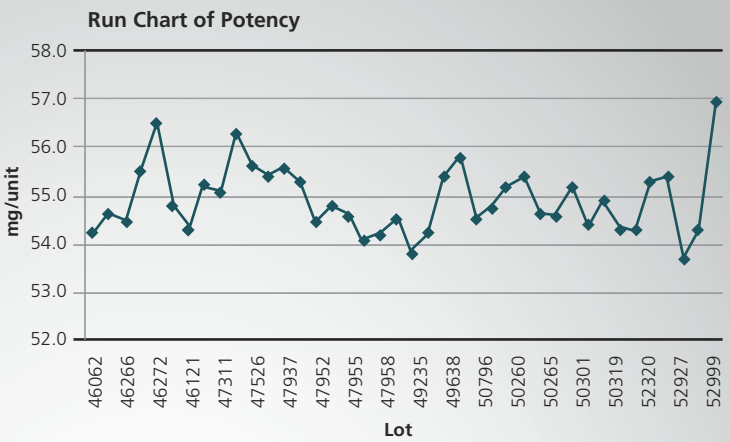

Figure 1: Run Chart of Potency versus Lots of Finished Products

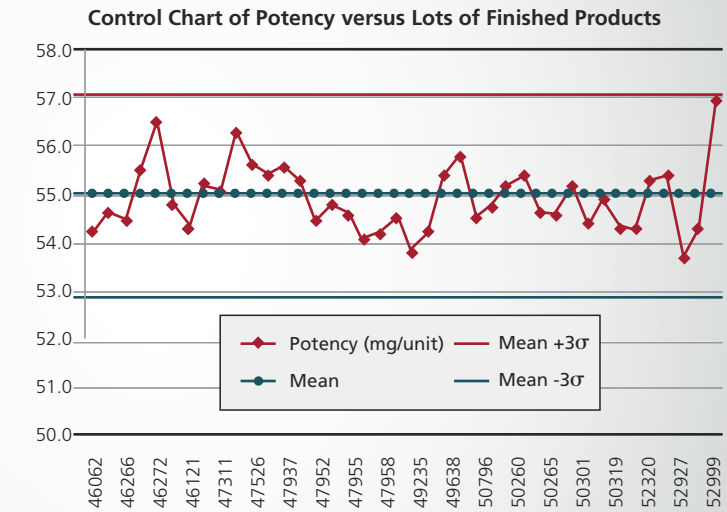

Figure 2: Control Chart of Potency versus Lots of Finished Products

DIFFERENCES BETWEEN OOS AND OOT

Out-of-specification (OOS) is the comparison of one result versus a predetermined specification criterion. OOS investigations focus on determining the truth about that one value while out-of-trend (OOT) is the comparison of many historical data values versus time and OOT investigations focus on understanding non-random changes.For example:

The specification limit of an impurity is not more than 0.10%:

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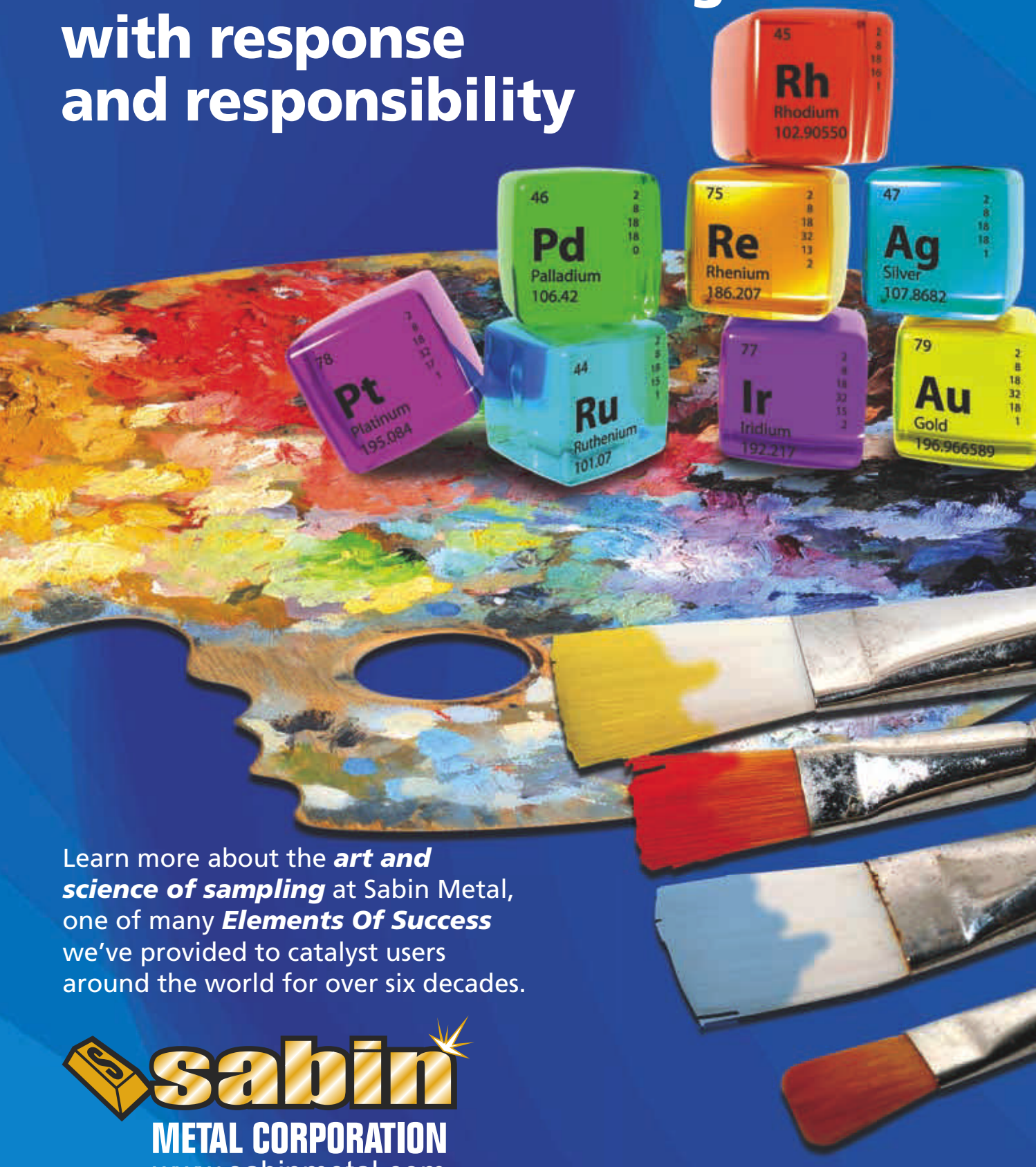

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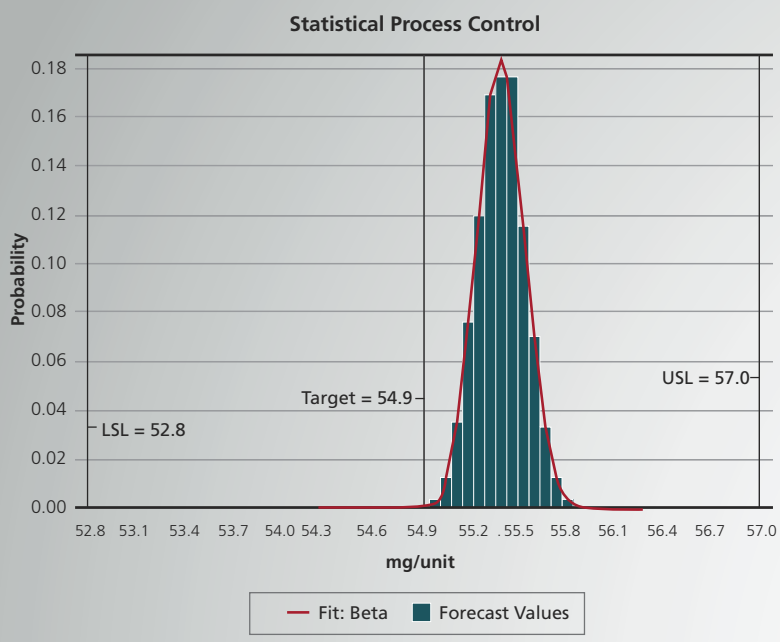


Figure 3: SPC Chart of Potency vs Lots of Finished Products

Normality test passed (p-value = 0.422)	
Metric	**Fit:Normal**
Mean	55.4
Standard Deviation	0.1
Cp	4.79
Cpk lower	5.89
Cpk upper	3.70
Cpk	3.70
Cpm	1.40
Z-LSL	17.66
Z-USL	11.10
Zst-total	11.10
Zlt	9.60
p (N/C) below	0.00
p (N/C) above	0.00
p (N/C) total	0.00
PPM below	0.00
PPM above	0.00
PPM total	0.00
LSL	52.8
USL	57.0
Target	54.9

Case 1: For a particular batch, the result obtained is 0.11%. This result is out of the specification limit and is called OOS. An investigation is required. Root cause analysis (RCA) is required for OOS investigation. Once a root cause is identified, corrective and preventive measures need to be taken.

Case 2: The result obtained is 0.08%. Although the result is well within the specifications, we should compare the result with the previous batches' trend. If we find the average value of the trend as 0.05%, then this batch result (0.08%) is called out-of-trend. Any result greater than 0.05% will be atypical results. A systematic root cause analysis is required. After identifying the root cause, we can decide the fate of the batch. OOT is dealt with on a case-by-case approach. A thorough understanding and control of the process is required.

We used the following tools to analyze data in this paper:
- Microsoft Excel
- Minitab
- Crystal Ball

In addition, we used the data set of 40 batches of potency shown as Table 1. The data is amended to satisfy the scope of this article.

STATISTICAL APPROACH BACKGROUND

There is a need for an efficient and practical statistical approach to identify OOT results to detect when a batch is not behaving as expected. To judge whether a particular result is OOT, one must first decide what is expected and in particular what data comparisons are appropriate.

Methodology, 3 sigma (3σ):

- Data of 40 batch results has been compiled for fixing the Trend range. A minimum of 25 batches data could be used
- Results of 40 batches are tabulated, mean, minimum and maximum values are established.
- Standard deviation is calculated for these 40 batch results. Excel spread sheet has been used for Standard deviation calculation.
- Standard deviation will be multiplied by 3 to get the 3 sigma (3 σ) value.
- Maximum limit is arrived at by adding the 3 σ value to the mean of 40 batch results.
- Minimum limit is arrived at by subtracting the 3 σ value from the mean of 40 batch results. Minimum value may come in negative also at times.
- The above maximum and minimum limits shall be

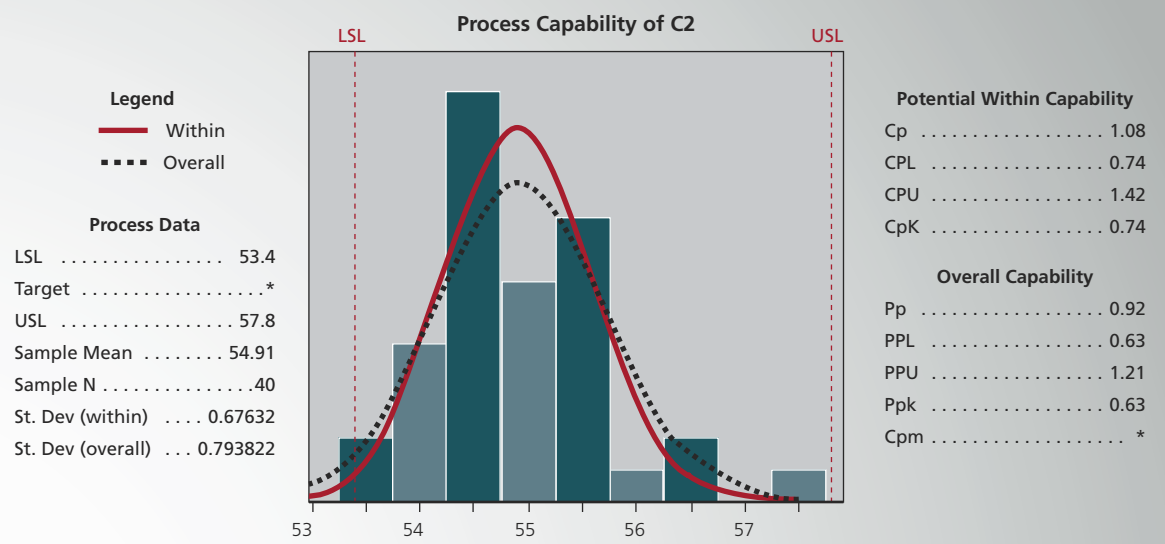


Figure 4: Process Capability Indices

taken as the Trend range for upper and lower limits.

- Any value that is out of this range will be considered as out-of-trend (OOT) value or outlier value.
- Wherever a specification has only "not more than," then only maximum limit for a trend can be considered. Minimum limit should be excluded.
- Wherever a specification has range, then both the Maximum and Minimum limits for trend should be considered.

RESULTS AND DISCUSSIONS

Once we arrived at our OOT limits by mean +- 3 σ values, we further authenticated these limits using:

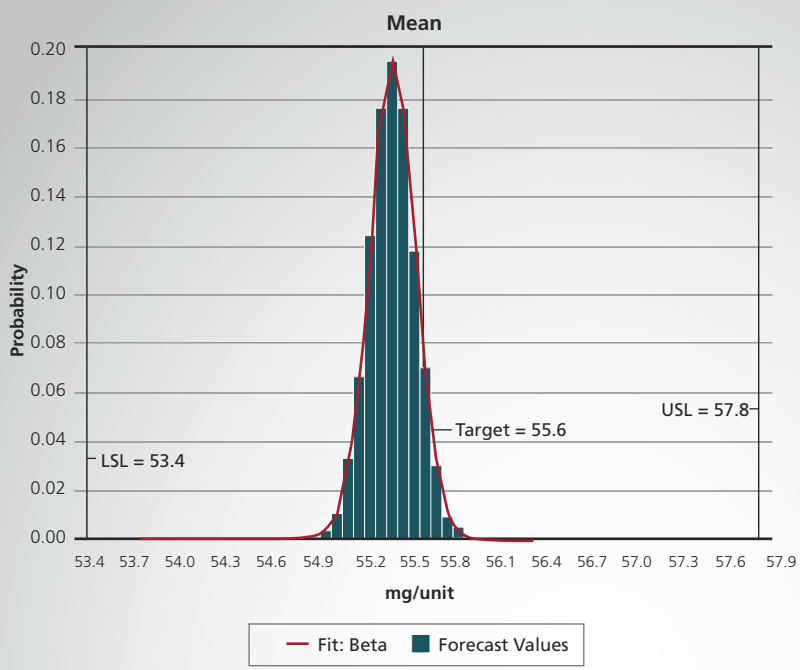
PROCESS CONTROL

To make sure if the process was under control when we established OOT limits, the following charting was done:

Run Chart: Run charts (often known as line graphs outside the quality management field) display process performance over time. Upward and downward trends, cycles, and large aberrations may be spotted and investigated further. In the run chart (Figure 1), potencies, shown on the y axis, are graphed against batches on the x axis. This run chart clearly indicates that Lot # 52999 with potency value of 56.9 is not an atypical result as it is inside of mean +3 σ value, but is borderline to the 57.0 limit.

Control Charts: The control chart is a graph used to study how a process changes over time. Data are plotted in time order. A control chart always has a central line for the average, an upper line for the upper control limit and a lower line for the lower control limit. These lines are determined from historical data. By comparing current data to these lines, we can draw conclusions about whether the process variation is consistent (in control) or is unpredictable (out of control, affected by special causes of variation). In the control chart of given data 40 lots (Figure 2), it is evident that lot #52999 is borderline to the control limit of Mean + 3 σ.

Statistical Process Control: SPC involves using statistical techniques to measure and analyze the variation in processes. Most often used for manufacturing processes, the intent of SPC is to monitor product quality and maintain processes to fixed targets. Statistical quality control refers to using statistical techniques for measuring and improving the quality of processes and includes SPC and other techniques, such as sampling plans, experimental design, variation reduction, process capability analysis, and process improvement plans.



Normality test passed (p-value = 0.852)	
Metric	**Fit: Normal**
Mean	55.4
Standard Deviation	0.1
Cp	5.04
Cpk lower	4.54
Cpk upper	5.54
Cpk	4.54
Cpm	2.79
Z-LSL	13.61
Z-USL	16.61
Zst-total	13.61
Zlt	12.11
p (N/C) below	0.00
p (N/C) above	0.00
p (N/C) total	0.00
PPM below	0.00
PPM above	0.00
PPM total	0.00
LSL	53.4
USL	57.8
Target	55.6

Figure 5: Monte Carlo Simulation Model for Potency Data on Mean

A primary tool used for SPC is the control chart, a graphical representation of certain descriptive statistics for specific quantitative measurements of the manufacturing process. These descriptive statistics are displayed in the control chart in comparison to their "in-control" sampling distributions. The comparison detects any unusual variation in the manufacturing process, which could indicate a problem with the process.

Several different descriptive statistics can be used in control charts and there are several different types of control charts that can test for different causes, such as how quickly major vs. minor shifts in process means are detected. Control charts are also used with product measurements to analyze process capability and for continuous process improvement efforts.

Figure 3 describes Statistical Process Control Chart of Potency versus Lots of Finished Products. We have taken the mean of 40 lots (54.9) as the target value and mean +3 sigma (57.0) as upper control limit and mean -3 sigma (52.8) as the lower control limit. Figurer 3 shows that all the data is shifted right to the mean.

This graph indicates that the process is under control but not centered to the mean as per given specifications. The product specifications given by R&D are always subject to update based upon the manufacturing data.

PROCESS CAPABILITY INDICES CP AND CPK

Cp is the capability index. It measures how well the data fits between the upper and lower specification limits. The higher the value, the better the fit. Cpk is the centering capability index. It measures how well the data is centered between the specification limits. The higher the value, the more centered the data.

Thus the Cp and Cpk indices are the primary capability indices. Cp shows whether the distribution can potentially fit inside the specification, while Cpk shows whether the overall average is centrally located. If the overall average is in the center of the specification, the Cp and Cpk values will be the same. If the Cp and Cpk values are different, the overall average is not centrally located. The larger the difference in the values, the more offset the overall average.

A process capability study is used to determine whether a process is stable and capable. Process capability indices are used to measure how well the data fits into the specification limits. Frequently used process capability indices include Cp and Cpk. Cp is used to evaluate the variation of the process, and Cpk is used to evaluate the centering of the process.

It is important for manufacturers to calculate and analyze the values of Cp and Cpk for their processes

9th ANNUAL

IMACS

INTERNATIONAL MEETING ON AUTOMATED COMPLIANCE SYSTEMS

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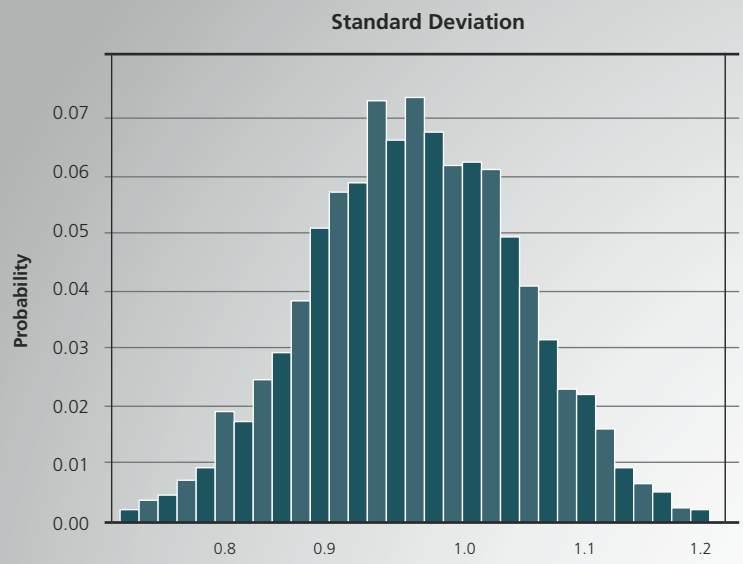

Statistic	Forecast Values	Precision
Trials	5000	
Mean	1.0	0.
Median	1.0	0.
Mode	-	
Standard Dev	0.1	0.
Variation	0.0	
Skewness	-0.0339	
Kurtosis	2.93	
Coefficient of Variation	0.0915	
Min	0.6	
Max	1.3	
Mean Standard Error	0.0	

Precision is calculated at 95.00%

Figure 6: Monte Carlo Simulation Model for Potency Data on Standard Deviation

and understand the interpretation of such data. It is recommended that the Cp / Cpk values be targeted at 1.33 or above [6]. Process capability studies assist manufacturers in determining if the specifications limits set are appropriate, and also to highlight processes that are not capable. Manufacturers would then be required to take necessary improvement plans / actions.

CALCULATIONS OF CP AND CPK FOR POTENCY OF GIVEN DATA

Lower Specification Limit= 53.4

Upper Specification Limit= 57.8

Mean= 54.9

Cp= Upper Specification Limit-Lower Specification limit/6*SD

Cp =(57.8-53.4)/6*0.7

Cp =(4.4/4.2)=1.048

Similarly

Cpk=0.714

Cpk can never exceed Cp, so Cp can be seen as the potential Cpk if the overall average is centrally set. In Figure 4, Cp is 1.048 and Cpk is 0.714. This shows that the distribution can potentially fit within the specification. However, the overall average is currently off center.

RATIO OF CP AND CPK

Cp/Cpk=1.048/0.714

Cp/Cpk=1.47 which is greater than 1.33 as required Process Capability by Minitab

Note that the results obtained by Minitab agree with Cp and Cpk results.

RISK ANALYSIS USING MONTE CARLO SIMULATIONS

Risk Analysis is applied to deal with uncertainty. The critical tool is Monte Carlo simulation, first used by scientists working on the atom bomb, and named for the Monaco resort noted for its casinos. Monte Carlo simulation is a computerized mathematical technique that allows pharmaceutical manufacturers to account for risk in the quantitative analysis of manufacturing and quality data and decision making. This technique has already been used by professionals in fields such as finance, project management, energy, engineering, research and development, insurance, oil & gas, transportation, and the environment.

Monte Carlo simulation performs risk analysis by building models of possible results by substituting a

range of values—a probability distribution—for any factor that has inherent uncertainty. It then calculates results over and over, each time using a different set of random values from the probability functions.

In order to analyze OOT data from the APR, a probability distribution function is assigned to the unknown variables, and then Monte Carlo simulations are run to determine the combined effect of multiple variables. The seed value of the individual variables is calculated by the probability density definition of each variable.

A standard sensitivity study shows us the sensitivity of the resulting improvements from the range of outputs from a single variable.

Monte Carlo simulations furnish the decision-maker with a range of possible outcomes and the probabilities that they will occur for any choice of action. Monte Carlo simulations can be run for extremes (either the 'go for broke' or ultraconservative approaches) or for middle-of-the-road decisions to show possible consequences.

Depending upon the number of uncertainties and the ranges specified for them, a Monte Carlo simulation could involve thousands or tens of thousands of recalculations before it is complete. Monte Carlo simulation produces distributions of possible outcome values. By using probability distributions, variables can have different probabilities of different outcomes occurring. Probability distributions are a much more realistic way of describing uncertainty in variables of a risk analysis.

DETERMINATION OF CP AND CPK VALUES FROM SIMULATIONS

Simulated Cp= 5.04

Simulated Cpk=4.54

Simulated Cp/Cpk=5.04/4.54

Simulated Cp/Cpk=1.11

In Figure 5, the ratio of Cp and Cpk of simulations has gone down from 1.47 to 1.11. This gives us an opportunity to look at Sensitivity Analysis to find out the drivers of Risk Analysis. This is an alert to improve our future APR reports. There is also a shift of all our batches to the left to the target values in the simulated model. This is a contrast to the model that we have on Statistical Process Control. The Statistical Process Control model was based upon controls while the simulated model is based upon our specifications. That means that the variability of shifting the model is coming up not only from specifications but from individual lots.

Figure 6 and Figure 7 are Monte Carlo Simulations for Potency Data on Standard Deviation and Sensitivity Analysis respectively. Figure 7 clearly indicates that the drivers of Risk are three lots with lot #s A53999, A47313

> Monte Carlo simulations can be run for extremes (either for "go for broke" or conservative approaches) or for middle-of-of-the-road decisions.

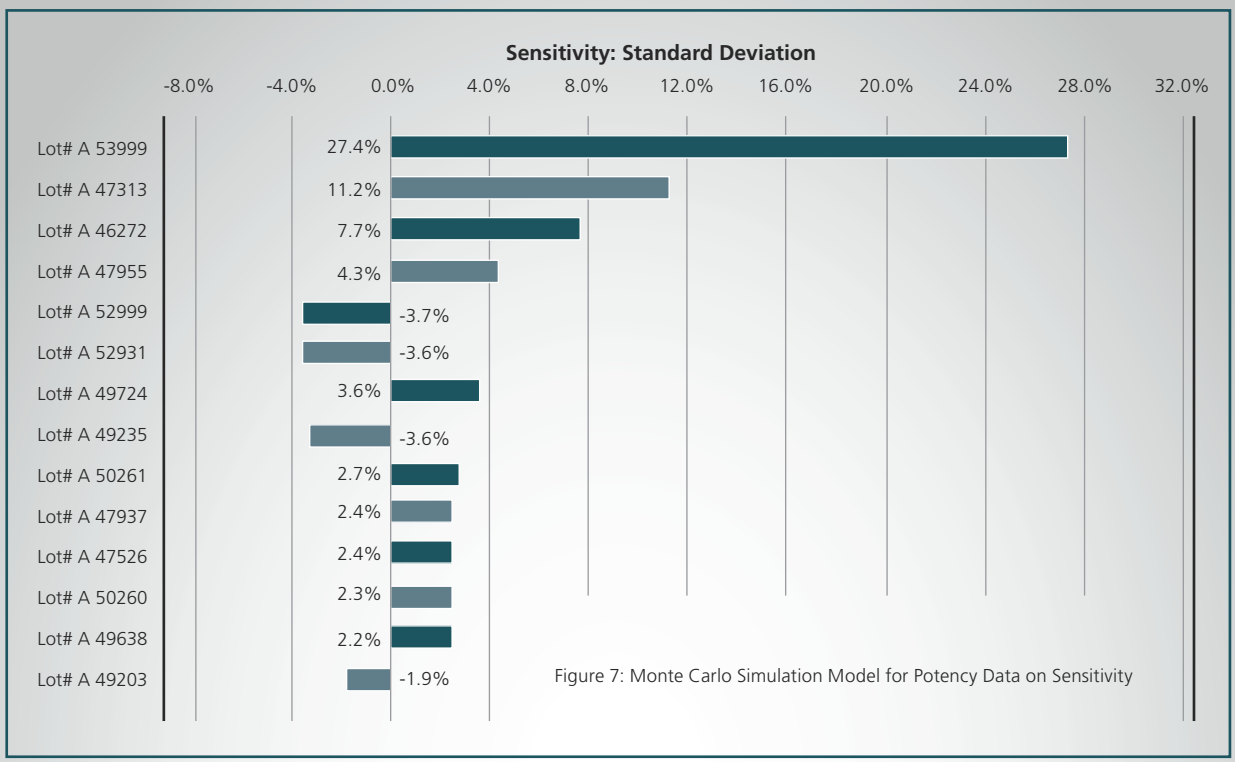

Figure 7: Monte Carlo Simulation Model for Potency Data on Sensitivity

and A46272. These lots contribute 27.4%, 11.2% and 7.7% to the variance. The raw materials and production parameters used in these lots should be further investigated to use as a mirror for future years APRs.

LIMITATIONS

One advantage of the Monte Carlo Simulation approach is that, as long as the assumptions are met, the rate of false positives can be set when one calculates the limits. However, a disadvantage is that, when applied to products with limited data, the appropriate limits may be difficult to determine. This can lead to wrongly centered, too narrow, or too wide OOT limits.

So far, we have studied trending for Annual Product Reviews using the data of one calendar year. We are in a process of extending the scope of this project for evaluating trending from year to year, which we expect to give us improved process understanding. Our ultimate goal is scoping out the Knowledge Space, and using APR's to build the Design Space and Control Strategy fundamental to Quality by Design.

References

1. *FDA, "Human and Veterinary Drugs, Good Manufacturing Practices and Proposed Exemptions for Certain OTC Products," Fed. Regist. 43 (190), 45013–45089 (Sept. 29, 1978).*
2. *Hoinowski, A.M., et al., "Investigation of Out-of-Specification Results," Pharm. Technol. 26 (1), 40–50 (2002).*
3. *FDA Guidance Document, Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production (draft).*
4. *US v. Barr Laboratories, 812 F. Supp. 458 (District Court of New Jersey 1993)*
5. *Hahn, G., and Meeker, W. Statistical Intervals: A Guide for Practitioners (John Wiley & Sons, New York, 1991).*
6. *Investigating OOS test results for pharmaceutical production, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), October 2006, Pharmaceutical CGMPs*

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Make the Most of Annual Product Quality Reviews

Now advanced by global regulators, the APR offers an opportunity to better understand and improve processes

By Ajay Pazhayattil,
Director, Quality and Regulatory Affairs,
Jarvis Street Pharma, Inc.

FDA'S CURRENT good manufacturing practices (cGMPs) require that the quality standards of a drug product be evaluated each year to determine whether there is a need to adjust drug product specifications, manufacturing and control procedures. Subpart J of 21 CFR 211.180 mandates establishing a written procedure for the annual product review process, and recommends the review of a representative number of batches, both approved as well as rejected. These guidelines stress the importance of analyzing the results of investigations, any deviations found and product complaints received. The APR report must explore, in depth, the reasons for any product recalls and returns.

No doubt, FDA's goal with the APR is to get manufacturers to look at their processes thoroughly and systematically, and to focus on areas where they might be improved. Other regulators are also on board with APR's.

Canadian GMP's were updated in 2009 to include an explicit section for Annual Product Quality Review (C.02.011). Health Canada's regulations require manufacturers to analyze previous reviews, examine finished product testing results and critical in-process controls, and review: failed batches, deviations, CAPA effectiveness, changes, stability studies, returns, complaints, recalls, critical equipment qualifications, and quality agreements. CAPA's from annual product reviews need to be communicated to senior management and completed in a timely and effective manner, with effectiveness verified via self-inspections.

In the EU, Product Quality Review, as well as the PIC/S GMP guide, requires a review of:

- starting materials including packaging materials used
- marketing authorization variations
- post-marketing commitments.

They also make the qualified person at the facility responsible for the review's accuracy and timely completion. Although these requirements are "harmonized" and, for the most part, somewhat similar, there are a few unique exceptions, as shown in Table 1.

STRUCTURE OF AN APR REPORT

The structure of a review report may vary, based on the products involved and manufacturer's documentation requirements. However, companies should follow a standard

DIFFERENCES IN GLOBAL APR REQUIREMENTS

US FDA	Health Canada	EU
Management review/notification Review of returned or salvaged drug products Review of regulatory GMP observations	Nonprescription Category IV drugs not exempted	Review of starting materials including packaging materials Review of Marketing Authorization variations Assessment of whether revalidation should be undertaken

Table 1.

FIGURE 1. APR GENERAL CONTENTS

1. Scope
2. Manufactured Batches, Batch Record, Yield Review
3. Change Control Review
4. Label and Artwork Change Review
5. Analytical Data Review
6. Stability Data Review
7. Validation and Qualification Review
8. Non-Conformances and LI Review
9. Rejected Batches Review
10. Re-Packaged Batches Review
11. Compliant Review
12. Field Alert and Recall Review
13. Retain Sample Review
14. GMP Agreement
15. Review of Previous APR
16. Conclusions and Recommendations
17. References
18. Approval

FIGURE 2. COMMON TABLES AND CHARTS

Typical items to be included in an annual product review:

- Summary of Lot Enumeration for Bulk Batches
- Summary of Lot Enumeration for Finished Product
- Summary of Batch Yield
- Summary of Analytical Results
- Summary of In-Process Results-Encapsulation
- Reserve Sample Annual Inspection
- Summary of Changes
- Description of Deviations and Non-Conformances
- Batches introduced to the Stability Program During Review Period
- On-going Stability Batches introduced Prior to Review Period

template to ensure that they aren't leaving out any requirements.

An APR is also an evolving document. It can range from a document containing a few sections with minimal requirements to an elaborate document with addenda. Each numbered sub-section (batch document review, for example) is typically followed by a summary. A

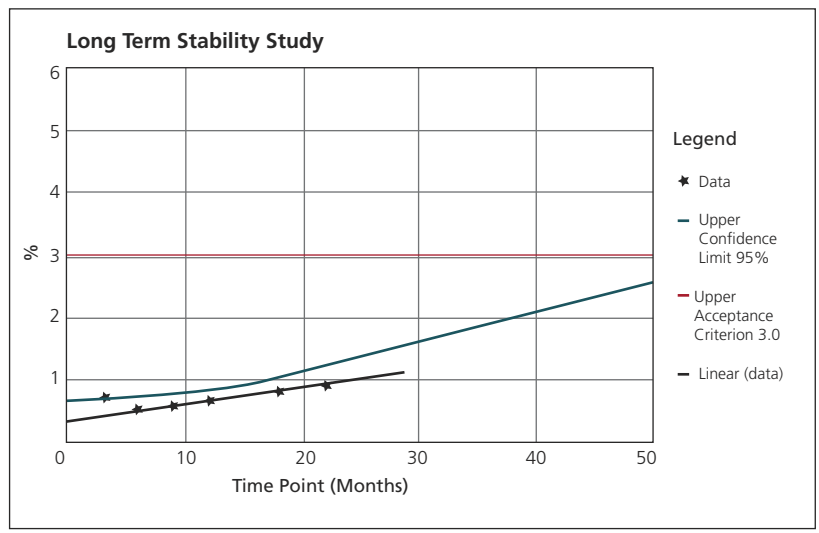

Figure 3. Long-term Stability Study

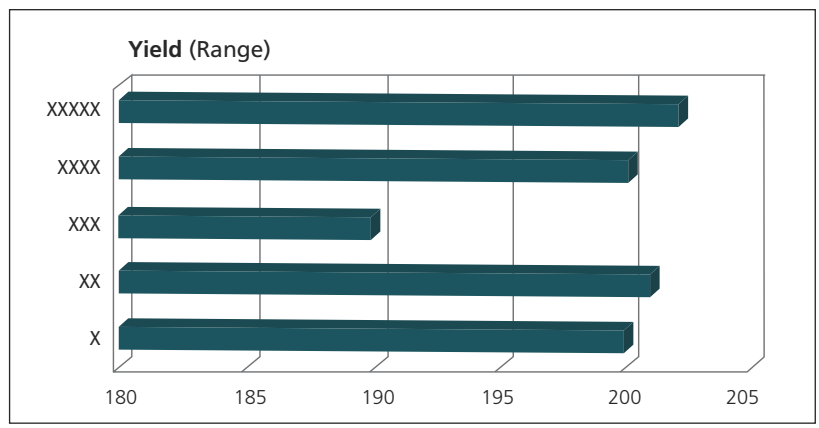

Figure 4. Batch-to-Batch Variation (Yield, Critical Parameters)

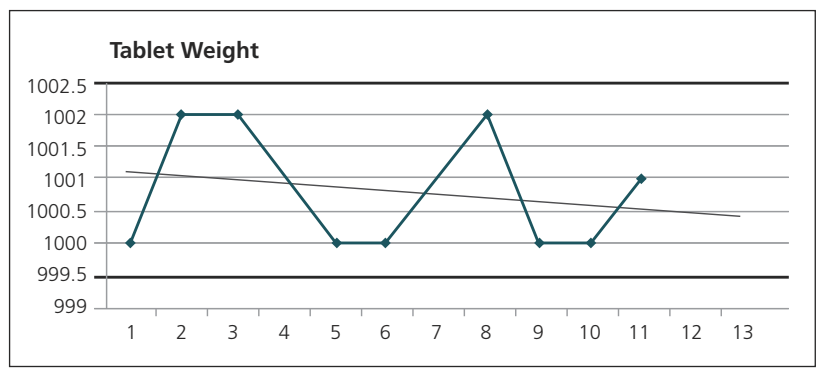

Figure 5. Inter Batch Variations (Critical Parameter/s)

graphical or tabular representation will help to dissect data and detect adverse trends. Figure 1 shows a sample list of contents; Figure 2 shows a typical list of tables.

The scope of the review needs to explain the purpose and the product SKU's covered. Information from the batch processing and packaging records can follow. This includes review of in-process, statistical process control (SPC) charts, yields, and analytical results, as applicable.

CHANGES AND CORRECTIONS

Change review can be broken down to changes in:

- raw materials
- packaging components
- master documents
- specifications.

The non-conformances/deviations section must review non-conformances, but also any corrective actions taken and their effectiveness. Ineffective or overdue CAPAs must be discussed in the summary. The crux of the APR document is the Conclusions and Corrective Actions/Recommendations section. This section should include summaries of each of the prior sections, and appropriate corrective/preventive measures necessary for each observation made. Any trend observed must be addressed. Figures 3, 4, and 5 are representative charts.

STREAMLINING DATA SOURCES AND APR ADMINISTRATION

Streamlining the entire process requires an APR schedule, based upon key regulatory submission dates. (For contract manufactured products, it's critical to prioritize and negotiate feasible reporting dates.)

Compiling APR raw data is a team effort, but the Compliance/QA department should take the lead and be ultimately responsible. An APR committee would typically include a representative from QA, QC, Validation, Operations, Stability, Engineering, and Materials Management. A draft report is completed upon critical analysis of the raw data, then discussed in APR committee meetings to determine effective CAPA's.

Another challenge for the APR administrator is data retrieval for review purposes. Firms with qualified data acquisition systems can use their database, whereas paper-based manufacturers may have to review individual batch documents for processing parameters, in-process testing, finished testing, yields, and so on.

Data must be provided to the APR administrator in a timely manner, and if they have been gathered manually, they will need to be verified by a second person. If spreadsheets are used, they must be qualified in advance.

Performing an APR is a requirement for the regulated market. But more than this, the review helps the manufacturer to understand processes better and to gather additional information for further improvements. It greatly helps in determining whether a product still meets the needs of patients, or whether it needs a change in formulation, packaging, specification or process.

FDA's Process Validation guidelines call for continued process verification. Thus, an APR program can serve as an ongoing system to collect and analyze product and process data that relate to product quality. The APR must be an integral part of the risk management/mitigation plan developed, per ICH Q9 recommendations.

The APR's conclusion section is really a stepping stone toward the future of the product, so it should be backed up by adequate, and accurate, data. This data should be distributed to all relevant and interesting stakeholders.

The information gathered and trends spotted can aid new product development as well, and so it is essential to distribute the report to all relevant and interested parties. The effort can also be reviewed and shared with Lean process improvement teams, while the CAPA's developed out of an APR are critical in avoiding potential risks to a product in the future.

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Valves and Fluid Control: Drifting Toward Simplicity, Flexibility

Prospects are good for a robust process equipment market in 2012; here's a look at new valves and flow control technologies.

By Paul Thomas, Senior Editor

AS PHARMA and biopharma ride the preventive and predictive maintenance wave, understanding and controlling specific pieces of equipment becomes critical. "The industry continues to expand its requirements for valve control, diagnostics and automation, says Rick Zinkowski, BioPharm Segment Manager for Bürkert Fluid Control Systems. "Be it de-centralized or centralized automation, clients are looking for cost effective multi-component solutions."

Bürkert and other process valve and instrument manufacturers are taking into account the impact of trends such as single-use applications and module-based system solutions, he says. It's all about flexibility, modularity, and multiple solutions, he says. "It's not just a single component any longer." Bürkert, for instance, is combining process valves with pneumatics, sensing devices and controllers to provide both centralized and decentralized solutions.

Are manufacturers getting more, and more precise, information about their valve operations today than even a couple years ago? Definitely, Zinkowski says. "End users have access to switch packages, positioners and other devices with are compatible with communication protocols, such as DeviceNET which can provide diagnostics regarding the specific performance of a valve assembly beyond physical position—such as recording cycle frequency enhancing PM programs while greatly minimizing and/or preventing unexpected failures."

From a business perspective, Zinkowski is "cautiously optimistic" about 2012. "Projects are moving from BOD to hard design," he says. "We are seeing the increased refurbishing and remediation of existing facilities, as well as green field projects. The FDA approved 20 new drugs through the first half of 2011, compared to the 21 such approvals in all of 2010 . . . which means end users are going to need to find additional capacity to produce these products."

If that's true, end users will be taking a hard look at the following new hardware for their shops. Here's a roundup of the latest valve and flow control technologies on the market:

The new **Bürkert** Type 8681 control head has been optimized for the automation of pneumatic hygienic process valves, Zinkowski says. It can be combined with all commercially available valve types that use a rising stem upper actuator configuration. The Type 8681 performs all pneumatic actuation, feedback and diagnostic functions, as well as bus communication, he says. Depending on the process valve, as many as three pneumatically actuated seat movements can be controlled independently.

Steriflow's SVC/SHC Series check valves are designed for vertical and horizontal installation in biopharma and parenteral drug manufacturing applications. The valves are the first in their class to be used for back-flow prevention in bio and parenterals, the company claims. The valves follow ASME BPE guidelines since no springs, wet guided stems, hinges or other mechanical return mechanisms are used. Typical applications would include back-flow prevention in WFI and USP purified water at pump out, or point-of-use downflows; sparge, blanket and purge gas; clean condensate and hygienic drain applications.

Spirax Sarco has introduced the CVS10 Sanitary Check Valve, designed to prevent reverse flow conditions and reduce the risk of cross contamination—via a high-surface finish, material certification, and concern for drainability. Sizes range from ½" to 2" with sanitary-clamp connections, while an optional soft seat version is available for high purity water and liquid applications such as WFI systems.

Asahi/America has expanded its Dymatrix manifold valve (MPV) portfolio to include those in USP Class VI PVDF, PP and Halar, as well as high-purity PTFE. The expanded material offering is aimed at making the valves easier for use in pharmaceutical production facilities—with smaller install footprints, fewer connections, and cost savings over traditional, bulkier actuated valves, the company says. The Dymatrix valves—designed and machined in Boston—can be IR welded into existing systems or installed using tri-clamp fittings.

The **Gemu** 1236 valve monitor is now available with IO-LINK enabled communication in a simplified system architecture. IO-LINK is an open standard that was developed by a consortium which includes most of those partners responsible for introduction of the AS-I, actuator-sensor-interface.. With a simple USB service tool, Gemu says, IO-LINK device parameter settings can be adjusted locally at the valve or remotely. Says Gemu, this "provides consistency and reliability that has all but eliminated false alarm feedback."

The **Festo** MPA-L valve manifold is also new. It is scalable down to a single valve slice, says Frank Langro, manager for marketing and product management, so directional valves can be adapted to any application. The sub-base is made from polymers which are lightweight and resistant to corrosion. The manifold is suited for most pneumatic applications for discrete and process automation, Langro says. It features up to 32 valve locations, and accommodates accessories such as pressure regulators D-sub, IDC / Ribbon cable connectors, bus networks, and Ethernet connections.

SPX Flow Technology's new APV MS4/MSP4 valve series contains rising-stem single seat valves with shut-off, divert, and tank outlet body configurations for aseptic processing. The single layer TFM diaphragm with a fan support mechanism is geared towards high-pressure operation, long diaphragm life (150,000 cycles on average, SPX says), and immediate leakage indication. The MSP4 specifically offers the valve stem, seat, and diaphragm made entirely of TFM for applications where elastomers are not accepted.

GEA Diessel has just released a new generation of stainless steel electromagnetic flow meters it calls IZMAG, specifically designed for pharma and biopharma applications. As with other electromagnetic meters, it has no moving parts, can be used at high temps or under vacuum conditions. In addition, GEA says, it is: bluetooth compatible; has 360° positioning; has automatic calibration and alarming; and has no snags or corners and is thus suitable for aseptic processing.

Finally, just introduced are **Swagelok** RHPS PRSTC spring-loaded, pressure reducing regulators, for control of gas and liquid pressures in sanitary systems. Inlet pressures as high as 230 psig can be controlled to outlet pressures ranging from 4.3 to 130 psig, Swagelok says, with a wide range of operating temperatures. Three body sizes are available: 1/2", 1", and 1-1/2", all with integral sanitary clamp end connections.

Coming to America: European Companies Buy In (and Lease)

"OUS" companies are enjoying the U.S. market, and creating a few jobs along the way.

BY PAUL THOMAS, SENIOR EDITOR

CHALLENGER, GRAY & Christmas has estimated that the drug industry cut some 300,000 jobs between 2000 and 2010, with a good chunk of those coming from the U.S. While positions have been created as well, it's safe to say that the U.S. has experienced a significant net loss in drug manufacturing jobs in the past decade.

One could get the impression that pharmaceutical business is fleeing the U.S. to distant shores, setting up shop in China, India, Brazil—anywhere but here. Indeed, those countries are the most rapidly growing markets in the world, and U.S. drug companies are looking to exploit—perhaps in every sense of the word—opportunities abroad and have shifted jobs overseas.

But there is hope that the decade of doom and gloom is behind us. Challenger believes the layoffs are dissipating, and U.S. Bureau of Labor Statistics figures seem to agree.

Let's pause to remember, then, that truly global drug companies want to be here—need to be here. I was reminded of this fact at a recent breakfast gathering sponsored by iBIO, the Illinois arm of the Biotechnology Industry Association. The event, "European Pharma in Chicago," featured speakers from APP Pharmaceuticals (part of Fresenius Kabi), Lundbeck, and Vetter.

The U.S. is a $335 billion market, with Europe a distant second and significantly larger than the $50 billion Chinese industry, noted Michael Rosen, representing the Illinois Science + Technology Park in Skokie, which hosted the meeting. "You cannot be a global player without being in the U.S. market," Rosen said.

The three speakers that followed acknowledged as much. APP's VP of Innovation and Development, David Bowman, talked about how his company was snatched up by Fresenius so that the German parent company could establish a foothold in U.S. pharma. Fresenius is now one of the leading sterile injectable manufacturers in the U.S. "Understanding the markets was the most critical part" for Fresenius, Bowman said. "You can't use one platform or strategy for the whole world. It doesn't work."

"You can't really have a global presence without a presence in the U.S.," added Anders Buur, VP of U.S. Drug Development for Lundbeck. Like Fresenius, Denmark's Lundbeck is tapping the U.S. drug market via acquisition, starting with its purchase of Ovation Pharmaceuticals in 2009. This gave Lundbeck the infrastructure it needed to better sell the likes of Celexa and Lexapro here; in 2010, 26% of the company's revenue was North American. "We acquired a company because the expert knowledge of the U.S. market and development was there already," Buur said. "That was a huge difference, and it would have been dangerous for us not to acquire."

Vetter Pharma took a different route to the U.S. As a CDMO, Vetter typically engages with clients during phase III of development. "There are some 2,000 compounds we are interested in," said John Moore, its key account manager. "Of those, about half are in the U.S."

"YOU CAN'T USE ONE PLATFORM OR STRATEGY FOR THE WHOLE WORLD. IT DOESN'T WORK."

How to get closer to current and potential U.S. clients? Vetter considered acquisition, but decided it was too risky: corporate integration can be tricky, Moore noted, and "failure has consequences." A second option was to build a green field facility—too much upfront capital and too many years until start-up, he said.

The German company opted for a third alternative—leasing. In just two years, the 24,000-square-foot Vetter Development Service site is now qualified and operating in the Illinois Science + Technology Park. Leasing involved significantly less time and risk, said Moore.

Will all this activity result in more manufacturing jobs in the U.S.? It should. For APP, Bowman noted, the acquisition by Fresenius has meant that all sites, including those in Illinois, New York, and North Carolina, are viewed as key "global" manufacturing facilities and more critical to long-term strategy.

Lundbeck's expanded presence in North America means more business for CMO's here, Buur noted.

Vetter now has 40 employees in Skokie, Moore said, half "expats" and half locals. Is there potential for commercial manufacture in the U.S.? There are no plans at present, Moore said, "but we would be well-positioned to do that if we wanted to."

The U.S. is not just an attractive pharmaceutical market but also a good place to manufacture. Pass it on.

To Wire... or Not to Wire

Why hasn't wireless monitoring completely replaced the traditional wired sensor?

By Jon Aldous, Product Manager, Vaisala

THERE ARE many reasons why wireless sensor communications seem to be the complete panacea for a wide area monitoring system—the impracticality of running hundreds of feet of cable throughout a warehouse, equipment continually being moved, or the physicalities of a cleanroom not allowing cable penetrations. So why hasn't wireless monitoring completely replaced the traditional wired sensor? In truth, there are times that wired systems are better—but for most scenarios, a hybrid system of wired and wireless is the ideal solution.

Warehouse temperature and humidity monitoring presents the ideal scenario for wireless sensors, but there are some common problems seen in these environments. The dynamics of a typical warehouse present ever-changing barriers for wireless signals—validation studies are typically performed on empty, half-full and full environments. This gives a confidence that the thermal and humidity levels throughout the day or seasons can be constantly met. But throw in mechanical forklifts, boxes full of foil-based packaging and fluid materials, and wireless signals can be easily blocked or severely degraded. On top of this, most wireless sensors operate either in the 915 MHz or 2.4 GHz license-free regions, as do WiFi access points, kitchen microwave ovens, mobile handsets and a myriad of other consumer devices.

Typical monitoring systems don't have to be in continual contact with the main system recording the data. Most important, though, is that any data collected during an offline period is captured, stored and transmitted during that connection period. If data rate isn't as important as redundancy, then a number of wireless connectivity scenarios are available.

Typical wireless statistics are based on line of sight, anywhere between 100 to 5,000 feet—outdoors! The line of sight within a closed environment is severely compromised. A sensor placed back-to-back, on the opposite side of a cinder block wall from the access point, has its signal soaked up like a sponge. Place that same sensor 20 feet further away along the lateral of that wall, and the signal has to pass through 20 feet of cinder sponge. The placement of access points and repeaters is essential to ensure complete wireless connectivity.

Wireless systems that use a mesh topology, in which the monitoring device is acting as both a measurement device and repeater, provide a fuller signal path for connectivity—but the tradeoff is the firmware complexity and the amount of power each repeater uses. To relay signal, the sensor must be on more often than if operating in normal point-to-point mode. Point-to-point mode works just like normal WiFi, a laptop-to-access point—low complexity, but the wireless signal can be easily blocked.

BATTERY SOURCE

Does your wireless sensor use the same battery source to measure and store the data, and send the data to the access point? Depending on the criticality of your measured data, relying on the same battery source to store and send is a business decision. Most wireless sensors will report back a timeline of battery exhaustion; this can be anywhere between four and 36 months depending on the network topology being used, data rates, packet resends, and connection times. Having a separate battery for data collection will ensure that the data will be continually measured and stored for up to ten years—even during transmitter battery change!

To return to the original question, why hasn't wireless senor monitors replaced wired? If the monitoring system requires continual connectivity for fast data update rates, and the data is being used for controlling of HVAC and production—then wireless may not be the correct system. If the sensors are in locations that are hazardous, dynamic or difficult to reach for continual maintenance, then a wired system may be the better option, and if the sensor requires power to operate, then you should consider running wire.

A functional monitoring system should be capable of being a hybrid of wired and wireless options—a mixture of low-maintenance battery-powered wireless and of fully wired sensors. With the correct mix of infrastructure—using either WiFi or proprietary mesh networking topologies, and wired sensors—users can get the best of both worlds, and a near maintenance-free system.

Control, Innovation and the Consumer

Isn't it time for pharma to engage, rather than exclude, its key stakeholders?

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

OVER THE years, pharma's key objective has changed very little: getting active pharmaceutical ingredient to the patient. Although we no longer dose extracts of willow tree bark, the practice of blending API with excipients to add bulk or facilitate flow dates back to the Romans. The Remington tablet press or gelatin capsules of 1875 remain virtually unchanged today.

Regulations haven't changed that much either, in the fifty years since most of them were drafted.

One thing that needs to change, and which could spur more innovation and positive change in the future, is the way that drug manufacturers and regulators communicate with the end users of pharmaceuticals. Both profess to care about the consumer, yet patients can find it very difficult to participate in any real discussion or dialogue with them.

Consider labelling and package inserts, which have not been optimized for the average consumer. Or look at how some companies have communicated product recalls.

For instance, when Novartis voluntarily recalled batches of some over-the-counter products in January, some news reports explicitly mentioned the most serious reason for the recall: the fact that opioid drugs might have been mixed up with the OTC analgesic and put in packages by mistake.

It would have been too much, perhaps, to expect the manufacturer to state, outright, that for a period of time the controls at its facility completely failed.

But consider the company's bland statement, which left out the critical safety information and also appeared to justify the recall as a "precautionary measure":

"Mixing different products in the same bottle could result in taking an incorrect product or receiving a higher or lower strength than intended or receiving an unintended ingredient, which could potentially result in overdose or an allergic reaction."

The statement is truthful, accurate and designed to prevent people from panicking. But is it informative or valuable? Why is it that we can justify and accept direct to customer advertising, including litanies of potential side effects, yet fail to inform consumers effectively, via mass media outlets, when we make a mistake?

I am active in this industry, have registered and receive recall notices from the FDA and other e-news media—and yet have not seen many recall notices for more recent events. So what are the chances of an average person seeing them? Recalled product may still be sitting on a number of medicine cabinet shelves today. Isn't communication and patient outreach just another aspect of an archaic system in desperate need of innovation and modernization?

I can envision a day when some indication of a manufacturer's capacity to control its processes is placed, in graphical form, along with other key information, right on the product label so that consumers can judge for themselves which manufacturers to trust. You may say that the public isn't ready for this information, but people have adjusted well to nutritional information labels.

STEVE JOBS AND APPLE REVOLUTIONIZED AN INDUSTRY BY DEFINING CUSTOMERS' NEEDS. **WHY CAN'T PHARMA?**

I've often asked whether innovation and modernization are related to, or even possible, in our industry. Is "design space" really a new fashion, or little more than the old process validation range?

Perhaps pharma's approach to innovation has not progressed because the industry has failed to address the most important factor, the people, underlying its business. Over time, this has prevented technology from improving and evolving.

For a glimpse of what is possible, look at other industries. Steve Jobs revolutionized telecom by reinventing the phone. The leap was not in technology, but Apple's way of looking at customers' needs. Indeed, Apple has proven most capable of defining customers' needs through innovative thinking, and considering both problems and technology in a different light. Pharma, in contrast, still clings to traditional thinking, impeding its adoption of such concepts as continuous manufacturing.

If we can modernize our thought processes, embrace diversity and reach out to the customers who buy the products we make, we may soon have a very different, and innovative, industry. What do you think? Please write me at aafnan@stepchangepharma.com.

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On Simplicity, Single-Use and Shire

CRB's Eric Unrau talks about what worked at Shire Lexington, and what limitations need to be overcome for single-use systems.

By Paul Thomas, Senior Editor

DRUG MANUFACTURING facilities of the future will need to be a lot smarter and simpler than those today. They will be "smaller, more nimble, more flexible, more responsive to evolving processes and changing purposes," says Eric Unrau, Director of International Operations for CRB Consulting Engineers. "This makes for overall reduced project investment, and faster project schedules for new facilities. The operational costs are lower, with a reduced environmental impact versus a more traditional process and facility. When done correctly, it is lower risk from a product quality and patient perspective and also a regulatory perspective."

Single-use equipment and systems will be a major facilitator of such facilities, Unrau acknowledges. But they won't be the be-all and end-all. They need to be put into context. We speak with Unrau about the importance of closed processes, about his company's work with single-use-focused projects (including Shire's recent award-winning facility in Lexington, Massachusetts), and ask him to clarify what factors might limit the adoption of single-use. (For the complete interview, see PharmaManufacturing.com.)

PhM: You're an advocate of fully closed processes. Why exactly? What are some benefits of fully closed processing that many people might not realize?

E.U.: Simply put, closed processing protects the product from the room environment. If that is true, then this allows the facility requirements to be dramatically reduced in terms of product protection—in other words, the facility is a non-impact system (as defined in ISPE's Baseline Guide). As the facility is no longer protecting the product, it can be simplified—better, faster, cheaper—and not just one of these, but all three. Process closure is safer and cheaper. Benefits can be numerous and depend specifically on the technology, product and project requirements. However, in general they can be: reduced risk of product contamination, reduced project cost and schedule, improved operations, and reduced operational costs. There are many others, but that is a start.

PhM: Shire's Lexington facility has received attention and accolades for, among other things, housing the first commercial 2,000-liter bioreactor. In your mind, what is truly groundbreaking about the Lexington facility that will be imitated in years to come?

E.U.: This was a great project. Shire pushed the envelope by implementing single-use systems in evolutionary, pioneering ways. In addition to setting the vision of a groundbreaking facility, Shire also had a number of other goals in the project, leveraging complementary areas of scope on the project such as design and construction of the facility vs. design and fabrication of the equipment is one area. Early occupancy of the building was achieved through close collaboration of design, vendor, quality and construction teams. This allowed for early procurement of single-use systems, early commissioning of those systems at the vendor's site, and even improved operator training prior to equipment coming to the site. There are other areas specific to the project which were highly beneficial to Shire in areas that are client confidential.

PhM: That Shire project was also a case study in how a commercialization timeline can be squeezed. CRB believes that timelines can be reduced significantly on average—what is this based upon?

E.U.: Experience! Despite needing to develop new technologies, the Shire project timelines were enviable compared to most traditional bioprocessing facility design projects. Schedule reduction on a project, and specifically focus on the ability to compress project schedule is nothing new. The differences in this particular case came from a few different sources. Closed processing, which allows for a simpler facility, means there is less to design, less to install, less to start-up and commission. All of this together leads to savings in time and money. Single-use systems can offer expeditious timelines for equipment procurement as well as the potential offsite commissioning and operator training, depending upon the systems and vendors used.

How this compares to a typical project without closed processing and single-use systems depends on a number of factors. However, for a typical biotech process, these factors can reduce a project timeline by up to 40%, and in some more extreme cases even beyond that number.

PhM: Single-use systems are synonymous with the drug manufacturing facility of the future. Among the various concerns expressed regarding disposables (scale limitations, disposal, etc.), which do you think is most significant and could truly limit their adoption?

E.U.: Single-use systems are an excellent tool in the toolbox of the future facility owner and operator. Certainly, the rapid adoption and growth of single-use systems in the marketplace in terms of solutions and options available to manufacturers today is a sure sign of their capa-

bilities and advantages. However, each project and facility needs to be designed specifically around the product and patient needs. In many cases, this does not lend itself to single-use systems. And remember, closed processing can be achieved in both traditional stainless steel equipment and systems, as well as in single-use systems; therefore, it is not always a default to use single-use systems today or tomorrow. Some of the limiting factors for single use systems are (in no particular order):

- *Scale:* Some processes require larger scale production and single-use systems become cumbersome and costly at large scale, or are entirely unavailable at the required scale.
- *Cost:* Some operations are more cost-effective over time in fixed vessels than in single-use systems; proper evaluations need to be done for each case.
- *Supply Chain:* Today and potentially tomorrow in some locations overseas, supply chain and ability to get single-use consumables is an issue, especially from multiple suppliers.
- *Production Technology:* Certain production technologies, both upstream and downstream in the biotech side, can limit single-use system application—for example, microbial fermentation; other areas include processes with higher volumes of solvent processing or other potential explosivity issues which require traditional stainless vessels.
- *Reliability:* Failure rates of 0.4% are still being reported.
- *Product Compatibility:* Some processes and constituents are not compatible with certain plastics used in the manufacture of single-use components. These can be very specific to the process.
- *Standardization:* Few standards exist in terms of platforms for consumables; the industry is working on this and will hopefully develop a solid platform in the future for all manufacturers to follow. This is under development now at ASME BPE and BPSA. Further, standardization will mitigate many of the risks discussed above especially supply chain.

There are of course other areas that could limit their adoption, but these are some of the current prevalent ones. One item to note is the increased interest in single-use systems outside of biotech API production, such as in fill/finish applications, which offers an area of continued growth for more single-use applications.

SINGLE-USE RESOURCES KEY REFERENCES ON SINGLE-USE EQUIPMENT ISSUES

EXTRACTABLES/LEACHABLES

Extractables and Leachables Best Practices
http://www.solvias.com/sites/default/files/solvias_whitepaper_web.pdf

A Primer on Leachables and Extractables Testing
http://www.us.sgs.com/cvg100506.pdf

Extractables and Leachables Requirements
http://www.cosmoscience.org/Presentations_2010/Session%203%20Talk%203%20CZweiben%20extract_leachable.pdf

FACILITY DESIGN AND CONSTRUCTION

Designing a Concept Facility Based on Single-use Systems
http://www.biopharmservices.com/docs/ConceptFacility.pdf

Transfer, Late-Stage Development and Validation Readiness of a Biodisposable MAb Facility
http://www.ncbiotech.org/sites/default/files/MULLAN_NCBC_14Apr11.pdf

Cost of Installing Single-Use Equipment
http://www.sartorius.or.kr/nh/fileadmin/sartorius_pdf/stedim/stedim/Quantitative_Analysis_of_Single_Use_Disposables.pdf

NEWS

Single-Use on the Cusp of Industrialization
http://www.genengnews.com/gen-articles/single-use-equipment-on-cusp-of-industrialization/3961

Perfusion Bioreactor Trends
http://www.bioplanassociates.com/publications/articles/2010-11/BioprocessIntl_Perfusion-Trends_6-15-2011.pdf

SUSTAINABILITY

Environmental Impact of Biodisposables: A Life-Cycle Analysis
http://www.biopharminternational.com/biopharm/Disposables/An-Environmental-Life-Cycle-Assessment-Comparing-S/ArticleStandard/Article/detail/746269

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EQUIPMENT & CUSTOM SERVICES

Protecting Pharma's Supply Chain

Until we can examine every supplier of excipient and API, we'll need to do our own detective work, but that will help us with Quality by Design

BY EMIL W. CIURCZAK, CONTRIBUTING EDITOR

RECENTLY, VARIOUS LinkedIn groups have been hosting some interesting discussions on the pharmaceutical supply chain. Pharma shares many characteristics with the food industry. I recently read [1] that one frozen pizza can contain as many as 50 ingredients from 10 or more countries. A law had been proposed in Congress that would have required companies to be able to trace the suppliers of any ingredient, at any point in its life cycle. That law was shot down. Right now, food companies only have to track who sold them something and whom they sold sold their product to.

Why does this concern us in the pharmaceutical industry? Many of the excipients we use are supplied by the same people who supply food companies. Remember, pharma buys only a small portion of the lactose, sucrose, cocoa butter, and other "fillers" that are sold. The typical pharma company has dozens of suppliers around the world for each material it uses to manufacture its products. Aside from any potential health problems they may pose (remember heparin?), the consistency of the raw materials is problematic, at best.

Sadly, most drug manufacturers today don't know what a "good" raw material really is. One discussion chain suggested that we include ingredient vendors in formulation planning sessions (on a forum started by my friend Hedley Rees, author of a critical new book [2]). Vendors may not know pharmaceutical production, *per se*, but they know the grades of materials they can provide. If proposed formulations were discussed with vendors (under a confidentiality agreement, of course), these vendors might be able to make positive suggestions as to the correct grades and specs for the materials used. While suppliers will seldom change material properties to meet *our* specs (remember: we are small customers, by comparison with food people), they can suggest the best grade for the process we describe to them.

That is fine for correct physical parameters, but what about purity and consistency? While we now have vendor validation programs where we audit a supplier for cGMP violations, it is not inclusive of all suppliers. Even the FDA cannot inspect all the venues with which it is tasked. An example of futility might be China, where the FDA needs an "invitation" from the government to inspect a facility. I'm sure no one in the government would alert the manager of the facility of the upcoming "surprise" visit, would they? There are a number of steps we can take on the "home front" to help ourselves.

While I was researching suppliers for my NIR raw materials work (we didn't have vendor validation in 1983), I traced every material back to its point of origin. I accounted for every place where material could be repackaged or relabeled as well as the origin of every material. One purpose was to determine whether any other material was produced at the point of origin. One example was talc; it was quarried in Alabama, crushed, packaged, and ETO-sterilized at the point of quarry. Since there was no chance of product mix-up, we did not need to do containerwise qualification, just a quick ID. Another example was aspirin. Several suppliers also made other materials and, consequently, we checked every container. One produced aspirin in an isolated building, packaged and shipped from there. This product only needed cursory examination upon receipt.

CAVEAT EMPTOR ISN'T JUST ABOUT $50 ROLEXES, BUT EXCIPIENTS AND API'S.

Until we can examine every supplier of every material, both excipients and APIs, we need to do our own detective work. The good news is that the data needed to produce meaningful tests (not LOD, sieve size and other USP tests) will apply to QbD processes. If we determine which are critical parameters, find accurate purity tests, and find the will to implement them, it almost doesn't matter that the sources may be questionable. Forget about $50 Rolexes. As it turns out, *Caveat emptor* applies to all points of the supply chain.

References

1. *"Your Food has been Touched by Multitudes," Bloomberg Businessweek, August 29- September 4, 2011, pp. 29ff*
2. *Rees, H. "Supply Chain Management in the Drug Industry: Delivering Patient Value for Pharmaceuticals and Biologics", Chapter 5, J. Wiley & Sons, Hoboken, NJ, February 11, 2011.*

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David Urdal, Chief Scientific Officer, *Dendreon*

Andy Hopkins, Sterile Products Inspector, *MHRA*

Ted Love, MD, Executive Vice President, R&D and Technical Operations, *Onyx Pharmaceuticals*

Matt Croughan, Professor, *Keck Graduate Institute of Applied Life Sciences*

Emily Shacter, PhD, Chief, Laboratory of Biochemistry, *CDER, FDA*

- **John E. Butler**, PhD, Global Project Leader, *Bayer Innovation*
- **Stephen Brown**, PhD, Chief Technology Officer, *Vivalis*
- **Tom Finn**, CMC Reviewer, *CBER, FDA*
- **Barbara Potts**, PhD, Principal, *Potts and Nelson*
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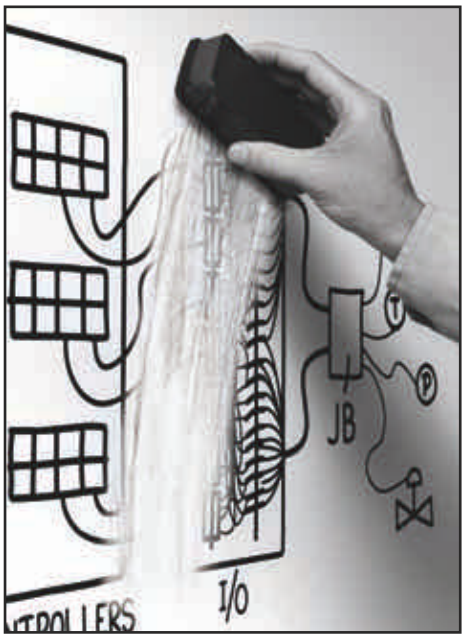

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