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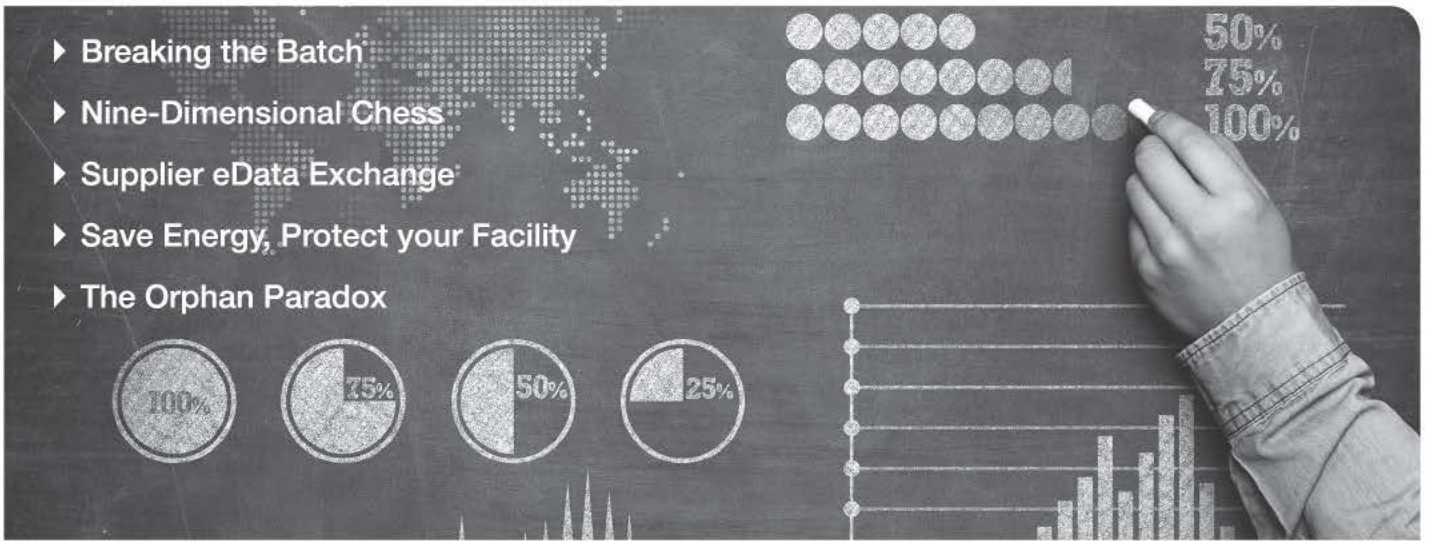

METRICS

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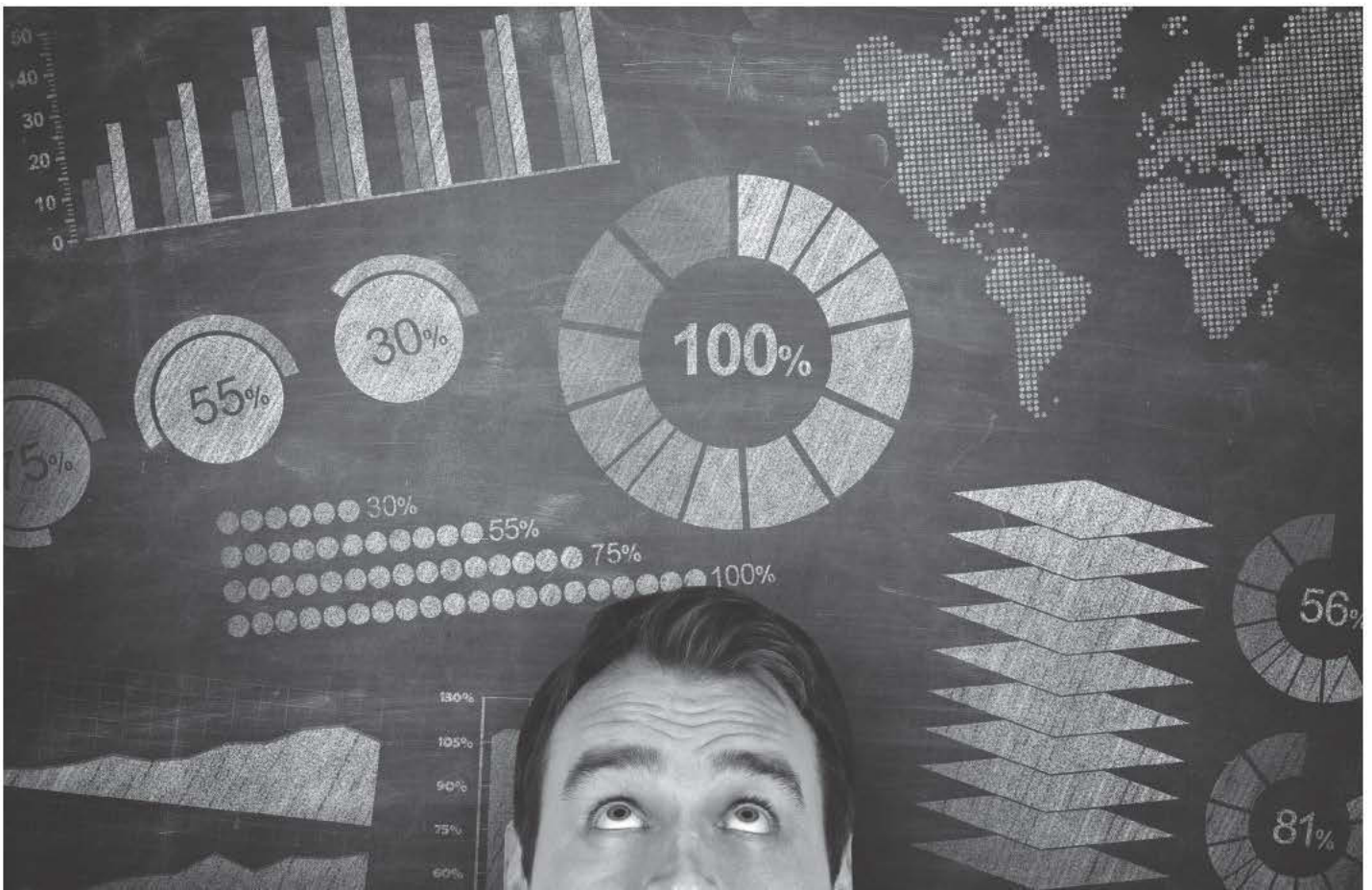

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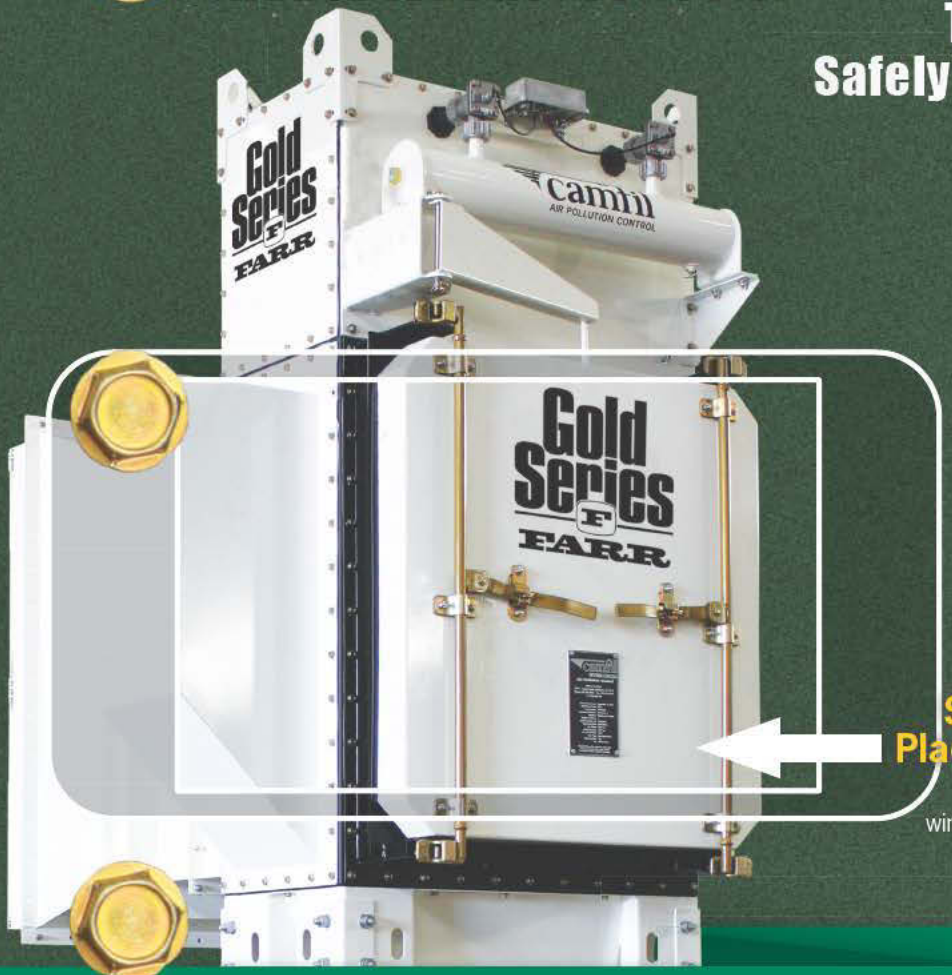


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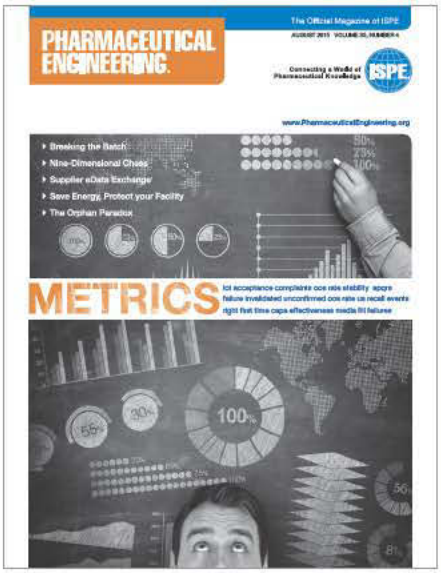

Cover Photo: iStockphoto

ISPE's Quality Metrics Initiative report was met with great enthusiasm in June at the ISPE/FDA/PQRI Quality Manufacturing Conference. And it raised many questions about manufacturing that both Novartis Pharma's Juan Andres (p. 11) and MedImmune/AstraZeneca's Andrew D. Skibo (p. 13) address. Coming at the topic from a completely different angle, authors Ting Wang, Bryan Looze, Tony Wang, Duncan Low and Cenk Undey speak to the need for eData exchange with suppliers to encourage superior knowledge management (p. 71).

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AUGUST 2015

06 San Diego Chapter, Vendor Night at Green Acre, San Diego, California, US

07 San Diego Chapter, Golf Tournament, San Diego, California, US

27 Midwest Chapter, Golf Event, St. Louis, Missouri, US

SEPTEMBER 2015

03 Nordic Affiliate, Advance Aseptic Processing Event, Copenhagen, Denmark

03 San Diego Chapter, Networking Event Padres vs. Dodgers, San Diego, California, US

09 DACH Affiliate, GAMP COP Workshop, Frankfurt, Germany

10 Ireland Affiliate, Joint Event, Dublin, Ireland

14–16 ISPE Philadelphia Training, Philadelphia, Pennsylvania, US

16 Spain Affliate, Jornada de Fabricación Estéril, Barcelona, Spain

17 Spain Affiliate, Jornada de Fabricación Estéril, Madrid, Spain

17 Boston Area Chapter, Regulatory Compliance, Andover, Massachusetts, US

21–22 Canada Affiliate, Annual General Meeting, Ottawa, Ontario, Canada

22 Belgium Affiliate, Connecting the Dots with Statistics, Leuven, Belgium

22 Chesapeake Bay Area Chapter, Golf Tournament, Ijamsville, Maryland

24 France Affiliate Institut de Pharmacie Industrielle de Lyon (IPIL) Lyon, France

24 San Francisco/Bay Area Chapter, Evening Meeting, San Francisco, California, US

28–30 ISPE Barcelona Training, Barcelona, Spain

28–30 2015 Pharma EXPO, Las Vegas, Nevada, US

30 Nordic Affiliate, Biotech Event, Strängnäs, Sweden

OCTOBER 2015

07–08 ISPE Process Validation Conference, Silver Spring, Maryland, US

07 Boston Area Chapter, Annual Product Show, Foxboro, Massachusetts, US

07 San Diego Chapter, Clinical to Commercial Meeting, San Diego, California, US

12 DACH Affiliate, Wassersysteme in Der Pharmaproduktion, Weinheim, Germany

13 Belgium Affiliate, GAMP Benelux COP Data Integrity, Zwijndrecht, Belgium

15 Nordic Affiliate, PAT (1 day), Copenhagen, Denmark

19–20 ISPE Raleigh Training, Raleigh, North Carolina, US

19–23 ISPE Boston Training Series, Boston, Massachusetts, US

21 Spain Affiliate, Jornada de GAMP y Automatización, Barcelona, Spain

22 Spain Affiliate, Jornada de GAMP y Automatización, Madrid, Spain

22 San Diego Chapter, Joint Facilities Reception Biocom and IFMA, San Diego, California, US

29 Midwest Chapter, Halloween and Get Pumped for Annual Meeting Party, Kansas City, Missouri, US

NOVEMBER 2015

08–11 ISPE Annual Meeting Philadelphia Marriott Downtown Philadelphia, Pennsylvania, US

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TRAINING

ISPE Training Institute Opens in October 2015

ISPE, the "Industry's Trusted Source of Knowledge," has been training pharmaceutical professionals since 1998. Our courses provide globally vetted content that ensures a safe supply of medicines, helps companies meet regulatory requirements, and lowers production costs while maintaining product quality and preventing drug shortages.

Located within ISPE Headquarters in Tampa, the new ISPE Training Institute boasts over 2,200 square feet of classroom space. With a world-class airport just minutes away and several hotels within easy walking distance, the new facility will provide even more high-quality, in-depth knowledge for pharmaceutical manufacturing professionals, while giving them opportunities to share best practices and network with others in their field.

Construction is slated for completion in October 2015, with the following three courses scheduled:

5–6 October: Monday and Tuesday
Practical Application of Computerized Systems Compliance: Applying the GAMP® 5 Guide: A Risk-Based Approach to Compliant GxP Computerized Systems
Instructor: Jim John, Senior Project Manager, ProPharma Group

8–9 October: Thursday and Friday
Science and Risk-Based Commissioning and Qualification—Applying the ISPE Good Practice Guide: Applied Risk Management for Commissioning and Qualification
Instructor: Steve Wisniewski, Principal Consultant, CAI

29–30 October: Thursday and Friday
A Risk-Based Approach to GxP Process Control Systems—Applying the GAMP® Good Practice Guide: A Risk-Based Approach to GxP Process Control Systems (2nd Edition)
Instructor: Mike Byrd, Director Computer System Validation, ProPharma Group

ISPE will deliver over 40 of its signature commercial-free courses at the new facility in 2016, utilizing industry guidance documents and best practices from subject matter experts working in the industry.

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* ISPE has been reviewed and approved as a provider of project management training by the Project Management Institute (PMI®)

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Skyrocketing Drug Prices Leave Cures Out of Reach for Some Patients

USA Today, 15 June 2015, Liz Szabo

Sophisticated drugs are opening the door, scientists say, to an era of "precision medicine." They're also ushering in an age of astronomical prices. New cancer drugs are routinely priced at more than $100,000 a year – nearly twice the average household income. Experimental cholesterol drugs – widely predicted to be approved this summer – could cost $10,000 a year.

A drug for a subset of people with cystic fibrosis, a lung disease that kills most patients by their early 40s, commands more than $300,000 a year. Even with insurance, patients might pay thousands of dollars a month out of pocket.
www.usatoday.com/story/news/2015/06/14/rising-drug-prices/71077100

Op-Ed: Don't Weaken the FDA's Drug Approval Process

The New York Times, 11 June 2015, Gregg Gonsalves, Mark Harrington and David A. Kessler

During the early days of the AIDS epidemic in the 1980s, there were no effective treatments against HIV, the virus that causes the disease. Because of this, many thousands of people died lingering deaths. The desperation of those times led to the rise of an activist movement that took to the streets and pressed government officials to expedite research on drugs to treat AIDS.

The danger of faster drug approval was that a devil's bargain would be struck: quicker access to experimental drugs but without first determining whether these drugs were safe and would improve health and extend life.
www.nytimes.com/2015/06/11/opinion/dont-weaken-the-fdas-drug-approval-process.html?emc=edit_tnt_20150611&nlid=33652061&tntemail0=y&_r=0

Drugmaker Sues FDA over Right to Discuss Off-Label Uses

The New York Times, 7 May 2015, Katie Thomas

Drugmakers have long argued they should have the right to talk to doctors about unapproved uses for their products, as long as they are being truthful. And in some cases, courts have agreed. But the federal government still frowns on the practice and, in recent years, has fined drug companies billions of dollars for talking to doctors about so-called off-label uses for their medications.

On [7 May 2015], Amarin Pharma took the unusual step of suing the US Food and Drug Administration, arguing that it has a constitutional right to share certain information about its products with doctors, even though the agency did not permit the company to do so.
www.nytimes.com/2015/05/08/business/drugmaker-sues-fda-over-right-to-discuss-off-label-uses.html

India Takes First Step Towards Regulating Medical Devices

Reuters, 12 June 2015, Zeba Siddiqui

India plans to set up a regulator to oversee the country's $4 billion medical device industry, according to a draft policy released this month, the country's first effort to regulate an industry that covers everything from thermometers to prostheses.

The policy document, welcomed by many in the industry despite concerns over a lack of detail, also outlines plans to boost local manufacturing and reduce reliance on imports.
www.reuters.com/article/2015/06/12/india-healthcare-regulations-idUSL3N0YW4QK20150612

Public Rarely Knows Full Reason FDA Rejects New Drugs

Reuters, 16 June 2015, Lisa Rapaport

Drug companies generally don't disclose all the reasons new medicines fail to win US marketing approval, even though regulators often reject treatments over concerns about safety or effectiveness, a study finds.

Researchers compared the details companies made public in press releases with confidential documents from the US Food and Drug Administration (FDA) known as complete response letters, which explain why a new medicine can't be sold.

Often, companies made no announcement when a drug was rejected or omitted most of the reasons the FDA cited for denying approval, the study found.
www.reuters.com/article/2015/06/16/us-drug-approvals-fda-letters-idUSKBN0OW2NX20150616

Venezuelans Can't Get Even the Most Basic Lifesaving Medical Supplies

Washington Post, 29 April 2015, Diederik Lohman

As Yamila's three-month-old daughter was recovering from heart surgery at one of the leading public hospitals in Caracas, Venezuela, doctors told her she needed to go out and buy basic medical supplies for her baby that the hospital had run out of. They gave her a list that included catheters, needles for administering IV fluids, antibiotics, and other medications, the mother told a Human Rights Watch researcher in November.

Leaving her daughter's side, Yamila went on a frantic search for medical supplies so basic that no hospital – let alone one of the country's largest teaching hospitals – should ever run out of them. But none of the hospitals or pharmacies she visited had them in stock. In the end, despite concerns about the quality of the supplies, and unsure whether she had the correct catheters and needles for a newborn, Yamila had no option but to buy whatever she could find on the black market – with no quality guarantees.
www.washingtonpost.com/posteverything/wp/2015/04/29/venezuelans-cant-get-even-the-most-basic-lifesaving-medical-supplies/

Generic Drugs: Much Ado about Something

The Economist, 30 April 2015 (print)

The plot is worthy of a Shakespearean comedy. Teva is in pursuit of Mylan. But Mylan dislikes its suitor and runs away to declare its love for Perrigo while seeking a poison pill in case it is forced to marry Teva. Perrigo, though, rebuffs Mylan.
www.economist.com/news/business/21650151-worries-are-growing-about-effects-dealmaking-among-generics-firms-much-ado-about?zid=318&ah=ac379c09c1c3fb67e0e8fd1964d5247f

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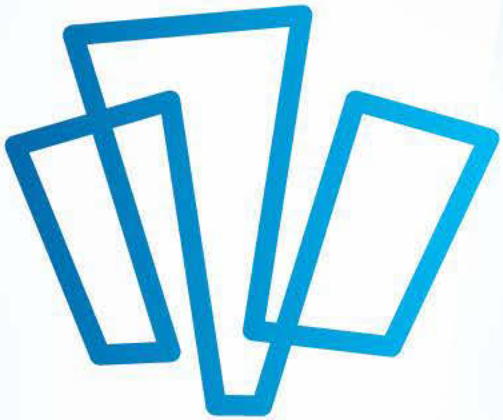

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INNOVATIVE MANUFACTURING PROMOTES QUALITY

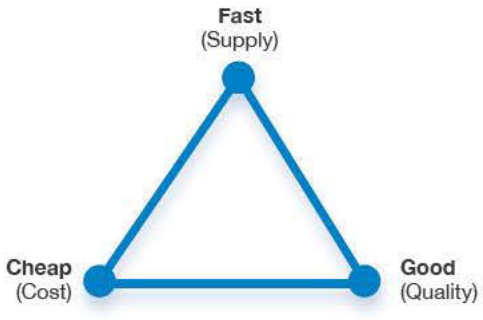
Juan Andres
Head Pharma Tech Ops, Novartis Pharma AG

Making and supplying quality medicine reliably is an undeniable mission for pharmaceutical manufacturers. New technologies and innovative approaches can help improve product quality and reduce the risk of supply shortages. However, we cannot rely on technology alone. It is essential to create a culture of "quality beyond compliance" to reach new levels of reliability. With this is mind, there are two important questions that we, as the pharmaceutical industry, should ask ourselves.

Why have other industries been able to evolve manufacturing very effectively?

In the pharmaceutical industry, the impact of being unable to manufacture our products is that somewhere in the world, a patient is not receiving a life-saving or life-enhancing medicine. This risk has long outweighed the expected operational benefits of moving away from traditional manufacturing methods that have served us well and moving towards new and innovative technologies. The risk/benefit ratio to innovate manufacturing has not been in our favor, especially when you consider that only one in 10 development compounds will make it to market. In addition, the forecast we get from the business is highly variable and patients most certainly do not want to wait for their medicine.

In other words, the undeniable duty of pharmaceutical manufacturing is to convert "uncertainty" into "certainty" of supply. We often see people make trade-off decisions like:



- Good and cheap, won't be fast
- Fast and good, won't be cheap
- Cheap and fast, won't be good



When we think about this in the context of the pharmaceutical industry, with our mission to supply patients with quality (good) medicines on time every time (fast) and at an affordable price (cost), the impact of making such trade-offs can be significant. It is, therefore, a key object of pharmaceutical manufacturing that we keep "the triangle" in balance. So when optimizing productivity, we cannot do it at the expense of quality or supply. This leads us to our second question.

How do we move forward to making and supplying quality medicines on time, every time, efficiently?

There are three key levers that drive reliability and efficiency (although there may be others):

1. A deep understanding of products and processes
2. A culture of quality beyond compliance
3. Investment in new technologies

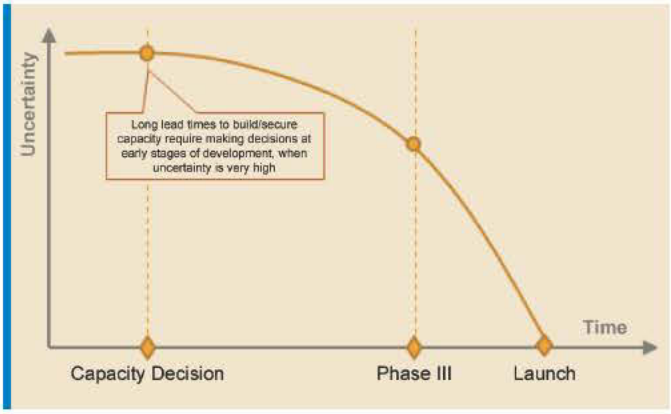
Detailed knowledge of process capabilities is critical to ensuring that we produce the right quality medicine, right the first time. Linking science with compliance and challenging traditional validation methods with the introduction of continuous verification processes ensures that we maintain a constant oversight of our process robustness and drives reliability in the right direction.

Excellence	Competitive advantage through prevention of quality issues
Competence	Quality mindset in all functions Design quality in and anticipate issues
Understanding	Quality systems and metrics reveal reality and drive action
Awareness	Quality unit will identify the issues
Innocence	Quality mainly outsourced to regulators

A sustainable product quality performance is key to achieving reliability, and the companies that succeed are the companies that recognize that quality is not the enemy of cost. By moving through the quality culture maturity model from innocence to excellence, a competitive advantage can be gained through the proactive prevention of quality issues. It is in the DNA of other

industries that the best way to improve efficiency is through improvement of quality and reducing variability.

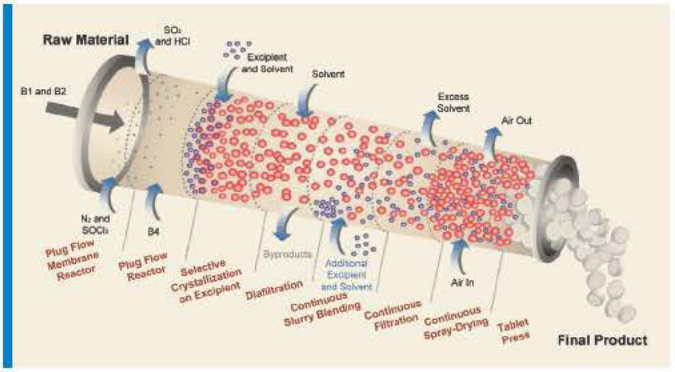
We can complement these foundations with new technologies. When we consider the advancement of medicines/therapies over the past 20 years, it's clear that manufacturing technology has not evolved at the same pace due to the risk of adding variability when new technology is introduced. However, not evolving and investing in new technologies will not only "leave money on the table" but can prevent the improvement of quality and increase the risk of supply shortages that too often affect our industry. Therefore the key is to anticipate the future technologies and invest in them in a way that minimizes adding variability.



Traditional technologies carry an intrinsic challenge. In Biologics API manufacturing, for example, due to the specialist nature of the equipment and long lead times to secure/build capacity, you have to invest when the level of uncertainty is still significantly high and therefore the probability of "guessing" wrong is also high. However, new technologies in Biologics such as single-use bioreactors made of disposable plastic bags and same scale equipment that can be applied for pre-clinical, clinical, and commercial manufacturing are changing the landscape and will help supply patients with the right product at the right time by reducing the time for capacity decisions and the investment cost.

Continuous manufacturing is another positive example of new technologies that could drastically change the way we understand drug manufacturing. It represents a unique opportunity to redefine the industry paradigm of how drugs are produced and pave the way to a faster, more precise, and more cost-effective manufacturing approach.

The principle of continuous manufacturing is that all steps of production are integrated into a single process in one location. However, this is a long journey that involves choosing the right development partner, regular exchange with health authorities,



selecting the right product candidate, and designing, constructing, and commissioning the first industrial-scale facility with Good Manufacturing Practice (GMP) capability before moving to launch. However, through key collaborations with partners and health authorities, this concept is close to becoming a reality and we can now envision "end-to-end" pharmaceutical manufacturing from drug substance to drug product being performed in a space the size of a tennis court.

The challenges are just as big as the potential:

- New process technologies for most unit operations
- New approaches for end-to-end integration of process technologies
- New development roadmaps for projects
- New screening tools to match projects and technologies
- New process control strategies
- New quality and regulatory pathways

But innovation can and will bring benefits in quality, supply, and cost. Technology has the potential to transform the current industry paradigm and deliver significant benefits, such as complete process understanding, improved product stability, reduced process and product complexity, few formulation changes, no scale-up, single-cycle process development, minimize bioequivalence and comparability issues, short lead times for supplies, streamlined technical development and manufacturing, a development scale equal to commercial infrastructure, and an overall smaller plant footprint.

Making and supplying quality medicine reliably is an undeniable mission for pharmaceutical manufacturers. Is it a dream or can it be done? Breaking the cycle of trading off quality, cost, or service is easier with new technologies if it can be done without introducing variability. However, we must be realistic; it requires investment, planning, time, and management commitment.

EVERY PATIENT, EVERY TIME

Assessing and Planning for Biologics Supply Chain Risks

Andrew D. Skibo
Head of Global Biologics Operations & Global Engineering, MedImmune/ AstraZeneca, and Chairman of the Board of Directors, ISPE

The ISPE/FDA/PQRI Quality Manufacturing Conference was held in early June in Washington, DC. Andrew D. Skibo, gave a keynote address titled "Biologics Supply Chain Risks: Point and Systemic Risks". This article is based on his presentation.[1]

Consider this hypothetical scenario: A healthy woman gives birth prematurely, at 34 weeks term. Although she is distressed to have her newborn transferred to the neonatal intensive-care unit (NICU), she is comforted to know that the NICU at her county hospital is designed to deal with preemies this age and even much younger. Her son's vital signs are monitored constantly. He is susceptible to infection by a virus called RSV because his lungs aren't fully developed. He should be given a vaccine that is routinely administered to preemies during RSV season to prevent this infection.

Unfortunately, there is a shortage of the RSV vaccine – a sole-asset-in-class product – due to a supply chain problem at our manufacturing plant. The supply base is narrow. Bulk mammalian cell drug substance production is always at risk of sporadic but lengthy interruptions due to particularly difficult to clear contaminations such as murine retroviruses. The drug that could save this baby's life is at risk of becoming unavailable. Fortunately, we know our supply risks and we manage accordingly. In this instance we maintain enough inventory to bridge a full season's worth of production of this very specialized product.

I know that the market for a drug like this cannot be shorted. In this case, the math representing human health outcomes is implacable. I don't ever want to wake up in the morning having to do that math. I don't take risks managing its supply chain.

TAKING OUR INDUSTRY'S HISTORY

The Risks To Quality Of Cost-Cutting

Three years ago, while thinking about the general risks to supply in our industry, I was reading a review by a leading consultancy that recommended that pharma could learn from the supply chain models and supply chain efficiencies of the big automotive companies. They noted one manufacturer in particular as a best in class example. I also happened to have the Business Section of that Sunday's *Washington Post* on my desk. The headline article highlighted the despair of key auto suppliers in Japan that were having to move production offshore to offset the cost pressures and just-in-time scheduling being mandated by this very same automobile manufacturer. These suppliers could no longer ensure that their products would be produced to the standards of quality that were historically associated with their family name.

The juxtaposition of these two articles startled me. One suggested we learn from the auto industry while the other demonstrated the adverse effects that this manufacturer's relentless cost cutting was having on supplier quality.

Fifteen years ago, pharma industry supply chains were fat. We had largely internal production, controlled the quality, maintained deep inventory, and had an average utilization of only 54%. What followed was streamlining and cost-cutting by all of big pharma. Concomitant with this, drug shortages and quality alerts both went up significantly. Many firms with previously stellar quality records were having quality issues, near misses and unpleasant conversations with the FDA. Had pharma's attempts to streamline our supply chains created a different problem?

We at first thought of these as disconnected events. I would argue that they were not. Like those Japanese automotive manufacturers, as we streamlined our supply chains to reduce costs did we increase the risks of being able to manage quality or supply product?

The Risks to Supply of Cost-Cutting

As an industry, there was no doubt that we had to streamline our networks, but in retrospect were we stumbling into risks that we weren't aware of? We were migrating from a supply chain that relied on three or four internal sources and end-to-end internal sourcing – in plants that had been making pharmaceuticals in our home bases for 15 years. If there was a challenge in one of those plants – an old piece of equipment that went down, for example – the market never saw it. You could move production around in the rest of your network, which was totally under your control. You had deep inventory. There was incredible resilience in the supply chain as it existed then.

Starting in 2010, drug shortages doubled in just over two years. The FDA believed this was connected to quality control. In 2013, it started a quality metrics and drug shortage initiative with major support from the ISPE. The thinking was that, if we could get a handle on the quality metrics of any one plant, we would have a sense what the risk might be of product shortages from that plant.

But this was generally not the root cause issue, as demonstrated by two hypothetical scenarios. First, consider a perfect plant, the poster child for quality metrics. Yet it operates at 95% capacity, the supply chain maintains only two months of inventory, it is manufacturing a sole-asset-in-class, Specialty Care, pharmaceutical, and it is located in a difficult part of the world. This is a high-risk scenario for drug shortage despite the plant's superb quality metrics.

Alternatively, consider the example of the same product manufactured in three older plants in our home base. The plants are fully in compliance but rely on equipment that is 20 years old. There are three nodes, all internal, operating at 54% capacity, and with 14 months of inventory. I'd argue that's a much lower overall product supply risk situation even though anyone of those older plants might have a higher probability of an equipment failure.

DIAGNOSING THE STATE OF THE SUPPLY CHAIN TODAY

The Perfect Storm

A confluence of factors accounted for this focus on cost. We've seen increases in:

- **Patent expirations.**
- **Drug development costs** – In the mid-'80s, it cost $75-100 million to get a drug from concept to approval. Today that number is $1.8 billion, or more than $7 billion if you factor in the cost of unsuccessful products.
- **Regulatory uncertainty** – Regulators are becoming more conservative, especially for lifestyle drugs or a "me too" product such as a third-generation product, for which the approval data would need to be impeccable.
- **The bar for reimbursement and access is high** – The pool of insurance company money is limited and a product has to offer a material advantage over what's already on the market, for it to be reimbursable.

These have been accompanied by decreases in:

- **R&D productivity** – The success rate for small molecule launches 15 years ago was about 6%. Today, that number is under 2% (10% for biologics). This is not a fundable business model, were we requesting venture capital to start our business today.

Many supply chain leaders in pharma came to the industry from high manufacturing cost, must-be-efficient supply markets such as apparel, footwear or automotive. They used their experience and met this perfect storm of factors, streamlining operations and reducing costs through:

- **Outsourcing** – An increased reliance on CMOs (contract manufacturing organizations). Many big pharmas brag that they've achieved 100% outsourcing for APIs (active pharmaceutical ingredients). 60% or more of all APIs are currently outsourced to emerging markets.
- **Increased utilization rates** to chemical company levels, approaching 85% - 90%.
- **Reduced inventories**, sometimes by as much as a factor of five.
- **Reduced investments** in internal networks

This focus on supply chain cost was absolutely necessary. Since 1990, R&D and all other costs except for manufacturing operations have come close to doubling. If supply chain leaders hadn't stripped out 40% of cost by streamlining the supply chain, the rising expenses of the rest of the business would have made earnings go down in relation to revenue.[2]

THE INDUSTRY PROGNOSIS

There's a Growth Spurt, Especially Within Biologics

We are entering a new era in which new BLAs (biologic license applications) are being submitted at an historic rate and approvals are doubling from what they were a few years ago. Nine of the top 10 drugs are forecast to reach over $1 billion in sales in the US five years post launch.[3] Growth of the pharma market is expected to grow, year on year, until 2020 when sales are expected to reach $1 trillion, which is double that of 2006.[4] This growth is coming from a few markets.

Large molecule

There is clear growth in the biologics space. R&D productivity is high. With 15%-20% of total R&D going into bio over the last 15 years, large molecules represent half of the pipeline in the industry. On a sales basis the portion of revenues for bio is expected to grow from 14% in 2006 to 27% in 2020.[5] Some projections suggest that 70%-80% of the pipeline in 2020 will be biologics.

Oncology

The oncology space shows the largest and fastest growth, especially immune-oncology products targeting the PD-1/PD-L1 pathway.[6] These breakthrough therapies see pipeline acceleration of as much as five years, which is enormous.

Biosimilars

We used to think that biosimilars would merely replace the bio-novels and that the capacity of one would decline while the other increased. That has turned out not to be true.[7] Among other reasons, biosimilars will be used in co-therapies with novels, at least in the oncology space. The value demand for a bio product doesn't collapse after a patent expires as it frequently can for small molecules.

Emerging Markets

Southeast Asia and Latin America are expected to lead the growth in pharmaceutical sales among emerging markets, which will grow from 30% to 40% of worldwide sales by 2017.[8] These are markets we can no longer ignore.

Personalized drugs

The predictive personalized drug market is expected to double from 2013 to 2019, which is what is partially driving the oncology space.[9]

Impacts of Cost-Cutting and Projected Growth on the Supply Chain

As mentioned earlier, as an industry we have made our phama supply chain lean. We are now at a low point of capacity agility and resilience.[10] Our industry's overall agility to support a return to growth with new products may be constrained. This is particular true for biologics, where there are at least 17 large bio drug substance plants in development right now. It takes five years to design, build, and commission one of these plants. As an industry, we are clearly facing potentially constrained bio drug substance supply until this wave of new plants are commissioned and licensed. 2017 through 2020 will be years to watch with caution as we plan for bio supply.

For the past 10-15 years big pharma has operated with a mature, product portfolio focused more so on Primary Care rather than Specialty Care markets. We operated in the efficient / mature end of the supply curve.

Now we are moving into the agile end of the supply chain curve: new product launches, more Specialty Care products, highly variable and unpredictable, first years demand. Variables such as the number of patients, the dose per patient, and production titer dictate a wide range of potential plant capacities that may be required. For new oncology products, the launch volumes required are notoriously difficult to project and can vary by a factor of as much as 17. How do you plan for that? Agility and flexibility are key.

As we said before, it takes about five years to design, build, commission, and license a big biologics manufacturing facility. The product development cycle used to be approximately 7-9 years. Now we see product developments cycles of three years. Yet it still takes five years to build a plant if you need one. Suddenly we're in a position where we are risk mapping for products we don't even have yet because they will come before you can get that plant designed, built, and licensed. It's a very different world.

It costs $750-$800 million to build a 4x15,000 l plant today. If you don't have the capacity, and you're not able to share capacity with another big pharma – a previously common occurrence – you could end up with a significant shortage. More importantly, we're not in this just for dollars; there are patients on the other end of that supply chain. If we short a statin, it will be meaningful in terms of lost revenue to our companies, but no patient suffers because there are other suppliers. If we short a PD-1/PD-L1 product, patients suffer. Many of these breakthrough therapies are saving lives, yet there is not 5X surplus capacity for these products available in the marketplace. If we get the launch / early year volumes versus supply wrong, there will be healthcare consequences, not just dollar consequences.

THE WAY FORWARD – SUPPLY CHAIN MODELING

Supply chain agility is now a buzzword in the industry,[11] with over three-quarters of businesses in big pharma agreeing that they need to change their supply chain model. Tellingly, only 7% have completed that change.[12]

Two years ago at AstraZeneca, we developed a proprietary capacity model for our biologics products. We run this model for hundreds of demand scenarios to assess whether the actual capacity of our current network needs to be augmented, to meet future demand. The model allows us to tell our executive committee and our Board, not only what we're asking them to build to meet future capacity, but very importantly what is the white space above that, for which we are not planning to build. If the extreme upside demand hits and we're not prepared, as a company we need to understand what we may not be able to provide that capacity on short notice, given the constraints in the industry. We can't build to all the upsides – there aren't enough very large plants available or the dollars to build them. How much of the wide-range of potential demand that we are planning to supply should be an executive decision, not just a supply chain decision.

Modeling Supply Chain Risk

When we change a manufacturing process in our industry, we routinely do a quality risk assessment. Since supply chain risk has as much impact on drug supply as quality risk, we need to be doing the same risk assessment for the supply chain. For this reason we are developing a model to assess supply chain risks.

Supply chain management requires mental thinking that is like nine-dimensional chess. If you're good at it you can see that, when you make a change here, and put that constraint in over there, then somewhere else in the matrix something happens that may create risk. Understanding this subjectively is helpful. When you approach your Board and ask for $800M to cure that risk, Board's expect more than subjective judgement. Boards like hard numbers.

Our model allows us to quantify risks so we can go to our CFO with actual projections of risk mitigation versus cost. Quantification allows us to sell objective modeling instead of appearing to base need on personal preference.

Modeling also helps us identify risks that we may not subjectively see. As an example, in our flu vaccine franchise, we are very good

about projecting incoming raw material needs, understanding the plant capacities, packaging, and shipping and in-house testing needs. But we missed the risk associated with limited capabilities of outside testing labs. Missing that risk could have had the same consequence for us as not ordering the raw material. We had backup plans that fortunately mitigated the issue. But that conceptual miss was one of the issues that made it clear that we needed an end-to-end risk model that would flag a risk if we didn't see the risk ourselves.

Eventually the model will respond dynamically, be live and self-correcting, and offer solutions to identified risks.

What Determines Risk?
Supply chain risk is determined by: **inventory policy**, **network utilization**, redundancy, and **visibility**.

Inventory policy
If inventory is reduced to free up cash, while someone else is reducing utilization and someone else is optimizing the number of nodes in the supply chain, we could collectively be building a weak supply chain.

Network utilization
With 95% utilization, there is little room for equipment malfunction or other risks. With 50% utilization, production is inefficient and expensive. How do you balance these options?

Redundancy
Remember our example of 15 years ago. Three plants in our home base, primarily insourced under our control with our quality systems, low utilization, and high inventories. The redundancy of this network leads to virtually no risk to the supply chain. Compare that to today – do we have that redundancy in our supply chain?

Visibility
Outsourcing means that we can't shine a spotlight on production the way we could when all plants were under our control. If we treat these supply contracts as commodity purchase orders, we have no visibility into our true supply chain. We discover a risk only when there is a problem. We may have a dual source structure, but suppose both suppliers use the same intermediate material supplier for a key step. What looks like two outsourced nodes is, in reality, only one. What if one of them is in a difficult part of the world, operating at 95% utilization, and we have greatly reduced inventory. This is a high supply risk that we may not see.

These variables have to be considered together. Optimizing them independently puts the drug supply at risk. Understanding the risks associated with a single production site (i.e., quality metrics) alone is of marginal value in evaluating overall supply risk. It's not correct to think that a company with outstanding quality metrics needn't worry about supply chain risks.

Takeaway: Quality metrics do not equal supply chain risk metrics.

Anticipating Supply Chain Risks – Two Real-Life Examples
We find that the output from our risk model has high value for measuring risks such as what impact would the failure of a particular node have on on-time delivery. Here are two examples where we used the model to successfully anticipate supply risks.

We had two supply sources providing DP for a key clinical material, one internal and one external. The external supplier unexpectedly received a warning letter and had to close its plant. At the time it was our planned sole source of this clinical trial material. This could have materially affected our trials. However, we never eliminated the internal node. When the warning letter hit, we were able to easily call upon the internal node. We produced the drug product internally with less than three weeks notice. Because we had planned for that potential risk we averted an issue on a major clinical program.

As another example, increasing volumes of a frozen supply chain product lead to potential constraints on air shipment, the historical method of choice. We planned to move to ocean ship for the next year. Ocean ship startup proved to be less robust than expected. Fortunately, our risk model told us that this was a potential risk and, instead of cancelling the air shipment option, we had held it in reserve. It was reactivated it immediately with no interruptions to supply.

What will supply chain risk assessment allow?
Modeling the supply chain risk ensures two things: first, we see the risk; second, that we have hard data to support requests or plans that will add cost to our network to mitigate the risk.

The supply chain doesn't operate in a vacuum. We need to communicate with our colleagues in clinical, finance, regulatory, commercial, R&D, and manufacturing to understand the whole network. Then we can make these decisions together. We really want our executive committee to be aware of what we're doing.

Cost-to-benefit analysis of de-risking is easier to implement before a shortage, but harder to sell to the CFO without concrete facts. Modeling tells us these costs versus benefits. Solutions may include white space in plant. A 70% utilization adds flexibility across products without adding inventory. This is especially true if we're in the agile, or growth, part of the supply curve. It does add cost. Is the balance, right?

Moving Beyond Efficiency
Until recently, most texts and journal articles regarding supply chain structures focused only upon efficiencies. Supply chain efficiency tools such as simplification, higher utilization, and the 3 Vs (visibility, variation and velocity) were discussed in depth. Many of the early texts about supply chain modeling are full of complicated formulas, focused upon these issues. There are factors for the number of nodes, leanness, and inventory. But most of the texts, most of the math, included no factors for risk. We weren't measuring risk; we were measuring how lean we could make the supply chain.

Bayesian risk analysis is frequently used for quality analysis. Few people have used it for supply chain analysis. It's complex, but it can be done, as E.D. Soberanis discussed in her PhD thesis regarding Bayesian network approaches for SCD.[18]

CONCLUSIONS

Big pharma does quality risk assessments for any process change. We should also do risk assessments for supply chain design and change. They have as much impact on product supply as a poor quality plant.

We must understand that analyzing the quality or product supply risk of a single node is of marginal value in understanding overall supply risk. Quality metrics have to lead to supply chain risk metrics.

I want us to assess and plan for supply chain risks because it's good for our industry. Just as importantly, none of us personally want to risk having a supply chain upset that affects our patients' health or lives.

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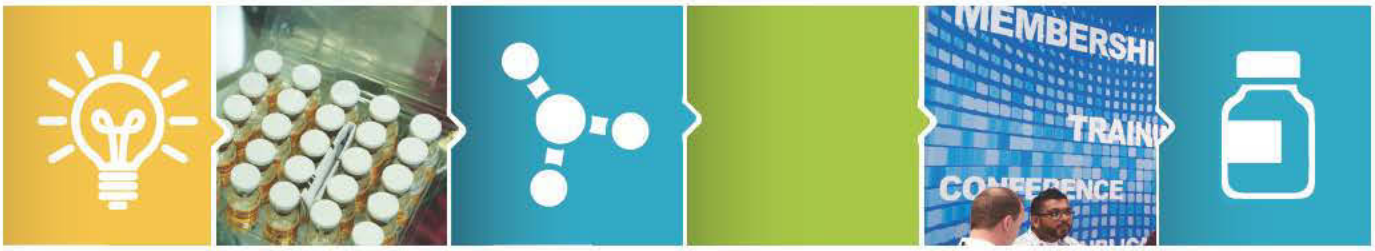

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TUESDAY, SEPTEMBER 29
COMPLIANCE TRENDS

Spotlight Session: Using Quality Risk Management to Evaluate Compliance for Multiproduct Manufacturing and Inventory Facilities in the Pharmaceutical Industry

- Other topics include serialization, track & trace, cleaning validation, and incident investigation.

WEDNESDAY, SEPTEMBER 30
PHARMACEUTICAL PACKAGING

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- Other topics include optimized packaging lines, container closure testing, best practices in transdermal patch packaging, and oral solid dose packaging.

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METRICS AND SUPPLY CHAIN COMMAND ATTENTION

2015 ISPE/FDA/PQRI Quality Manufacturing Conference, Washington, DC. 1-3 June

Hosted by the ISPE, the US Food and Drug Administration (FDA), and the Product Quality Research Institute (PQRI), the annual Quality Manufacturing Conference celebrated its fourth anniversary from 1–3 June 2015 at the Mayflower Renaissance Hotel in Washington, DC. The event featured over 76 speakers from industry and government in more than 38 education sessions and panels. The three-track conference covered manufacturing innovations, quality systems advances, and regulatory insights, with topics that included modernization, continuous manufacturing, facility operations, drug-shortage prevention, foundations for quality, life-cycle knowledge management, and data integrity.

The last day of the conference was dedicated to regulatory issues, a feature that conference Co-chair and ISPE Board Vice Chair Joe Famulare, Vice President of Genentech, hailed as "unique." Discussions at these sessions were led by representatives from ANVISA, the Medicines & Healthcare products Regulatory Agency (MHRA), and the FDA, with a focus on inspection trends and global harmonization.

In addition to education sessions and regulatory discussions, participants discovered cutting-edge technologies from 21 exhibitors, with products and services designed to improve processes and maintain compliance.

Conference highlights were keynote presentations that focused on each of the three conference tracks and updates on three ISPE initiatives: results of the ISPE Quality Metrics Pilot Program Wave 1 report, the development of a benchmark drug-shortage-prevention gap analysis tool, and a promising partnership with the Pew Charitable Trusts to explore additional causes

of drug shortages. The gathering also included the 2015 Facility of the Year Award banquet.

Keynote Presentations

Janet Woodcock, MD, Director of the Center for Drug Evaluation and Research (CDER) at the FDA, began the first session with a much-anticipated presentation on the agency's quality initiatives. She noted that while the FDA is transitioning to a new paradigm, merging department functions and creating new ones, momentum and progress continue. The agency released established conditions draft guidance in May 2015 and hopes to issue its quality metrics draft for review and comment soon.

The FDA plans to place more emphasis on quality by design, training, and risk assessment and will audit how well it addresses these in its assessments. "This is one of our most important initiatives," said Woodcock. Turning to regulatory convergence, she noted the urgent need for common standards around the world. The FDA is pursuing mutual reliance with the European Union on drug manufacturing – the first in what she hopes will be a series of agreements with international regulatory agencies.

Although the agency's transition is a challenge, Woodcock remains optimistic about the industry as a whole. We must resolve the problems of the past, she said, to benefit from future opportunities. "It's important," she concluded. "It's about science, technology, engineering, and manufacturing. Science and technology will get us out of the conundrum we're in. We need a revolutionary change in manufacturing as well as therapy."

In his keynote address, Juan Andres, Global Head of Technical Operations (Manufacturing and Supply Chain) at Novartis Pharma, encouraged the audience to create a culture of quality, develop a deep understanding of products and processes, and invest in new technologies.

"Medicine has evolved faster than technology," Andres observed. "We keep producing new drugs on old platforms." Continuous manufacturing, he said, could drastically change the landscape.

In Basel, Switzerland, a multipurpose pilot facility the size of a tennis court is testing a number of new process technologies, approaches, and process-control strategies. "We wanted to break the traditional chemical operations in pharma," he said, calling the new plant a "tool box" for upstream and downstream technologies. The challenges, he said, are just as big as the potential.

The conference's final keynote address was delivered by Andrew Skibo, Head of Global Biologics Operations and Real Estate for AstraZeneca's MedImmune. The industry's "perfect storm" of rising patient expirations, drug development costs, and regulatory uncertainty, he said, combined with declining revenue and R&D productivity, created pressure to streamline operations and reduce costs. "We are now

BREAKOUT SESSIONS

at our lowest point of capacity agility and resilience," he observed, adding that there is limited capacity to support new growth.

Today's model is all outsourced. Inventory has dropped to a quarter of what it used to be, observed Skibo, and there's no visibility in the network until something goes wrong. "Drug shortages have doubled in the last five years," he added, "and that's not an act of God."

Supply-chain risk analysis would allow companies to identify risk that they may not see and quantify what those risks mean financially. Both problems and solutions are complex, he admitted, likening them to "nine-dimensional chess."

Skibo cautioned attendees to analyze the overall supply-chain risk, not just a single node, and include quality metrics. "We do quality risk assessment for process change," he noted. "Why don't we do supply risk assessments for supply-chain design and change? It's the only way we can tell if we can deliver product."

Wave 1 Quality Metrics Report

Diane Hagerty, Vice President of Global Technical Operations Quality Systems and Processes for F. Hoffmann-La Roche, presented an update on the ISPE Quality Metrics Pilot Program Wave 1 report.

In a detailed analysis of data on a range of quality metrics submitted by 18 companies and 44 sites representing a broad swathe of the industry, the report identified a potential set of five relatively-well-established metrics—the "critical few"—that may serve as a starting point for the program's next phase: Wave 2. "Wave 2 provides a platform to continue refining the set

of 'critical few' metrics and transitioning to an industry-led initiative," explained Hagerty.

Wave 2 objectives are to:

- Increase the number of sites, technologies, and geographies represented
- Continue to build data for targeted metrics (or a refined set based on FDA input)
- Evaluate logistics and effort of gathering product-level data at an application level
- Enable continued objective data-driven dialog with the FDA and other health authorities

Wave 2 data collection began in July. Based on a positive experience in Wave 1, one company has already signed up for Wave 2 and is enrolling all its sites in the project. More information about the project is available at www.ispe.org.

Gap Analysis Tool

At one "Modernization in Manufacturing" education session, Bryan Wright, Regulatory Advisor for ISPE, discussed a game-changing tool that will help industry assess the robustness of a supply chain. The ISPE's Gap analysis tool, currently in development, is the third phase of the Drug Shortages Prevention Initiative. The tool is designed to highlight the "gap" between the desired state and the current state of a quality system, identify root-cause areas that may give rise to shortages, and allow

EXHIBIT HALL

companies to mitigate those risks by effecting any necessary changes.

The goal is to develop an easy-to-use template. "We envision that companies will use the tool as part of their overall drug-shortage prevention program," explained Wright. The tool will provide a succinct way to measure an organization's distance from the best practices recommended in the Drug Shortages Prevention Program, assess potential risks in the supply chain, and take proactive measures, where possible, to prevent shortages.

Once complete, the tool "will be part of our education and training programs to support implementation and effectiveness across the industry," continued Wright. While stressing that "this is a tool for industry, not for regulators," he noted that it must also satisfy potential EU and US regulatory expectations about preparedness to prevent or mitigate drug shortages.

ISPE/PEW Partnership

Stephen Mahoney, Senior Director of Global Quality and Compliance for Genentech, debuted another important ISPE initiative: a partnership with the Pew Charitable Trusts to examine how drug-supply disruption and drug shortages are influenced by related and dynamic factors. These include:

- Underlying quality and manufacturing issues
- Choices related to manufacturing quality and business continuity planning
- Larger market forces

Research will likely consist of guided interviews with decision makers inside companies, with a follow-up questionnaire. Participants will be drawn from companies that manufacture branded and generic products with significant (but not exclusive) US market presence. The goals are to produce a policy paper that describes both technical and nontechnical issues that drive drug shortages, introduce potential policy solutions to address drug shortages, and identify strategic opportunities with external stakeholders to leverage knowledge for the ISPE Drug Shortages Prevention Initiative.

Mahoney encouraged interested attendees to contact him if they wished to get involved in the project. Additional information will be published on the ISPE website and in *Pharmaceutical Engineering* as it becomes available.

Next Year

John Bournas, CEO of the ISPE, called the 2015 Quality Manufacturing Conference "an important event with solution-based approaches to improve processes and ensure a quality drug supply"—and the next one promises to be even better.

If you weren't able to attend this year's gathering in Washington, DC, mark your calendars for the fifth annual ISPE/FDA/PQRI Quality Manufacturing Conference, 6–8 June 2016, at the Bethesda North Marriott Hotel & Conference Center in Bethesda, Maryland.

By the Numbers

4	**Facility of the Year Award category winners** ▸ Astellas Pharma, Inc. Tube labeling project Equipment Innovation category winner ▸ AstraZeneca China Farmers' fields to pharmaceuticals Project Execution category winner ▸ IDT Biologika Multipurpose biologics and vaccines production facility: Isolator vaccine filling unit Facility Integration category winner ▸ Pharmalucence: A Sun Pharma Company Aseptic fill-finish facility Honorable mention
8	**Sponsors** ▸ Pharmatech Associates, Inc. ▸ PTI Packaging Technologies & Inspection ▸ Deloitte & Touche LLP ▸ Novartis Pharmaceuticals ▸ Genentech, Inc. ▸ DME Alliance Engineering Consultants ▸ DPS Engineering & Construction ▸ AstraZeneca
23	**Exhibiting companies**
38	**Education sessions and panel discussions**
76	**Speakers**
199	**Registrants**

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BENCHMARKING HOLDS COURT

2016 ISPE Europe Annual Conference, Frankfurt, Germany 14-16 March 2016

The ISPE will host its third annual Europe Conference 14–16 March 2016 in Frankfurt, Germany. As always, the conference will showcase innovations and trends in pharmaceutical manufacturing, with an executive forum and education tracks dedicated to operational excellence. In the past, the conference has proven to be an excellent platform for dialogue between process experts, mid-level and senior management, regulators, industry suppliers, and academics.

The 2015 conference was met with glowing reviews from the 300 attendees and 15 regulators. Some highlights included:

Executive Forum

This pre-conference forum was an open session that enhanced the dialogue between the shop floor, middle-management experts and senior management. The focus this year was on benchmarking, with speakers from the Benchmarking European Medicines Agencies (EMA) Secretariat, McKinsey and the Developing Countries Vaccine Manufacturers Network. Special presentations by speakers from Porsche Consulting (auto) and Nestlé (food) highlighted how to measure and manage complexity in other process industries that depend on individualized products, quality, and integrity.

Keynote Presentations

Sanofi provided a look into the future of biopharmaceuticals, which represent the fastest growing sector within pharmaceutical drugs. Merck highlighted the challenges posed for quality and compliance by the need for data integrity on all levels of the value chain. Pfizer completed the picture of industry challenges by describing the need for a new quality culture in companies that includes all employees in a comprehensive quality team.

Conference Tracks

The conference itself provided a platform for the latest tech trends, regulatory

updates, and developments in production facility design. Regulators and legislators from the Medicines & Healthcare products Regulatory Agency (MHRA) and EMA were present. Conference attendees could choose between four education tracks.

Regulatory Trends and Developments in Europe and Beyond provided a forum for industry and regulators to discuss the implications of the revised European Commission's GMP Guidelines, in particular Annex 1 "Manufacture of Sterile Medicinal Products." These standards and rules for manufacturing drugs in aseptic conditions are among the most complex regulations for our industry, with the most stringent provisions and highest impact on cost and quality oversight. This track also delved deeply into the hot topic of drug shortages and included an update on the ISPE Drug Strategy Prevention Plan (DSPP), which was created to address the manufacturing and quality issues that cause shortages. The development from guidelines to implementation is an iterative process, and discussions like these are helpful for both engineers and regulators, who are able to learn about daily industry practice.

Managing Quality Under the New Paradigm addressed the state of life cycle CMC management and its role in quality systems, including inspections, audits, findings, best practices, and how to respond to an audit or a US Food and Drug Administration (FDA) warning letter. There was a good discussion on the growing role of what is known as "quality by design" as the standard for new drug development and also within the life-cycle management of legacy drug products.

Facilities of the Future was popular with process engineers and production teams. Innovations in process technology were discussed, such as continuous manufacturing, advanced aseptic processing, lean GMP operations, and quality by design. Highlights included discussions on how to make facilities flexible and implement lean production; the impacts of regulations on facility design; the increase in mid-size production facilities; and the rise of single-use technology, which complements the rapidly growing biotech sector.

Supply chain integrity presentations outlined the provisions that regulators and legislators have taken to protect the supply chain from counterfeit medicines, including, for example, the use of 2-D barcodes on products, which can be read at a pharmacy or at any stage of dispensing.

Looking Ahead to March 2016

At the conference in 14–16 March 2016, attendees can expect to gain insight into emerging developments in regulations and their practical implementation via good engineering and process technology, innovation technology, and quality control that will enhance productivity. The conference will have an executive forum, high-level keynote speakers, the conference tracks, a poster session, and optional plant tours. As usual at ISPE, you will meet exhibitors presenting innovative solutions for process technology and engineering.

One of the hot topics will be the FDA initiative on metrics. Classical lagging indicators on performance are no longer sufficient; there must also be a focus on leading indicators to bring more transparency to the measurement of the company culture. The means of measuring culture using these survey-based metrics will require lots of discussions.

REGISTER ONLINE

Secure your place at the 2016 ISPE Europe Annual Conference as soon as registration opens, in November 2015. For more information, contact us at ispe@eurokongress.de.

ISPE BOSTON AFFILIATE NEWS

John E. Bournas to deliver keynote address at Boston Product Show 2015

The Boston Product Show 2015 has announced that ISPE President and CEO John E. Bournas will be the keynote speaker at this year's event, which will take place on 7 October 2015 at Gillette Stadium in Foxborough, Massachusetts.

Now in its 24th year, the Boston Product Show is recognized in the pharmaceutical industry as an outstanding one-day life sciences show. The show is free to attend, including no-cost parking, food and seminars, and attracts more than 2,500 ISPE members and non-members annually. Mr. Bournas will deliver the Keynote Address during the morning's plenary session.

"This is our flagship event and all the revenue generated allows us to do many worthwhile things for membership throughout the year such as educational sessions, student activities and social events," said Mark Levanites, Product Show Committee Chair at the Boston Area Chapter.

Revenue is generated at the Product Show though the product showcase, where more than 375 vendors are expected this October. Like last year, this year's show will also include a career fair with leading firms in the bio-tech and pharma industries, including live interviews and job networking. In addition, each year the Product Show provides an extra perk for football fans with an autograph session with a member of the New England Patriots, whose home field is Gillette Stadium. This year's player attendee will be cornerback Malcolm Butler, who famously made a game-saving goal-line interception with 20 seconds left in Super Bowl XLIX, which assured the Patriots the championship.

The event is organized annually by the Boston Area Chapter of the ISPE. Founded in 1992, the Boston Area Chapter is one of the ISPE's largest and most active Chapters and has been voted the ISPE's "Chapter of the Year" in each of the last four years. Representing 1,700 Members in a swath of New England centered around the Boston/Cambridge biotech hub, the Chapter provides an exciting array of educational, career development, networking, and recreational opportunities.

Over the years, the Chapter has experienced steady membership growth with a noted spike when they merged with the now defunct New England Chapter.

"We have a very dedicated base of volunteers that are hard-working, determined and passionate about the ISPE," said Boston Area Chapter Manager, Amy Poole. "When we took on the New England Chapter members, we immediately formed a task team to make sure that we served those members. We launched a year-long program to simulcast to those remote areas so that people don't have to travel to Boston to attend our educational sessions."

The Chapter has a special relationship with its younger Members, with unique activities and educational programs designed just for them. Student Chapters active on the campuses of local colleges and universities and an exciting and dynamic Young Professionals group ensure that Chapter activities cater to the needs of Members new to the world of pharma and biotech.

The Boston Area Chapter is a volunteer organization led by an elected Board of Directors and seven committees, each responsible for one of the Chapter's core activity areas. The Board defines the Chapter's overall vision, mission and goals, while the committees develop and execute the Chapter's activities. "It really is the strong group of volunteers that make this all possible. You put a task in front of them and they won't stop until they get it done," concluded Amy Poole.

700 PARTICIPANTS ATTEND BOURNAS PRESENTATION IN BEIJING

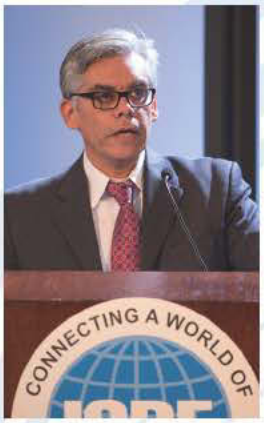
ISPE President and CEO John Bournas delivers the keynote speech at the ISPE China Annual Spring Conference on 20 April, in Beijing. Close to 700 participants also attended Bournas' presentation of ISPE global initiatives, including the Drug Shortage and Quality Metrics Pilot Program. The 2016 Conference will be held in Shanghai, China.

FOYA 2015 BANQUET

"Each winner has captured the spark of innovation and transformed it so that quality medicines are available to patients around the world." John E. Bournas

Attendees gathered on the evening of 2 June to honor the 2015 Facility of the Year category winners, a preliminary to the Facility of the Year Award (FOYA), which will be bestowed at the ISPE annual meeting in November.

More information about the awards and winners is available at www.facilityoftheyear.org.



GUIDANCE DOCUMENTS SLATED FOR PUBLICATION IN 2015

Science and Risk-Based Cleaning Process Development and Validation Baseline Guide

Applying the life cycle approach to cleaning processes and validation for pharmaceuticals, this guide is focused on the cleaning of equipment product contact surfaces, providing a framework for scientific risk-based approaches to the cleaning of manufacturing equipment and medical devices. It addresses how established and accepted risk assessment methods can be used to develop health-based limits, and provides a new approach to meeting regulatory expectations for cleaning.

Sustainability Handbook

In current phrasing, "sustainability" refers to the wide range of measures considered necessary to help avert issues associated with climate change and an increasing world population. This handbook has been written around the premise that there is a viable path to achieving sustainability that responds to all of the precepts of the life sciences industry. Key objectives include providing a global pharmaceutical sustainability baseline for the life-sciences industry, as well as promoting the development of sustainability policies and guidelines that apply to specific organizational needs. Intended for use at the front end of projects, it is designed to provide information that will be useful to the project team in understanding sustainability criteria. This handbook is also provides information that may be useful in the development of new projects, e.g., Greenfield, Brownfield, or retrofits.

Operations Management Good Practice Guide

This Good Practice Guide is intended to offer a framework for the management of pharmaceutical operations, provide a structured description of processes and technologies within the pharmaceutical industry, and identify and develop industry good practices. It addresses all operations along the supply chain, from the selection of raw materials to the distribution of final product, and also covers how pharmaceutical systems can be organized and operated to guarantee the production, storage, and distribution of products while ensuring product quality throughout the supply chain. Industry professionals and stakeholders will have the opportunity to build and use a common language and learn how to use generic and specific tools while acquiring a deep understanding of the Operations Management processes and supporting technologies.

Risk-Based Manufacture of Pharmaceutical Products, 2nd edition

Updated to align with the 2014 revisions to the EU GMPs, this Baseline Guide provides the framework for a risk-based approach based to manage the risk of cross-contamination in the manufacture of all classes of pharmaceutical products. The guide is designed to give professionals in the pharmaceutical industry a consistent approach on setting acceptable limits to assess the potential of cross-contamination to cause an undue risk to patient safety. This approach is intended to allow manufacturers to implement appropriate controls to facilitate safe and affordable drug product without overengineering.

The principles described in this guide can be applied to large- and small-molecular-weight APIs, preclinical and clinical materials, and commercially marketed products in all dosage forms. Although its primary focus is the GxP issue of cross-contamination, industrial hygiene issues are mentioned where appropriate to highlight similarities and differences between the two areas of concern.

Controlled Temperature Chamber (CTC) Mapping Good Practice Guide

A controlled temperature chamber is a unit, equipment, or room in which temperature of an interior chamber is controlled, maintained, or regulated to specific user requirements. This guide provides guidance on good practices for mapping controlled temperature chambers, warehouses, and refrigerated storage areas used to store raw material, work in progress, or finished product and which operate under current good manufacturing practice. Expanding on the ISPE Concept Paper "Controlled Temperature Chamber Mapping," the guide includes topics such as commissioning, testing strategies, acceptance criteria, qualification approaches, system monitoring, operational issues and periodic review.

Decommissioning of Pharmaceutical Equipment and Facilities Good Practice Guide

Decommissioning is a process to remove something from active status; this includes putting facilities or equipment into storage, demolitions, or the closedown of a pharmaceutical or medical device facility. Each of these processes must be managed in a planned, controlled, and cost-effective way that ensures a consistent supply of product for patients and positive future for employees. Intended as a "one-stop shop" for basic information required for the decommissioning of equipment or facilities and the disposal of assets ranging from a single item to a whole facility, the guide compiles advice and experience from a wide range of people in the industry to help readers benefit from their lessons learned.

Sampling for Pharmaceutical Water, Pharmaceutical Steam and Process Gases Good Practice Guide

Covering the critical utilities of pharmaceutical water, steam, compressed air and process gases, this guide applies to manufacturers of pharmaceuticals, medical devices, biologics, cosmetics, and related products as well as equipment manufacturers, vendors, and other industries outside of the pharmaceutical world. This guide applies to all aspects of sampling from valve design, the number, location, and placement of sample valves, sampling technique, frequency, and sample storage, including delivery to the testing lab. Intended as a single-volume reference for standards and best practices, the guide aims to establish good practices to maintain pristine samples and to avoid contamination from error, human contact, and atmospheric or environmental conditions that can result in costly out of specification work and production stoppages. The guide is expected to benefit laboratory, QC/QA, and operations personnel.

Coming in 2016

Some of the first documents expected to publish in 2016 include:

Oral Solid Dosage Forms Baseline Guide, 3rd edition

Management of Engineering Guidance Documents Good Practice Guide

IT Infrastructure GAMP Good Practice Guide, 2nd edition

ISPE QUALITY METRIC INITIATIVE. Report from the pilot project: wave 1

ISPE has been leading the charge to bring industry and regulators together to discuss quality metrics ever since it was brought to the forefront of industry thinking in the Food and Drug Administration Safety and Innovation Act (FDASIA).

ISPE has been at the forefront of gathering clear and objective data through its Quality Metrics Pilot Program. The new ISPE Quality Metrics Initiative Pilot Program–Wave 1 Report contains critical learnings on quality metrics using real data provided by 44 sites from 18 companies – a first for the pharmaceutical industry. Wave 1 included questions on process capability similar to those being considered by FDA as well as a comprehensive survey of quality culture and its impact on quality performance.

ISPE Quality Metrics Wave 2 Study Underway

A Wave 2 of the pilot has commenced, which will enhance understanding of relationships revealed in Wave 1. Recruiting for Wave 2 is currently underway and provides participants experience in preparing for the logistics and efforts associated with gathering of product-based data, including the FDA proposed metrics set. Feedback from Wave 1 highlighted benchmarking with peers of a site's performance as an important output.

For more information on the Pilot Wave 2, contact qualitymetrics@ispe.org.

ISPE will present early insights from Wave 2 of the Pilot and its response to the FDA Guidance during the 2015 ISPE Annual Meeting to be held 8 – 11 November in Philadelphia, Pennsylvania.

VISION BEGETS INNOVATION

Unveiled at the FOYA Banquet held 2 June in Washington, DC, FOYA's new visual identity conveys the program's renewed focus on innovation and its distinctive place in our industry.

"We wanted a visual identity that reflected the many facets of FOYA as well as the collaboration required to achieve success and win an award," said Shane Osborne, vice-president, membership and marketing communications. "We also wanted a symbol that is unique and represents the innovation that is at the heart of FOYA."

As FOYA enters its 12th year, it carries ISPE's hope that our vision of a world without drug shortages will inspire engineers around the world to find solutions.

FOYA 2016
Facility of the Year Awards

ISPE
AFFILIATE AND CHAPTER CHALLENGE
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through recruiting and retention

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Highest YP Growth Percentage

PRIZE #3:
Free 2016 Annual Meeting Registration a $2,500/€1,500 Value
to use as a prize at a local event
Topmost 2015 Annual Meeting Attendees
as a percentage of Affiliate/Chapter membership

Prizes will be awarded in three Affliate/Chapter size categories:

- Small: 1 – 299 Members
- Medium: 300 – 799 Members
- Large: 800+ Members

One of each prize will be awarded in each of the three size categories—so every Affiliate and Chapter has three chances to win! Winners will be announced at the 2015 ISPE Annual Meeting.

For recruitment materials, tips to start your recruiting efforts and full prize details and contest rules, visit **www.ISPE.org/Challenge2015**

Laila Jallo, PhD, didn't plan on becoming a pharmaceutical engineer; she only knew she wanted to help people and have a positive impact on society. Then life's opportunities brought her down a path that allows her to inspire young minds and, perhaps, impact more lives than she could have imagined.

MEET YOUNG PROFESSIONAL LAILA JALLO, PhD

Mike McGrath

Born in Ghana, Jallo completed her undergraduate studies in chemical engineering at Kwame Nkrumah University of Science and Technology (KNUST) in Kumasi, Ghana, in 1998. She got married in 2001 and moved to the United States. It was there that she enrolled at the New Jersey Institute of Technology (NJIT), located in Newark, New Jersey.

"I was looking for whatever I could do to help people," she says. "At first, I went in to become a biomedical engineer. I didn't know about pharmaceutical engineering because it was quite new at the time and part of the chemical engineering program."

There were a few courses in the program that she didn't enjoy, but then she attended a seminar in which Piero M. Armenante, PhD, distinguished professor and director of the pharmaceutical engineering program at NJIT, spoke about pharmaceutical engineering. Jallo says that's when she knew: "I thought, 'That's it! That's where I'm going.'"

Under the mentorship of Professor Armenante and Rajesh N. Dave, PhD, distinguished professor and director of the New Jersey Center for Engineered Particulates, she completed her Master's degree in pharmaceutical engineering at NJIT in 2006. She then went on to complete her Doctorate in chemical engineering at NJIT in 2011.

While studying at NJIT, Jallo was supported by the National Science Foundation's Engineering Research Centers (ERC) program, which allowed her to meet with many pharmaceutical companies. It was also during this time that she joined ISPE as a student member.

Following a brief period of postdoctoral research with GlaxoSmithKline, Jallo was hired as an assistant professor at California State Polytechnic University, Pomona (Cal Poly Pomona) in 2012. "They hired me because of my pharmaceutical engineering background," she says. "The chemical engineering and materials department at Cal Poly Pomona is trying to diversify to bring in more pharmaceuticals and biotechnology."

When she joined Cal Poly Pomona, Jallo moved to revive the university's ISPE Student Chapter. "They had a Chapter, but it was not active. It took us a year, but we reactivated it starting with a few students and now we're trying to build it."

The focus is now on strengthening the Cal Poly Pomona ISPE Chapter. This past academic year, the Chapter was registered both regionally and nationally. Jallo continues to participate as an adviser.

The Chapter has been successful at making some local connections, but Jallo says that they don't want to be limited by geography. "As an adviser, you try to help make the link when students want to bring in speakers," she says. Now that the Chapter is a member at the regional and national levels, I'm hoping we can bring in more speakers from the industry."

In her job as an assistant professor, Jallo has found a way to contribute to the industry and to society as a whole. "When I think of the pharmaceutical industry, whatever part you play, you're going to have an immediate effect on people's lives," she says. "I'd like to encourage more students into a field like that, even though my school is mostly an undergraduate institution that focuses on other industries. Now we are trying to get students to learn more about the pharmaceuticals. It's an opportunity to go work and contribute to society too."

And there's an added bonus: Jallo enjoys California, whose climate is much closer to the climate of her native Ghana than New Jersey's is. "The weather's great here; it's hot but dry. In New Jersey, the summers are hot and humid and the winters are cold," she says with a laugh.

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Consultant Amanda Bishop McFarland Joins ValSource

ValSource, LLC, 16 June 2015

ValSource announced that Amanda Bishop McFarland has joined North America's largest independent validation services company as a consultant. Prior to joining ValSource, Bishop McFarland spent five years with Genzyme, most recently serving as Senior Continuous Process Improvement Analyst.

Bishop McFarland comments, "ValSource provides me [with] the perfect opportunity to share my QRM [quality risk management] and microbiology knowledge to influence change in our industry." She specializes in quality risk management, program implementation, partnership development, and contamination control.

Roche Employees Unite to Raise Funds for Children in Need

Roche Group, Media Relations, 16 June 2015

Roche employees participated in the 2015 Roche Children's Walk at more than 131 company sites across the world. The funds raised through the event will be used to support children in need, either in the local community or in Malawi in Southeast Africa, one of the world's least-developed countries.

"The Roche Children's Walk is a key event in our company's calendar," says Severin Schwan, CEO of Roche. "It represents our firm conviction that support for social and humanitarian programmes should be long-term and foster sustainable solutions. Over the years, the funds raised have improved the lives of many vulnerable children. We will again match the money raised by employees."

GEA Launches New Group Structure

GEA Group Aktiengesellschaft, 12 June 2015

GEA has launched the optimized new Group structure developed as part of its "Fit for 2020" initiative, marking a fundamental shift in both its internal structure and organization and its external customer relations. Starting immediately, the Group is bundling and reporting the development and manufacturing of products and the provision of process solutions in two new business areas: "Equipment" and "Solutions."

Honeywell Technology Modernizes Mill for Europe's Largest Forest Industry Company

Honeywell Technology, 11 June 2015

Honeywell Process Solutions (HPS) today announced that Europe's largest pulp, board and paper manufacturer will use HPS process automation, safety system, and manufacturing optimization technologies to modernize one of its key mills and help it meet rising demand for renewable packaging board.

Stora Enso Oyj is implementing Honeywell's technologies as part of a modernization and optimization effort at its paper mill in Varkaus, Finland. Headquartered in Helsinki, Stora Enso is the largest pulp, board, and paper producer in Europe and one of the largest in the world.

Janssen Supply Chain Expands Collaboration with Rutgers School of Engineering with $6 Million Funding Arrangement to Implement Continuous Manufacturing Initiative

Rutgers University, 11 June 2015

Janssen Supply Chain has furthered its strategic partnership with the Rutgers University School of Engineering by providing over $6 million to expand ongoing research efforts supporting the company's introduction of continuous manufacturing techniques for pharmaceuticals.

The funds from Janssen, part of the Janssen Pharmaceutical Companies of Johnson & Johnson, will increase research and development efforts at the Rutgers Engineering Research Center for Structured Organic Particulate Systems (C-SOPS) over the next several years. The Center is helping Janssen transition several products to continuous manufacturing, including developing a specially designed manufacturing line at a Janssen facility in Puerto Rico.

Shire Appoints Olivier Bohuon to Its Board of Directors

Shire plc, 11 June 2015

Shire plc announces the appointment of Olivier Bohuon to the Shire Board of Directors as a Non-Executive Director. Bohuon will also be a member of the Science & Technology Committee of the Shire Board. Both appointments will be effective from 1 July 2015.

Bohuon has served as Chief Executive Officer of Smith & Nephew plc, a global medical technology company, since 2011. He has extensive international business and leadership experience across a number of pharmaceutical and health-care companies in Europe, the Middle East, and United States. He also serves as a Non-Executive Director of Virbac Group SA.

New Synexus Board Gears Up for Expansion through Organic Growth and Acquisition

Synexus, 9 June 2011

Following the completion of the management buyout of Synexus, the new board confirms its intention to expand the footprint of the company through organic growth and acquisition.

Synexus, already the world's largest multinational company dedicated to the recruitment and running of clinical trials at its own research centers across the globe, intends to become a major player in the United States, continue to expand its existing network of sites in Europe and Africa, and develop a presence in Asia and South America.

The new board members of Synexus are Charles Woler, Chairman, and Benjamin Harrild, Hywel Evans, Ged Gould and Simon Braham, all non-executives. Christophe Berthoux, CEO of Synexus, and Paul Chambers, Financian Director of Synexus, will remain on the board.

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Allied Minds Names Kevin Sharer, Former Chairman and CEO of Amgen, to Board of Directors

Allied Minds, 5 June 2015

Allied Minds, an innovative US science and technology development and commercialization company, today announced the appointment of Kevin Sharer, former Chairman and Chief Executive Officer of Amgen, to its Board of Directors.

Sharer led Amgen for two decades, starting as President and Chief Operating Officer in 1992 and then eventually taking over as Chief Executive Officer and Chairman. Amgen has credited Sharer with an expansion that resulted in operations in 55 countries and a more than fourfold increase in revenue to almost $16 billion. During his tenure, the company received regulatory approval for drugs, including Neulasta, for preventing infections in cancer patients undergoing chemotherapy; Prolia, for osteoporosis; and Xgeva, for the prevention of bone complications, such as fractures, for cancer patients.

Körber Medipak Systems Opens New Location in São Paulo

Körber Medipak Systems, 19 May 2015

Körber Medipak Systems has opened a new location in São Paulo. Due to growing populations in Latin America, with current figures at over 600 million people, the pharmaceutical industry is recording strong growth in the region, particularly in Brazil. The services of the new location are meeting the increasing need for solutions for the pharmaceutical and biotech industries in Latin America, from Mexico to Argentina.

Change in Roche Board of Directors

Roche, 8 May 2015

Roche announced today that DeAnne Julius (66), member of the Board of Directors since 2002, has decided that she will not stand for re-election to the Board of Directors at the AGM in 2016. The Board decided that Julie Brown (53), Chief Financial Officer of Smith & Nephew plc, will be nominated for election as a new member of the Board of Directors by the AGM in 2016.

Christoph Franz, Chairman of Roche: "As a Board member and Chairman of the Audit Committee, DeAnne Julius has made important contributions to the success of Roche. On behalf of the Board, I want to express my profound gratitude for her valuable services and wish her all the best for the future." Franz added: "I am very pleased that with Julie Brown we are able to propose a leader with significant international commercial and financial experience in the health-care industry to be elected as a new member of the Board."

Finnish DNA Diagnostics Company Genoscoper to Partner with Mars Veterinary

Genoscoper Laboratories, 5 June 2015

Finland-based Genoscoper Laboratories and Mars Veterinary, a division of Mars Petcare, team up to combine proprietary genome technologies and DNA-based product solutions to advance the well-being and relationship between pets, pet owners and veterinarians through valuable insights into pets as individuals.

Genoscoper Laboratories, a Finland-based DNA diagnostics laboratory, specializes in highly developed DNA testing and is the first laboratory in the world to introduce a canine genome-wide panel-testing method that combines disease gene testing with advanced genetic diversity measurement. Mars Veterinary will integrate aspects of the Genoscoper MyDogDNA testing platform into its existing DNA veterinary products that are sold through affiliate Mars Petcare businesses, Royal Canin and Banfield Pet Hospital.

AmpliPhi Biosciences Announces Scott Salka as New CEO

AmpliPhi BioSciences Corporation, 1 May 2015

AmpliPhi BioSciences Corporation, a global leader in developing bacteriophage-based antibacterial therapies to treat drug-resistant infections, today announced that Scott Salka has been appointed as the new CEO. Salka will replace Jeremy Curnock Cook, Interim CEO and Chairman of AmpliPhi, effective May 18. Curnock Cook will remain in his role as Chairman.

"Mr. Salka's leadership will enable AmpliPhi to execute on its mission to develop innovative therapeutic solutions aimed at the growing problem of combating antibiotic-resistant bacterial infections," said Curnock Cook. "His extensive experience in building biotech companies with a focus on technology development and discovery will accelerate the progress of our bacteriophage candidates towards the clinic, and his skill set, combined with over 25 years of experience, will further strengthen AmpliPhi's position in this exciting field."

Able to handle the moving quality targets?

With ever-changing compliance rules differing globally, partnering up with a compliance specialist is key

In the new pharma reality, you need to deal with ongoing changes in current Good Manufacturing Practices (cGMP) in order to stay in compliance with regulatory expectations. Not only are regulations changing, but a growing number of countries are enforcing their own regulatory requirements. This increasingly complex set of rules and guidelines needs to be integrated in your various facilities across the globe. That is not an easy task and we know that.

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SCIENTIFIC AND REGULATORY CONSIDERATIONS FOR IMPLEMENTING MATHEMATICAL MODELS IN THE QUALITY BY DESIGN (QbD) FRAMEWORK (PART 2)

Theodora Kourti, John Lepore, Lorenz Liesum, Moheb Nasr, Sharmista Chatterjee, Christine M.V. Moore and Evdokia Korakianiti

This article is the second of a two-part series and presents points to consider for building and using models in the regulated pharmaceutical industry and offers examples of how models can play a part in the Quality by Design (QbD) framework.

A model, in general, is an alternative representation of reality. A mathematical model is a description of a system using mathematical language. Mathematical models are used extensively in process industries to describe the chemical and physical phenomena taking place during production.

The Quality by Design (QbD) framework for drug development and manufacturing is a science and risk based approach that begins with predefined objectives for meeting the desired clinical performance and emphasizes product and process understanding and process control. In the QbD framework, mathematical models can be utilized at every stage of product development and manufacturing. Models have been implemented in pharmaceutical industry for developing and controlling processes and have appeared in regulatory submissions. Models can also be indispensable for the implementation of continuous manufacturing processes. Overall, application of models throughout a product's life cycle from development through manufacturing can enhance process and product understanding. In general, these modeling approaches, some well-established in other industries26,27,28, are still evolving in the pharmaceutical industry.3,4,7,14,16

There are many considerations in the development, validation and maintenance of models depending on their use. The first part of this series gave an overview of models and showed how they fit in the QbD framework. The second part gives examples of model use in a QbD framework, provides points for consideration for the building and use of models in the regulated pharmaceutical industry.

Examples of Models in QbD Framework

Example 1: Mechanistic Model of an Epimerization Reaction

This example summarizes an experimental program intended to achieve a mechanistic understanding for an epimerization reaction used to produce a key building block of a drug substance molecule. The methodology is based on using a combination of risk assessment, mechanistic, empirical and statistical approaches to develop a robust design space.

Prior knowledge coming into this study includes the reaction mechanism, potential reaction pathways, and a risk assessment of what attributes in drug substance may be important to understand.

This information was used to develop an Ishikawa (fishbone) diagram, which provides a good linkage of desired attributes with the parameters that may influence product quality. In Figure 5, blue boxes were understood to not have interactions with other factors. In these cases, explorative experiments were conducted to achieve process understanding, and where there was uncertainty about the determination, DOE was used to confirm the absence of interactions. The orange boxes were determined to have variables with a significant potential to interact, and in these cases, DOE was used to achieve greater process understanding.

The remainder of this discussion focuses on the epimerization reaction. The epimerization changes the stereocenter on the primary amine in the reaction scheme shown in Figure 6. It is important to control the cis starting material, so reaction conversion requires thorough understanding. Further, downstream processing requires a cis:trans ratio of 19 or higher in order to achieve target purity and maintain target productivity. The conditions in the downstream crystallization of the final intermediate can be tuned to accommodate variable cis:trans ratios, but 19 was chosen as a minimum optimal point for productivity purposes. Factors influencing reaction outcome are also shown in the Figure 6.

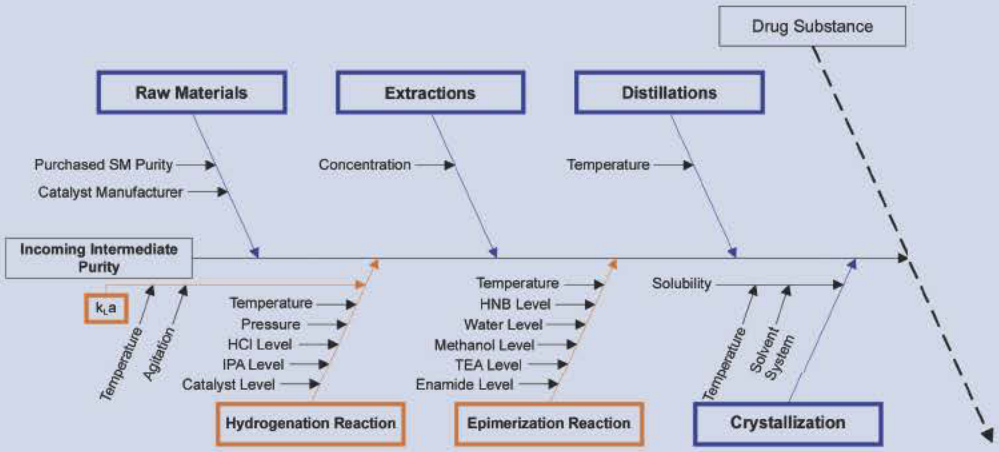
The sensitivity analysis was conducted via a 2^{6-2} (1/4 fraction) factorial design with three center points (19 total runs) to study the epimerization. The ranges selected for testing were informed by prior experience with the reaction (i.e., proven acceptable ranges) with the interest in providing maximum manufacturing flexibility. The results are shown in Figure 7. Note that in this case, HNB and temperature were identified as the most significant factors.

Further analysis and efforts to fit the statistical model with reaction data (including center oints) showed that there was significant curvature in the model - Figure 8. The analysis of the temperature as a variable revealed significant non-linearity, as the predicted behavior (see trend lines in Figure 8) did not align with the data observed (see individual data points in Figure 8). Given that temperature was a significant factor, and that chemical reaction theory holds that reactions run at lower temperatures require longer periods of time to achieve equilibrium, the curvature was hypothesized to be a consequence of the time-temperature effect on conversion. Note that the DOE could have been established using criteria that could have addressed the curvature issue; however, an alternative course was taken here as an illustration of how first principles and DOE can be used in combination.

In this case, a chemical kinetics model was designed and fit with commercially available kinetic modelling software. This model initiated on first principles allowed explanation of the time temperature issue noted above:

$$[Cis] + [\mathrm{HNB}] \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [Cis + \mathrm{HNB}] \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} [Trans + \mathrm{HNB}] \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} [Trans] + [\mathrm{HNB}]$$

Figure 5 Ishikawa Diagram describing multiple unit operations contributing to drug substance attributes.



The abbreviations in this figure are as follows: SM = Starting Material, KLA: Measure of liquid/gas mass transfer at phase interface, HCl, IPA, HNB, and TEA are all specific reagents.

The revised model in Figure 9 showed excellent agreement with the data, and was found to be capable of extrapolating to analyze different reaction time endpoints.

Figure 10 shows a plot of this new information in the same format as the interaction graph shown above; much better agreement with the experimental data and a much better curve fit is obtained.

As a result of the refined model shown in Figure 11, the epimerization factors HNB stoichiometry and temperature were constrained in order to ensure sufficient conversion while retaining the standard high productivity crystallization and rejecting remaining incorrect diastereomers.

The number of lots produced in support of acquisition of process knowledge, combined with support of clinical studies is typically too small to generate error bars in the traditional sense. This limited data was compensated for by running Monte-Carlo simulations over the proposed design space. The inputs included the distributions from the DOE data combined with random noise around the DOE model. The simulations aligned very well with pilot scale and early manufacturing scale lots, and it was concluded that the process as designed will achieve the target cis:trans ratio of 19:1 with no special adjustments. Figure 12 shows the range of outcomes from the simulation.

Example 2: Feed Forward Control Based on Latent Variables

The next example demonstrates the use of feed forward control action within a design space. A model that describes the design space for the entire tablet manufacturing process as shown in Figure 13 can be derived by relating quality to both the raw material properties and the process parameters of the unit operations. Figure 13 depicts a database where each row represents a batch and the corresponding columns include the process conditions and quality experienced by the material as it is processed through the units. The empirical models derived are causal and based on carefully Design of Experiments (DOE). Such modeling provides

Figure 6 Representative structures of cis (at left) and trans (at right) diasteromers

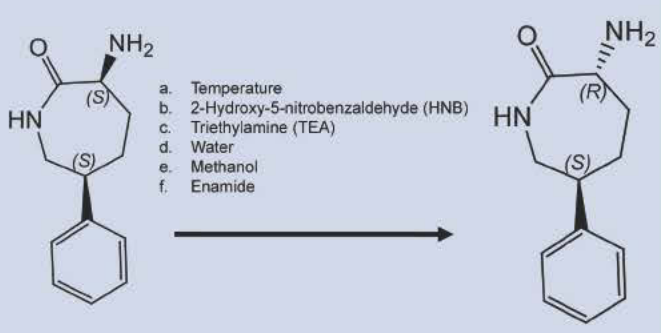
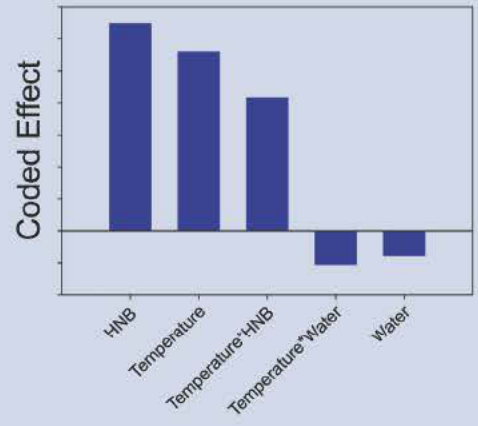


Figure 7 Sensitivity diagram for coupling reaction



flexibility in the control strategy, because it allows for real time adjustments within the design space.

Figure 14 illustrates a feed forward control scheme for Unit N based on input information on the "state-of-the-intermediate product" from unit N-1. The settings are calculated and adjusted such that the target value for Quality Y is met. A multivariate model was built to relate product quality to the process parameters of unit N and the "state-of-the-intermediate product" from Unit N-1. From this model, a quantitative understanding was developed showing how process parameters in N and the state-of-the-intermediate product from N-1 interact to affect quality. Using multivariate analysis assures that the multivariate nature of quality is respected. In this case, the five batches that project in an area within the red circle (two blue batches and three green) have the same state of intermediate product – meaning that up to that time the five batches experienced same raw material and processing conditions. The green batches, when processed with typical operating conditions in Unit N, marked green, resulted in quality below average. By taking a feed forward action and processing them with different operating conditions, marked blue, in unit N, the quality improves with values above average.

Figure 8 Statistical analysis of conversion data set

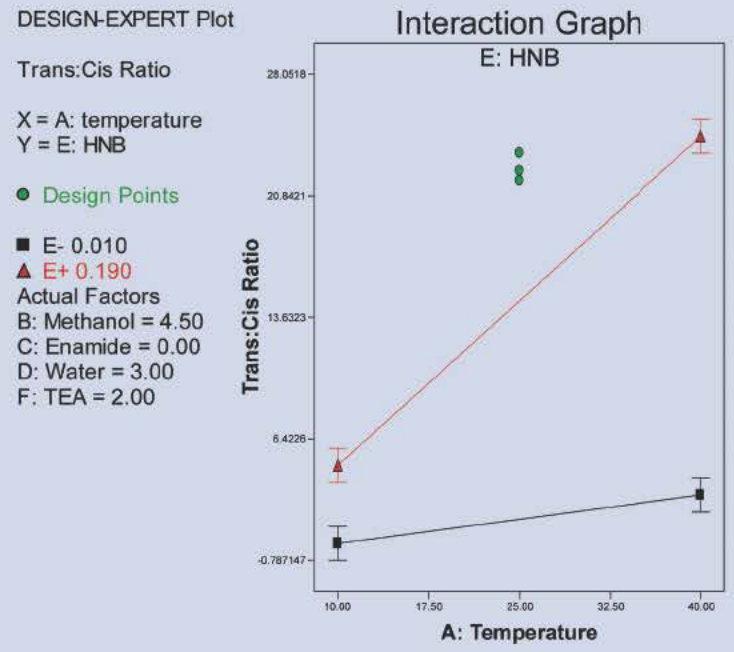
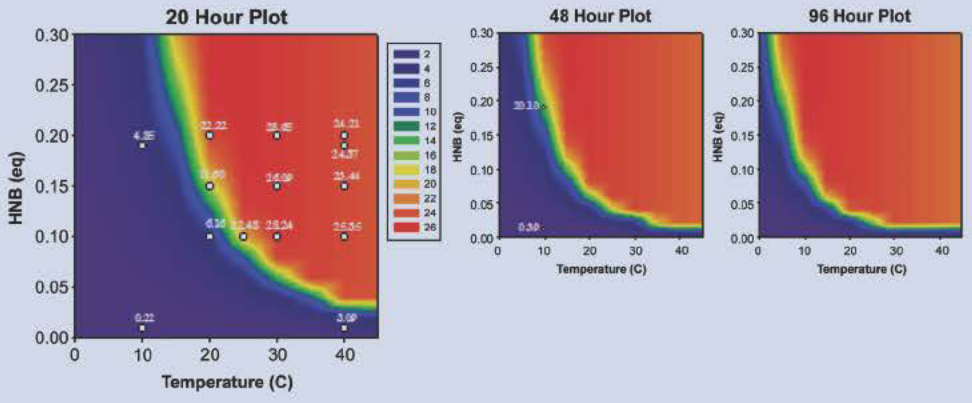


Figure 9 Prediction of reaction completion time as function of HNB and temperature



Example 3: Multivariate Process Control Applied to a Granulation Process

In Figure 15, MSPC was applied to a high shear wet granulation process. The granulation process consists of different phases, of which only the quality relevant parameters were considered for modeling. The four phases taken into account for modeling were:

1. Pre-mixing: the dry powder is stirred for a fixed period of time.
2. Water addition: the binding solution is continuously transferred to the granulation vessel.
3. Rinsing water addition: the rinsing water is transferred to the vessel.
4. Kneading: the granulate is kneaded for a fixed time.

Different process variable were included into the model, which can be divided into the following different categories:

1. Speed of stirrer and chopper
2. Power consumption, torque and temperature of the granulate
3. The properties of the pump and the addition rate
4. Environmental condition as atmospheric pressure and bowl temperature

Figure 10 Application of chemical kinetic model to conversion data set

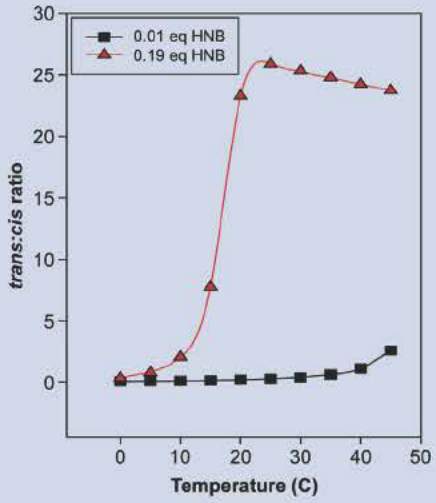


Figure 11 Design space for reaction parameters

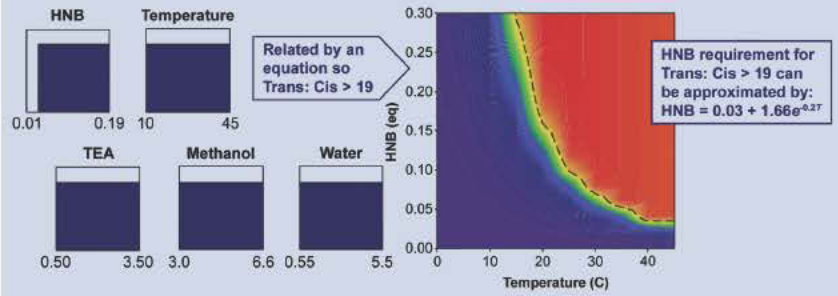
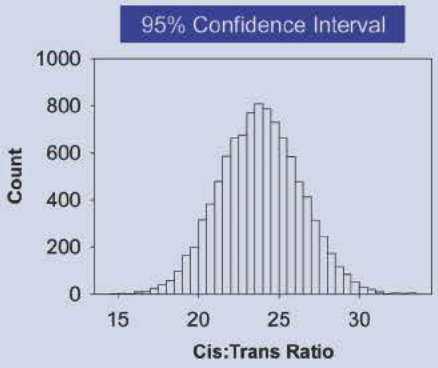


Figure 12 Prediction of cis:trans outcome from Monte Carlo analysis



The aim of MSPC is to capture the current state of the process and to recognize whether there is a tendency to deviate from typical behavior, in a statistical sense.

Figure 15 shows a latent variable, in this case the score of the first principle component derived from multivariate analysis (PCA) of process data, displayed as a function of time. The alert limits highlighted in red are set at average score ±3 standard deviations at each time point. In this particular case, it was deemed that the first principle component is sufficient to detect atypical process behavior.

By the formation of a process signature, the process dynamics and variability can readily be visualized. For instance, while the dry mixing phase is a static process, the solution addition phase shows a linear increase of the average score over time. Furthermore, the variability at the start and end of a phase is more pronounced than the middle of the phases.

Figure 13 Layout of database for an integrated design space

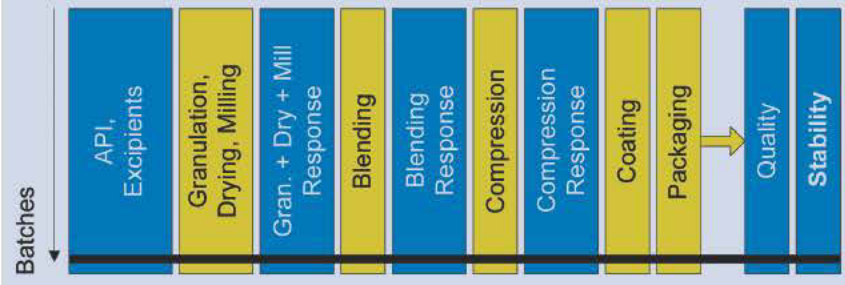


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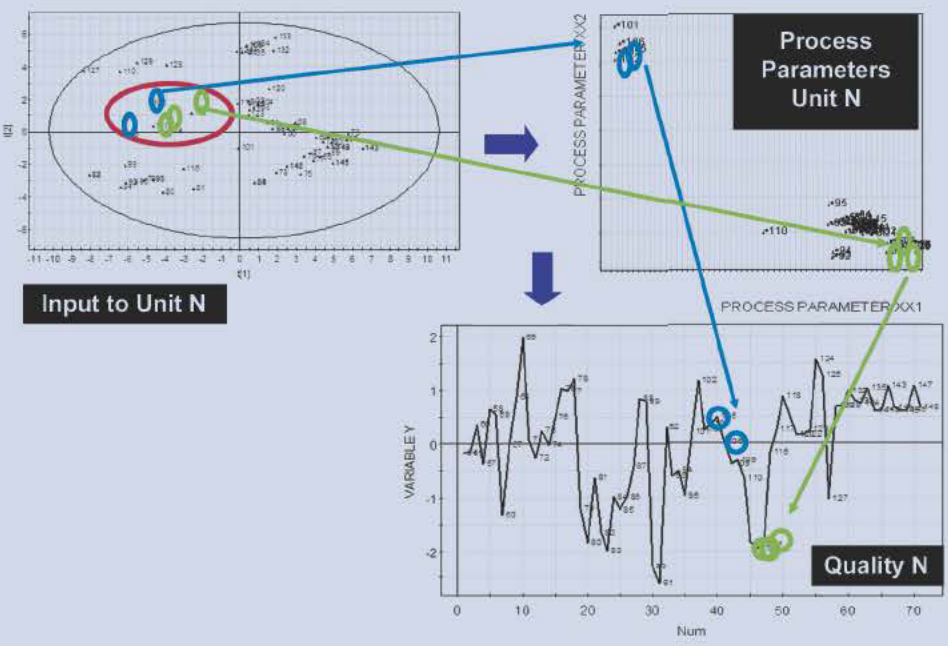
Figure 14 Feed forward control action using information from multivariate projection space.[9]



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The MSPC charts described in this example are one of the alternative ways of creating and presenting monitoring charts for batch processes. A detailed discussion of the analysis and MSPC of batch processes and the available methodologies as well as the advantages and disadvantages of certain approaches, can be found in the Kourti[19] and Wold, et al,[20] articles.

The Lifecycle of a Model in a Production Environment

As evident from the section on Overview of Models, different types of models are used at various stages of the lifecycle of the product, from product development to scale-up, and through continual improvement. Each model has its own lifecycle, depending on the function it performs. The development of the model is just the beginning of its lifecycle. The validity of the model should be ascertained during its lifecycle, from development to external validation and during implementation, with the rigor of the activity being commensurate with the purpose of the model. The implementation of models in a production environment inherently has a number of challenges and obstacles which should be anticipated prior to their efficient and successful application. For models that support PAT for example, achieving a sufficient predictive performance with the given constraints of the eligible methodology is one of the challenges. Beside the scientific constraints, the methods have to be validated to demonstrate that they are comparable with conventional methods usually performed on the finished product in the Quality Control (QC) labs. The general need for the validation of these process models stems from the fact that the information and outputs retrieved from the model will be used for quality decisions to release the product.

The lifecycle of a model involves the following steps which are iterated as necessary:

- Model development
- Model validation (includes internal and external validation)
- Model implementation
  - Comparing real time results with the reference method; this is referred sometimes as Parallel Testing Phase.
  - Release for usage
  - Model maintenance (which may necessitate model update)

The phase prior to the real time implementation phase is often referred to by other industries as the "*off-line phase*." The following statement relates to the implementation of multivariate statistical models: "*The off-line phase of development is essentially the work done to determine the feasibility of meeting business objectives through the application of Multivariate Statistics (MVS) technologies. The off-line phase can be broken down into the following tasks: data selection and preparation, model development, and evaluation. Each step is done keeping in mind the original objectives and incorporating as much knowledge of the process as possible.*"[21]

Model Development

Model development typically includes the steps listed below. These steps are usually executed in a sequential manner, but often it may be necessary to return to an earlier step, thus imparting an iterative nature to this process. The general steps to consider for model development are:

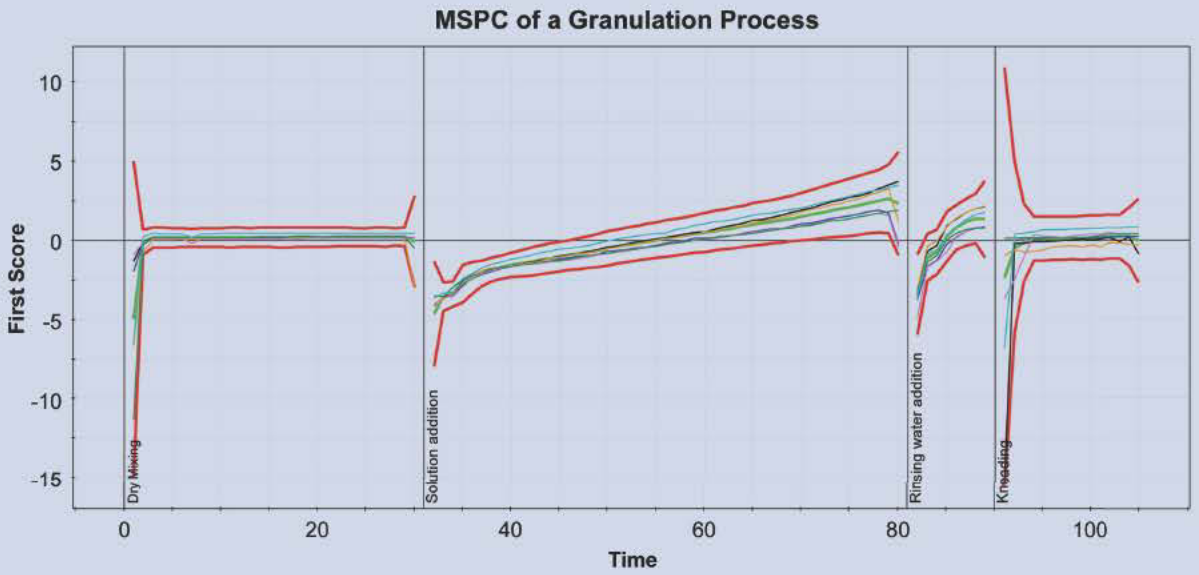
a. Defining the purpose/objective of the model and the acceptance criteria.

b. Deciding on the type of modelling approach (e.g., first principles, mechanistic, empirical, or hybrid) and experimental/sampling methodology to support the model's development.

c. Defining the variables to include in the model, which can be based on risk assessment, scientific and process knowledge and experience.

d. Understanding the limitations of the model assumptions in order to correctly design experiments, to interpret the model results, and to help develop appropriate risk mitigation strategies.

Figure 15 Assessment of different granulation batches as a function of time in different phases by a MSPC model



e. Collecting experimental data to support the model development. These data may be collected at development scale or at commercial scale, depending on the nature of the model. Since the performance of the model is contingent on the quality of the data that was used to derive the model, it is important to ensure that appropriate data is used for model building.

f. Defining any pre-processing of the data or variable transformations. For example, for MSPC models for a jacketed reactor, rather than using variables like the input (T_{in}) and output (T_{out}) temperatures and the flow (F) of the cooling liquid, one may use the calculated variable (T_{in} - T_{out}) * F which is related to the heat content and should not exhibit seasonal fluctuation like the temperatures.

g. Developing models, based on the scientific understanding, the collected experimental data, and the objectives of the model.

h. Assessing the validity of the model with internal metrics and external validation, as applicable, prior to implementation. Validation metrics are discussed in detail in the next section. This stage typically includes assessing potential limitations, risks gaps and mitigations. Risk analysis can be used to set thresholds of methods and acceptance criteria for validation. Other points to consider at this stage are:

- **Uncertainty:** for both mechanistic and empirical models, significant uncertainty may exist in the model predictions, due to the following reasons: (a) underlying assumptions and simplifications used in model derivation, (b) variability (noise) in measurements and (c) error in the model fit. When developing models, it is important to evaluate the uncertainty in the model, assess what uncertainty the model can tolerate and then define an approach to mitigate the risks imparted by the uncertainty. For example, evaluation of uncertainty in a design space model can lead to a more robust design space and can help identify appropriate risk mitigation steps when moving to areas of uncertainty.
- **Range of Variables:** ideally, the range of variation of parameters for model development and validation should be representative of the expected range of variation of these parameters during model implementation (e.g., conditions that would generally be expected during operation including the variability anticipated in future production). The importance of the range of variables for data based models has been stressed by practitioners in other industries. "*In the case of a predictive model, the training set should span the operating space in a balanced way. Balancing the way data are collected requires care to ensure that certain regions in the operating space are not over or under represented in the training set in the overall set of observations. The number of observations to be taken from a particular region of the operating window will vary depending on the application.*"[21]

i. Documenting model results including initial assumptions and plans for transfer to commercial scale and maintenance and update of the model throughout its life cycle, as applicable. Model maintenance considerations are imperative for high impact models. The level of documentation depends on the impact of the model, as is discussed later.

Scale-Up and Transfer Considerations
When the objective is to implement a model that was developed at pilot or laboratory scale to commercial scale or to transfer a PAT calibration model to another instrument, the scale-up/transfer issues may be addressed in one or more of the following ways:

Scale-Up of Design Space Models: a scale-up approach can include, but is not limited to:

- Using appropriate scale-up correlations
- Defining a model in terms of scale invariant or dimensionless parameters
- Implementing an enhanced monitoring/testing scheme of sufficient duration to verify the quality of product manufactured when moving to areas of design space not previously verified at commercial scale.

PAT Models: A calibration model developed at the laboratory instrument and process equipment should be verified when transferring to the commercial scale. For situations where commercial conditions cannot be simulated in laboratory or pilot scale data, the method should be developed based on full scale data.

Model Validation
In general, validity of a model's performance needs to be established prior to its implementation for decision making purposes. The goal of validation, whether it is applied to a process or an analytical method, is to demonstrate that the process or the method is suitable for its intended use in the intended process conditions and scale. In this section, the concept of validating models will be discussed, highlighting the different aspects to be considered. Data considerations for model development and validation are also discussed.

Considerations for first principle models, or phenomenological models, follow a similar thought process to that developed for empirical modelling, but with a number of major distinctions. When a system can be described accurately with existing tools that exemplify thermodynamic and rate phenomena, those tools can usually be successfully leveraged to describe the system. As a consequence, these models would not typically require the same level of validation as an empirical model. Often, there is no basis for using an independent data set, as the verification has been done through the prior knowledge and widespread use. Thermodynamic functions are state based, and as a result, tend to be path independent.

As an example, in drug substance processes, equilibrium process conditions are widespread. A phase diagram describing crystal form as a function of composition or temperature is a classic case. The model is developed based on existing equilibrium theory. During model development, the model is often tested at extreme conditions, to evaluate its response to such conditions; however, once developed, the model would be expected to behave consistently across scales given compositional control within the range shown to deliver the desired crystal form. A similar case is the use of kinetic models, which by their nature relate system concentrations, temperature and time and more.

Internal Validation
In the development phase, after the model generation, internal validation assessment is typically carried out to verify the performance of the model. The model prediction is compared to actual values with data available at the time of method development.

The data set used for model generation is referred to as the *Calibration Set or Model Building Set or Training Set*.[21] This set should include the variability anticipated in future routine production and is representative of the commercial process (e.g., equipment, steps). When the model is used for prediction of a property (i.e., water content or assay), data covering the expected range of variability should be used. When the model will be used for MSPC (that is, to detect variability beyond common cause variation), only data of compliant batches which are representative of typical operating conditions should be used to define the control limits.

The data used for verifying the model performance during the development form the *Internal Validation or Test Set*. The confirmation of the model by these data is referred to as internal validation. These data are excluded from the dataset available for modelling and are used as an independent data set for a confirmation of the model with respect to accuracy and robustness. For some processes, there may not be sufficient data available to exclude them from the data set for model building since all data are needed for establishing the model. In this case, techniques such as cross validation, random (Monte Carlo) re-sampling, or boot strapping[22] can be used.

For mechanistic models, when DOE are performed for the calculation of constants or coefficients, internal validation also should be performed.

External Validation
External validation is performed with an independent data set after the model is completed and fixed. This data set, called External Validation Set or Validation Set, contains data that were not used to build the model. Verification of the model with an appropriate dataset is especially important to demonstrate robustness – Figure 16.

The experimental procedures, parameters to be validated, and acceptance criteria that must be met should be defined in advance. In a compliant environment, they are typically defined in a validation written protocol, issued prior to the execution of the validation, and maintained within the firm's quality system. Since the model physically exists in the form of the digital data, the model and the related data methods are typically "locked" before external validation to prevent any modification of the methods.

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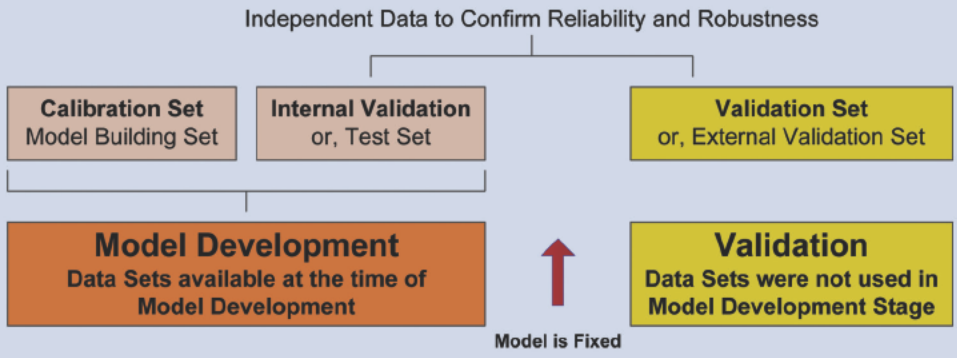
Figure 16 Categories of data involved in development and validation phase



The amount and type of data that should be included in the external validation set depends on the model that is validated. The user should consider both the number of batches required and the range of variation that will be covered. A predictive model that is expected to be valid for the entire design space could be tested with bracketed studies or by covering higher risk areas. For a statistical process control model, the model's ability to detect abnormal situations should be part of the external validation, along with checking that the model is correctly compliant and representative of the batches being manufactured. Unless abnormal situations have actually occurred and data exist that can be utilized to test the model, disturbances may be "altered artificially" to create such cases. This can be achieved by creating off-line artificially altered process data to investigate if the model detects the deviations.

Validation Parameters and Acceptance Criteria

In general, the validation parameters and the related acceptance criteria strongly depend on the intended purpose and scope of the model. For predictive models of quality attributes, the acceptance criteria depend on the predicted quality attribute and should be defined as part of the established validation procedures and control strategy associated with a thorough risk analysis. For example, the acceptable difference between the model prediction and the values resulting from an analytical measurement could be different for a dissolution model (with higher inherent method variability) than for an assay model. Examples of acceptance criteria for validation of empirical qualitative and quantitative models are given in Table A.

Qualitative Models or Pass/Fail Models

These are models where certain estimated "metrics" are tested against limits. This category includes, but it is not limited to 1. MSPC models, where metrics like Scores, Hotelling's T^2 or the Residuals (DmodX or Squared Prediction Error-SPE) are checked against limits,[9] 2. models like the Caterpillar Algorithm for blending end point detection[12] where end point has been achieved provided that a metric falls within limits, and 3. identification models. For qualitative or pass/fail models, specificity and robustness are the main parameters to be confirmed and tested. Compliant batches should fall within the defined threshold or control limits of the specific metrics of the model.

The robustness for MSPC models used for process monitoring can be assessed by evaluating the performance during a longer period of time where it is observed how the model is coping with the natural variability of the process. For these models it should be demonstrated that they are capable of flagging batches that are outside the range of previous typical operation. For these types of models, robustness test typically cannot be designed at the time of launch and set up due to financial impact of producing batches under non normal conditions. It is possible sometimes to test the capability of flagging abnormalities, by deliberately configuring process data off -line to simulate a process deviation. The outcome when these data are applied to the model can then be evaluated. For NIR models, robustness can be tested during development by varying different measuring conditions, operators, presentation to the probe.

Quantitative Models or Predictive Models

For quantitative models (e.g., predicting potency of a tablet using NIR or predicting dissolution), the accuracy can be determined by comparing the predicted values to the reference method. The prediction error of the model should be comparable to the reproducibility of the reference analytical method. For the assessment of linearity, the accuracy (e.g., the bias to the reference) over the expected range and the random distribution of the residuals within a defined bandwidth are reliable indicators. As part of the proof of specificity, the ability to avoid false positive results can be demonstrated. A test is often performed to assess whether the new point belongs to the same population as the points used to develop the model; this is done by assuring that both Hotelling's T^2 and DModX (or SPE) of new point are within limits. The idea behind this approach is that the outlier diagnostics, which are used as a filter prior to the application of the model, are specific enough to detect/discriminate data which are atypical compared to the data which were used for modeling and which are representative. If these diagnostics are detecting something unusal, e.g., in the form of Hotteling's T^2, SPE, the model should not be applied in order to avoid false positive or false negative results. In analytical testing in the lab, this is usually performed using special samples either spiked or adjusted to a specific concentration. For a process model applied on-line in production, this is less feasible due to financial restriction of manufacturing non-compliant material.

Table A Examples of acceptance criteria for validation of empirical qualitative and quantitative models.

EXAMPLES OF QUALITATIVE MODEL VALIDATION

Validation Parameter	Specific Metrics	Acceptance/Rejection Principles
Specificity/Selectivity	Membership criterion, e.g. Hotelling's T^2 or Residual analysis	Points falling within predefined limits are accepted Points falling out of limits are further analyzed for their root cause
Robustness	Number of batches, over a certain period of time, large enough to cover typical variability related to raw materials, environmental and process influences	Batches exhibiting the typical common cause variation of the process are accepted by the model

EXAMPLES OF QUANTITATIVE MODEL VALIDATION

Validation Parameter	Specific Metrics	Acceptance/Rejection Principles
Selectivity/Specificity	Testing Model Applicability: check that the new data come from the same population as those used to develop and validate the model	Batches that reveal an unusual situation or are not produced at expected normal operating conditions are flagged and filtered out prior to quantification
Accuracy	Root Mean Squared Error of Prediction (RMSEP/BIAS to the reference method)	Comparable to established acceptance criteria for conventional method transfers taking the inherent precision of the two methods, (i.e. the model and the reference into account)
Linearity	1. Distribution of residuals 2. Accuracy across the range	1. Are randomly distributed 2. Residuals stay within a defined bandwidth over the complete range
Precision	Repeatability Reproducibility	For batch model, sometimes repeatability or reproducibility is not possible to measure as a batch is unique and multiple measurements are not feasible
Robustness	Number of batches over a certain period of time covering environmental and process variability (e.g. different raw material batches)	Batches exhibiting the normal variability of the process are accepted by the model with no impact on the predictive performance

For mechanistic models, the extent of testing would be expected to be consistent with the parameter/attribute being modelled and the importance of the model. For example, reaction rate, phase diagram, distribution coefficient, all would have different metric and acceptance criteria.

The robustness and stability of the model can be assessed by having a sufficient number of data available, which were produced over a longer period of time covering anticipated variability in environmental and process condition, e.g., different batches of incoming material and seasonal changes in air humidity. Another way could be to assess the impact of potential factors identified previously in the frame of a risk assessment on the performance of the model using DoEs.

Implementation Phase

Subsequent to validation, the model is integrated into the company's quality systems and there is on-going evaluation as part of regular maintenance. For example, the implementation of a high impact model in a production environment consists of verification at production scale phase, release for usage and maintenance phase.

Verification at Production Scale Environment

In this phase of production scale verification, the model output is assessed against traditional testing of quality to ensure that it can perform as intended in a production environment. The need and extent of the production scale verification depends on the variation covered during validation in the intended production conditions and scale. The range covered and the batches required for this purpose depends on the type and purpose of model. This testing phase enlarges the body of data in order to make a statistical assessment of model capability prior to the final implementation. For predictive models, this approach includes comparison of the models prediction with the reference method. For MSPC models, the ability to differentiate between typical and abnormal situations is tested. For process control models (e.g., feed forward/feedback), this phase makes sure that process control algorithms and procedures deliver the required outcome.

For predictive models, companies often choose to test at or near the target operating conditions at this stage. Alternatively, it is also possible to evaluate systematic variation within the design space. If testing of the model occurs only at target processing conditions, a procedure could be included within the production quality system to help assure that the model performs as desired when there is variation (planned and unplanned) in the processing conditions. Some tools that could be used are: MSPC to detect unplanned disturbances and risk assessment to assess performance in planned disturbances (e.g., change of raw material).

MSPC models can and should[9] be tested off line prior to real time implementation, by utilizing process data to assess Type I and Type II errors and to make decisions about real time implementation.

Release for Usage
Once the model is released, it is used as an element in the GMP system that warrants routine maintenance.

Model Maintenance
After the model is released for usage, the model is generally checked periodically based on certain criteria, as discussed later in in the Maintenance Model section of this article.

Usage, Incident and Change Management Considerations
After the validation of the model, procedures for its implementation within the production system should be considered; that is, how to incorporate and integrate the model into the control procedures and release flow of the quality systems. These procedures typically encompass the definition of process flow, incident and change management, and define what is seen as an out of control incident. For these procedures, it is suggested to include a clear definition of thresholds and control limits. One possible outcome of an incident might be that the applied model is not covering the present variability which could entail an update of the model.

Usage and Implementation
For the application of a model in production, the automated data flow between sensors, the model and the distributed control system is highly essential for a compliant and secure usage. The control metrics and logic should be clearly defined and embedded into the manufacturing recipes. Based on method specific parameters, a warning can be automatically generated if a certain control limit or threshold is exceeded. Examples for such deviations could include a certain critical process parameter, latent sum variable (as a score) or a residual deviated out of the predefined acceptable ranges.

Furthermore, fall back scenarios can be in place in case that the data flow might break down, e.g., in case of a sensor failure or a breakage of a data connection or server. Ideally, procedures would be in place to handle such unplanned incidents in a systematic pre-planned manner. In particular, for multivariate models, the event of having partially missing data could automatically generate alerts to the process expert who can then react.

Incident Management
For applying models in the production environment, clear procedures for the usage should be established including defining what is seen as an "unusual event." In MSPC language, an "unusual event" occurs if operation falls outside typical limits, and may need to be analyzed further; this does not necessarily mean a bad product. A clear definition of thresholds and control limit can be developed in combination with a thorough risk assessment.

In the case of an "unusual event," the incident is usually checked to assess whether this finding is being escalated to real process deviation and whether/when QA needs be informed. The investigation typically includes a thorough examination of all process steps involved, equipment and sensors and personnel engaged to trace back the incident to the root cause of the model out of trend occurrence. In particular, a QC testing plan for the involved material might be considered.

One possible outcome of the incident might be that the applied model is not covering the present variability. This scenario would typically entail an update of the model.

Maintenance of Models
Typically, models are evaluated periodically and may need to be updated due to an instrument or process drift. Additionally, unaccounted variability (e.g., changes in raw material) could result in out-of-spec predictions from the model. It is important to monitor the performance of the model over the lifecycle of the product as well as to monitor that the assumptions of the model still hold. An approach for monitoring model performance can include periodic comparison of model prediction with a reference method. Early identification of model defects allows making adjustments to the model (e.g., recalibration) before failures occur.

For data based models, maintenance has already been discussed as a crucial stage in the model lifecycle in the literature. "*Continued evaluation of system performance relative to project objectives and the actions taken to ensure ongoing performance are part of system maintenance. Maintenance can encompass many activities including the updating of model parameters and control chart limits. Various methods can be used to maintain model parameters and control limits. These methods can include periodic off-line rebuilding of models, the development of automated model updating methods, or some combination of these activities. In either case, the goal is to ensure that the empirical models used in MVS analysis retain a high degree of fidelity to the process so that client needs continue to be met.*[21] *Having long-term maintenance strategies in place is important in ensuring continuing success*."

"*Once a model has been developed, it is often the case that the tacit assumptions underlying its validity are forgotten or neglected*." A discussion on model validation and detection of parameter changes under closed-loop conditions can be found in Jiang, et al, (2009).[23]

Empirical process models can be re-evaluated at defined intervals as part of an ongoing method evaluation throughout the life cycle of the model and the associated process. The main focuses of planned assessments are:

- A reassessment of the accuracy of the method including a comparison with the reference method (e.g., repeat certain parts of the validation)
- Statistical assessment of performance of the model (similar to Annual Performance Review (APR)/Product Quality Review (PQR))
- List of all deviations encountered in the evaluation period
- Final assessment of the validity of the method and statement about the necessity of a model update

The outcome of the method reassessment under regular method maintenance is the conclusion whether the performance of the model is still appropriate and accurate to support further use of the model. If the performance is inacceptable, corrective actions

should be taken. For example, the model could be developed, taking into account new data, process insight and experience.

The frequency of checking the adequacy of model performance depends on the variability, complexity and the number of batches produced per year. An alternative approach to having a fixed time would be to execute this kind of assessment after a defined number of batches produced, which is similar to the concept of frequency testing.

Other incidents, such as change in a sensor, change in raw material, or change in manufacturing equipment could trigger reassessment of model relevance, potentially followed by a redevelopment and adaptation of the method.

Regulatory Considerations for Model Implementation

Points for consideration for regulatory submissions are discussed in this section. These points are additional to the information that is documented under the firm's quality system. For example, for high impact models, information in the quality system typically includes: development report, validation report, Standard Operating Procedures (SOPs), release process, maintenance, and incident management.

Considerations of Model Related Information in Regulatory Submissions

In accordance with ICH QIWG Points to Consider5 section on models, the level of detail for describing a model in a regulatory submission is dependent on the impact of its implementation in assuring the quality of the product. Additionally, documentation of model related information in regulatory filings is dependent on the intended use of the model and the risk associated with it. For example, if a MSPC model is used for monitoring only and not for control purposes, it can be regarded as a low impact/risk model. However, an MSPC model used as a part of a RTRT strategy could be considered a high impact model.

The applicant should consider including the following information for various types of models:

I. **Low-Impact Models:** a discussion of how the models were used to make decisions during process development.

II. **Medium-Impact Models:**

- Model assumptions
- Tabular or graphical summary of model inputs and outputs
- Relevant model equations (e.g., for mechanistic models) either in the submission or via a reference
- Statistical analysis where appropriate
- Comparison of model prediction with measured data
- Discussion of how the other elements in the control strategy help to mitigate uncertainty in the model, if appropriate

III. **High-Impact Models:** data and/or prior knowledge (e.g., for established first principles driven models) such as:

- Model assumptions
- Appropriateness of the sample size
- Number and distribution of samples
- Data pre-treatment (e.g., variable transformations, any filtering of the data, spectral pre-treatments)
- Justification for variable selection (wavelength selection for spectral data)
- Model inputs and outputs
- Model equations
- Statistical analysis of data showing fit and prediction ability
- Rationale for setting of model acceptance criteria
- Model validation (internal and external)
- General discussion of approaches for model verification during the lifecycle.

Other considerations in accordance to regional requirements (e.g., EMA 2014a,b)[24,25] could include:

- Describing details about the composition of the data sets used for model development (e.g., number of independent batches that were used, number of samples per batch, criteria used for separating the batches into sets, demonstrating that these datasets are representative of the expected process variability in routine production)
- Procedures for handling outliers
- For chemometric models, the rationale for selection of number of principal components, demonstration of the linkage between the weightings of the variables in the principal components to the process, method of error estimation, Root Mean Square Error of Cross Validation (RMSECV), Root Mean Square Error of Prediction (RMSEP), etc.
- If data from a reference analytical method is used to generate an empirical model, demonstration that the reference method is fit for purpose (e.g., full description and validation of the reference methods).

Considerations for Model Verification

Usually, models are developed with data generated at lab or pilot scale. One of the key points to be discussed in the regulatory submission is the applicability of the model at commercial scale. This can be conveyed by providing evidence of scale independence, available commercial scale data, or by discussing plans for model verification at commercial scale. As already stated above, the level of detail to be provided for model verification depends on the impact of the model on product quality. For example, for a high impact model, such a plan could include the parameters that will be varied, the ranges that will be covered, the CQAs that will be tested, the acceptance criteria, and the number of new independent data that will be used.

Considerations for Maintenance of Models

The approach of model maintenance and update can be designed relative to the importance of the model in the control strategy and its potential to affect product quality. Clear metrics

for model update may be established depending on the impact of the model. As discussed earlier, model maintenance information could include the following: risk based frequency of comparing model prediction with the reference method, triggers for model update, and approach for model recalibration. The reporting of model updates is according to regional requirements. Details about model maintenance are documented in the firm's quality system. ◂

Disclaimers

1. By E. Korakianiti: the views expressed in this article are the personal views of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.
2. By the rest of the authors: the views expressed in this paper are the personal views of the contributing authors and do not necessarily reflect the official position of their respective organizations.

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CONTENT UNIFORMITY DISCUSSIONS: CURRENT USP <905> DEVELOPMENTS REGARDING <905> AND A COMPARISON OF TWO RELEVANT STATISTICAL APPROACHES TO ASSESS CONTENT UNIFORMITY

James Bergum, William Brown, Jon Clark, Thomas Parks, Thomas Garcia, James Prescott, Charles Hoiberg, Sami Patel, and Ravindra Tejwani

This article compares the performance of two statistical approaches (tolerance interval and ASTM E2709/E2810) to assess dosage unit uniformity. The potential impact that the approaches can have on the USP <905> monograph is also discussed.

Abstract

The ISPE Blend Uniformity and Content Uniformity (BUCU) Group was formed in August 2013 to address the gap resulting from the withdrawal of the draft stratified sampling guidance document. The Group's proposed modifications address the US Food and Drug Administration's (FDA's) concerns, including insufficient blend testing and the use of USP <905> for release testing. The framework defined by the Group provides flexibility for sampling plans and statistical approaches/acceptance criteria used for the assessment of dosage unit uniformity. The following article compares the performance of two statistical approaches to assess dosage unit uniformity: One is based on a tolerance interval, and the other is the ASTM E2709/E2810 approach. The potential impact that the framework will have on the USP <905> monograph is also discussed.

Introduction

The FDA withdrew the draft stratified sampling guidance document in August 2013 because it wasn't consistent with its current thinking.[1, 2, 3] The reasons for its withdrawal included:

1. The desire to test triplicate blend samples to allow variance component analysis to detect non-uniform locations in the mix
2. The acceptance criteria were based on USP <905>,[4] which is insufficient for batch release
3. The desire to use of statistically based sampling plans
4. Linking the assessment of blend and content uniformity to the 2011 validation guidance document[5]

ISPE sponsored the formation of the Group in July/August. The Group's recommendations were published[6, 7] and consisted of a framework that could be used to assess blend and content uniformity throughout the three stages of process validation. The framework provides greater confidence that future samples of dosage units taken from the batch will comply with USP <905>. It also allows flexibility for the use of different sample sizes and statistical approaches to assess dosage unit uniformity by inserting them into the appropriate boxes. Figure 1 can be used for both Stage 1 Process Design and Stage 2 Process Qualification, and Figure 2 contains an approach that can be used during Stage 3 Continued Process Verification. The diagrams contain statistically valid sampling plans that are but one set of plausible sampling plans that can be used. They are for example purposes only and should not be considered firm numbers or requirements. Justification for the sampling plans and acceptance criteria selected should be based on stage appropriateness, existing product and process knowledge, and the consideration of consumer and producer risks.

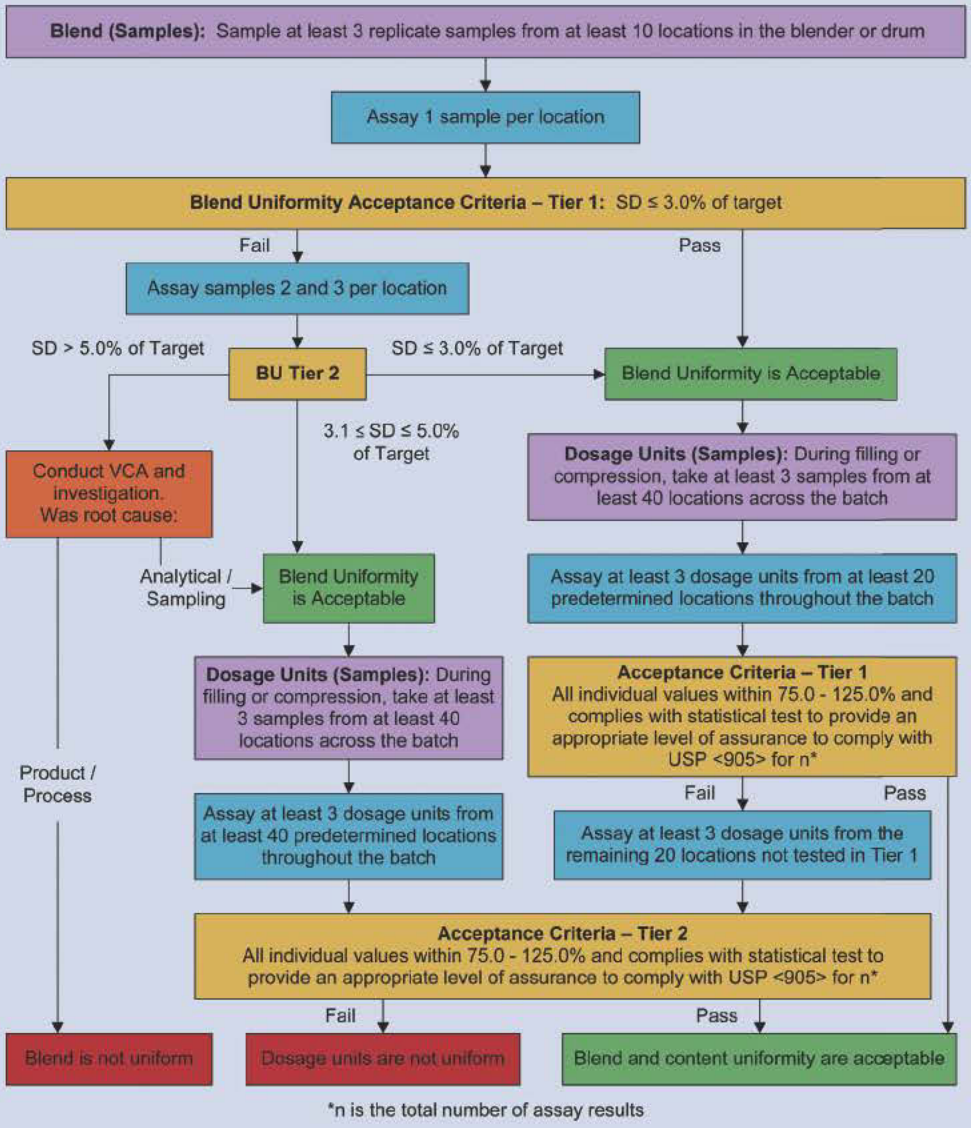
Comparison of ASTM E2709/E2810 and Tolerance Interval Approaches

Using a sampling plan that tests one dosage unit from multiple locations, Figure 3 contains operating characteristic (OC) curves that demonstrate the performance of a tolerance interval approach and the ASTM E2709/E2810 approach for the same level of confidence (90 percent) and probability of passing the USP uniformity of dosage unit (UDU) test (95 percent) for various sample sizes.[8] All curves are to the left of that for the USP <905> test. As the sample size increases, estimates of both the true mean and true standard deviation become more precise causing the curves to move to the right (lowering the producer's risk while maintaining the same level of confidence without increasing the consumer's risk). For the same sample size, the tolerance interval curves are to the right of those for the corresponding (more conservative) ASTM E2709/E2810 curves. Although not shown, OC curves for other statistical approaches could be generated and compared to the tolerance interval and ASTM E2709/E2810 approaches contained in Figure 3.

Figure 4 contains an approach that can be used for routine release testing during Stage 3 Continued Process Verification that demonstrates the impact that decreasing the confidence from 90 percent to 50 percent (while maintaining a 95 percent probability of passing the USP UDU test) has on the position of the curves. Decreasing the confidence level to 50 percent still results in curves far to the left of the USP curve. The plans are two-tiered using 10 dosage units in the first stage and 20 dosage units in the second stage when needed (referred to as Tier 10:30).

Using a sampling plan that tests more than one dosage unit per sampling location, Figure 5 shows the OC curves for ASTM E2709/E2810 when the lot mean is 100 percent. OC curves are displayed for both the example validation sampling plans using 20 or 40 locations with three dosage units tested per location (denoted by 20 x 3 and 40 x 3, respectively) at 90 percent confidence and the Tier 10:30 routine release sampling plan. Both the validation and routine OC curves are at 50 percent confidence with a 95 percent probability of passing the USP UDU test. Since the probability of passing the USP test depends on

Figure 1 Process flow diagram for assessment of blend and content uniformity for process design and process qualification batches



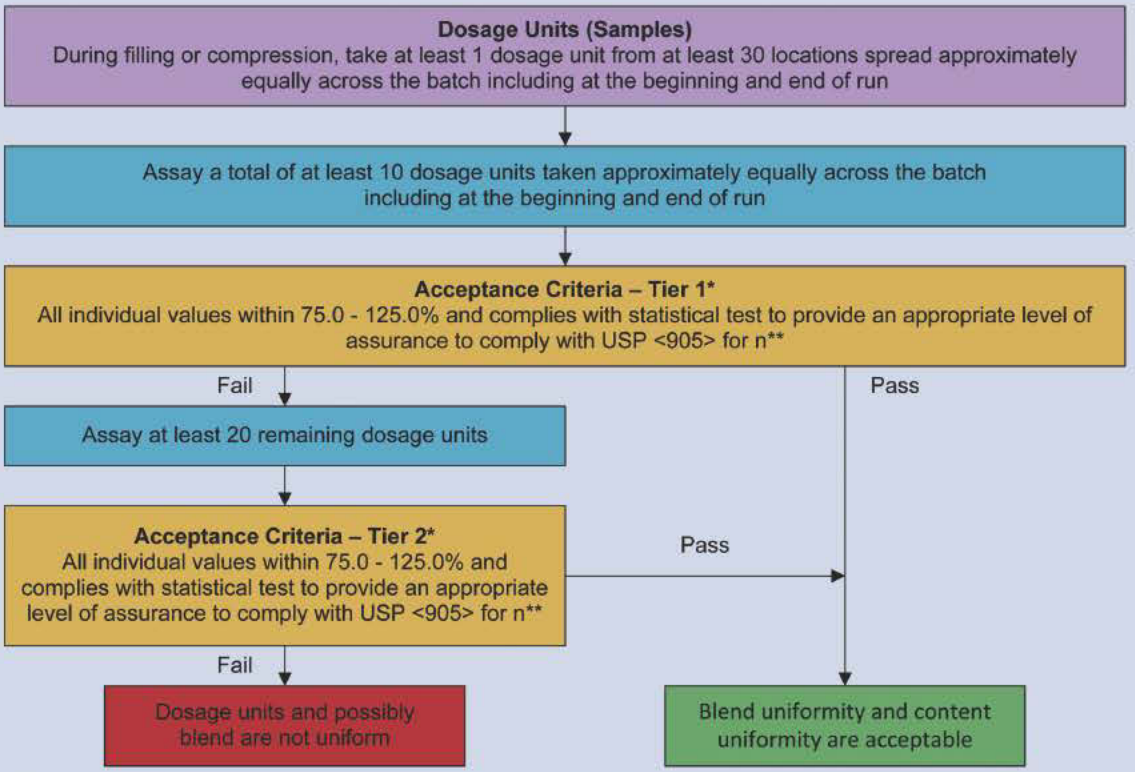
the percentage of total variation due to between locations, two OC curves are presented for the 20 x 3 and 40 x 3 plans, one for no variation due to between locations and the other where 90 percent of the variation is due to between locations. Note that the curves move to the right (reducing the producer's risk) as the number of locations increases and/or when the percentage of total variation due to locations decreases. The tiered routine sampling plan is generally to the right of the validation OC curves but still far to the left of the USP UDU test curve.

Impact on USP <905> and Future Contributions by USP

The regulations require in-process controls on the adequacy of mixing and variability in drug product characteristics.[9] Validating the correlation between blend uniformity and uniformity of the product is a costly process. The tools described in our papers justify this expenditure by promoting an efficient use of data from the finished product that confirms the state of control over the process as well as providing a measure of likelihood that samples taken from the batch will comply with USP <905>. The approach is consistent with principles associated with Quality by Design (QbD), which can have its own set of advantages within individual companies as well as the FDA.[10] One outcome of our work may be for USP to provide a way for companies to use manufacturing data to demonstrate compliance with <905> without intrusion into the FDA GMP-compliance role. Would the pharmaceutical industry be willing to accept this shift by USP? In order for this approach to demonstrate compliance with USP <905>, specific information describing how this may be done will need to be added to USP. A current USP Expert Panel is charged with work toward potential revisions that should give alternative approaches for <905>. This will be in the context of harmonization efforts to avoid creating additional testing requirements for distribution in multiple regulatory markets. USP experts on several committees and an Expert Panel are involved.

The Group endorses USP efforts to provide guidance on alternative ways a firm decides that a product can meet USP <905> if it is taken from the market and sampled and tested. This decision must be taken at batch release and is subject to risk analysis by the manufacturer. The risk that a sample taken from the market will not meet <905> is the responsibility of the manufacturer. Any USP chapter would presuppose the process validation discussed by the Group's papers but not specifically discuss it because it is more properly a topic for FDA guidance. Another difficult piece is

Figure 2 **Process flow diagram for assessment of blend and content uniformity for continued process verification (Stage 3B) batches**



*Acceptance criteria for Stage 3 Continued Process Verification may have reduced assurance to comply with USP <905> compared to that used for Stage 2 Process Qualification.

**n is the total number of assay results.

how to make the correlation between final product and the blend that produced it. That correlation could be investigated and discussed by USP experts with the understanding that no proposed revision will be effective without significant FDA participation.

Two levels of volunteer engagement in the USP standard-setting process are used in this thought exercise: Expert Committee and Expert Panel. Expert Committees are impanelled for a five-year term and participate as individuals with a firm conflict of interest agreement. Expert Panel members participate without the conflict of interest agreement and serve Expert Committees in an advisory role. Expert Committees are responsible for the content of USP. Revisions to USP are proposed in *Pharmacopeial Forum (PF)*, an online publication. Comments received in response to PF proposals are considered and resolved by the Expert Committee before the revision becomes part of the official USP text. It seems like a long road, but we feel that our papers have mapped the journey starting with the limited revisions to USP.

Moving the effort for ensuring quality from relying entirely on final product testing to a model of controlling manufacturing in a way that produces only quality material has been a long evolution. The FDA has been clear that it is ready to accept these practices as part of an overall system of control and has published arguments supporting this. There is the natural wish to avoid testing multiple times to ensure what is effectively the same attribute, even distribution of active ingredient from dose to dose. With the procedures described in this series, potential root cause analysis is strengthened, product manufacturing efficiencies are achieved, and product variability is controlled. It should be possible to add enhanced compendial compliance to this list of benefits.

Figure 3 OC curves for various sample sizes at a constant level of confidence (90 percent) and probability of passing the USP UDU test (95 percent) for the ASTM E2709/E2810 and tolerance interval approaches

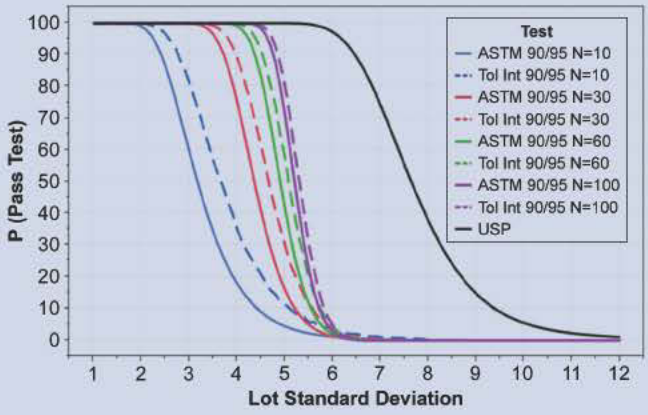
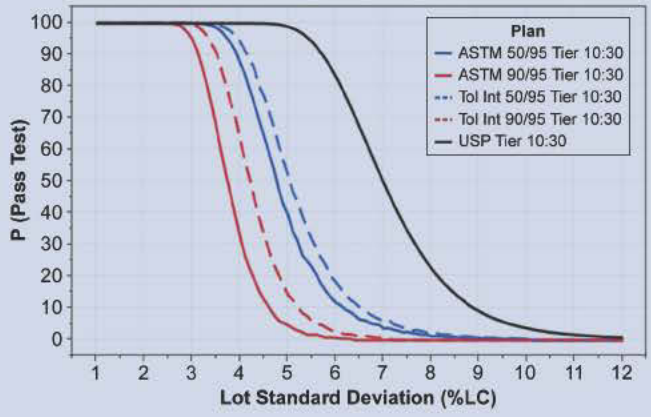


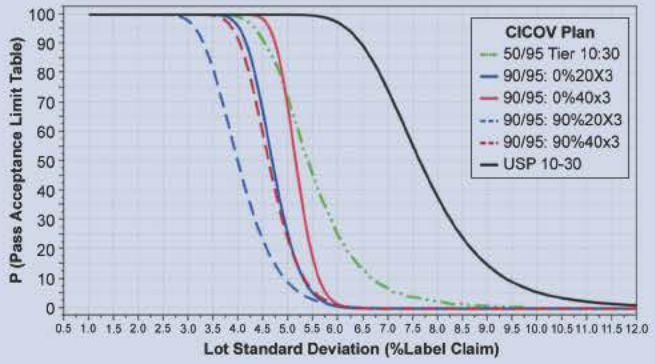
Figure 4 OC curves for various levels of confidence and coverage for the ASTM E2709/E2810 and tolerance interval approaches (two-tiered 10 + 20 testing approach)



Additional Information

The Group has a website[11] with public access. It contains ASTM E2709/E2810 tables, a list of frequently asked questions (FAQs), references to applicable publications and presentations, and information about current and future activities. The site also includes slides from some of the presentations given during the Group-sponsored BUCU session at the 2015 IFPAC Conference.[12] The Group is also willing to have discussions with any regulatory agencies and/or professional organizations that have interest in the topic.

Figure 5 OC curves for sampling plans 20 × 3 and 40 × 3, varying confidence/probability (pass USP), true lot mean = 100 percent, and USP UDU vs. true lot standard deviation



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James S. Bergum, PhD, received his Doctorate in statistics from Montana State University in 1981. He worked in nonclinical biostatistics for Wyeth from 1981 to 1988 and Bristol-Myers Squibb from 1981 to 2012. His primary responsibility was to provide statistical support to research and development, including design and analyses of experiments, analytical assay development and method validation, process validation, stability, drug safety evaluation, and teaching short courses to scientists. He developed a statistical method that resulted in two ASTM methods (ASTM E2709 referenced in the FDA guidance for Process Validation and E2810) that can be used to evaluate development, process validation, or release data. After retiring in 2012, Bergum started BergumSTATS, a statistical consulting company specializing in statistics related to chemistry, manufacturing, and control (CMC) issues. His current interests are statistical methodologies that can be applied to product development, process validation, and manufacturing.

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Jon Clark is Vice President, Chemical Medicines, for the United States Pharmacopeia. He directs the efforts to develop monographs in the United States Pharmacopeia in close co-operation with manufacturers. Updating standards in the USP through the next five years is his main priority. Clark has many years of experience in the global pharmaceutical industry. He joined the FDA in 1992 and was Associate Director for Program Policy, Office of Pharmaceutical Science, in the FDA's Center for Drug Evaluation and Research for 10 ye ars, advancing quality guidance and leading grant efforts that funded NIPTE, a consortium of research universities. Prior to this, he conducted reviews of the CMC portions of both NDA and ANDA applications, in the Offices of New Drug Chemistry and the Office of Generic Drugs, respectively. Prior to joining the Agency, he developed drug substance synthesis processes during his 12 years at Schering-Plough. Clark has a strong understanding of how USP-NF standards work in relation to the CMC part of a filing and is also cognizant of specific issues that are evolving at USP. These include monograph updating, the elemental impurity topic, ICH guidance, PDG, and allied areas of focus. In his roles at the FDA, he had direct responsibility for advancing quality guidance, many of which speak to standards in USP-NF. Clark earned a Master of Science in chemistry from Rutgers University and a Bachelor of Science in chemistry from the University of Michigan.

Thomas P. Parks, PhD, received his Doctorate in statistics from Baylor University in 1998. He started his statistical career at Eli Lilly and Company in 1998 supporting the manufacture of various large-molecule active pharmaceutical ingredients. In 2007, he transitioned to supporting parenteral container closure systems and in 2012 began supporting dry products. In his various roles, he participated in process improvement, deviation investigations, validations, stability studies, experimental designs, and many other areas in manufacturing where statistics and statistical thinking are applied. Prior to receiving his Doctorate, Parks worked in the aerospace industry in several engineering positions related to solid propellant rocket motor manufacturing and wind-tunnel testing.

Thomas P. Garcia, PhD, is a Research Fellow at Global CMC (GCMC), Pfizer Inc., in Groton, Connecticut. He earned a Bachelor of Science in pharmacy from Albany College of Pharmacy in 1983 and a PhD in industrial and physical pharmacy from Purdue University in 1989. Garcia spent 14 years in the pharmaceutical industry in process development and technology transfer, where his primary interests were powder mixing, blend sampling, and the use of statistical techniques to optimization and assess process capability and robustness. He joined GCMC in 2003 and has been active in defining regulatory strategies related to QbD dossiers. Garcia is an Adjunct Associate Professor in the Department of Pharmaceutical Sciences at Albany College of Pharmacy and Health Sciences and held the same position at Campbell University from 1996 to 2000. He was a member of the SUPAC IR Industry Training Committee, served as Chair of the PQRI® Blend Uniformity Working Group, and was a member of the ISPE PQLI® Control Strategy Task Team.

James K. Prescott is a Senior Consultant and Director at Jenike & Johanson, Inc., in Tyngsboro, Massachusetts. Jenike & Johanson is a specialized engineering firm focused on providing reliable bulk solids flow while achieving product quality requirements. Prescott's focus has been primarily on pharmaceutical applications,

such as solving and preventing content uniformity problems, maintaining reliable feed, reducing product weight variations, developing specialized feeders for low feed rate/high accuracy applications, and standardizing handling equipment. He holds patents on equipment related to segregation testing and equipment to control segregation. He earned a Bachelor of Science in aeronautical engineering from Rensselaer Polytechnic Institute and a ME in mechanical engineering from Worcester Polytechnic Institute. Prescott is a member of the USP committee working on standards for shear cell testing and the ISPE Blend Uniformity and Content Uniformity Working Group, and he was a member of the PQRI® Blend Uniformity Working Group.

Charles P. Hoiberg, PhD, earned a Bachelor of Science in chemistry from the College of William and Mary and a Doctorate in biochemistry (with a minor in chemistry) from Pennsylvania State University. He worked over eight years at Sterling Drug Inc. in R&D before joining the FDA, where he held numerous positions. After 25 years of public service, he retired from the FDA. When he left the Agency, he was the Deputy Director of the Office of New Drug Chemistry and the Associate Director for International Activities, Office of New Drug Chemistry, Office of Pharmaceutical Sciences, Center for Drug Evaluation and Research. He was Coordinator for the CDER International Conference on Harmonization Quality and the ICH CDER Quality Topic Leads for the Common Technical Document-Q Guideline and the Q3A(R) and Q3B(R) Impurity Guidelines negotiations. Hoiberg has been a frequent lecturer at domestic and international programs for DIA, FIP, AAPS, PDA, ISPE, ICH, etc., on various technical and regulatory topics. He has served as the Chairman and other positions on the ISPE International Board of Directors and is currently on the Board of Directors of the FDA Alumni Association. He is an Executive Director in Pfizer's Global Regulatory CMC group.

Samir Patel received his pharmacy degree from Karnataka University in India. He has worked in the pharmaceutical industry for over 17 years in the area of Technical Services and Validations. At Teva Pharmaceuticals since 2000, he has held positions of increasing responsibility and led process engineering, technology transfer, validation and commercialization of new drug products, harmonization, commercial product support, product robustness, and continuous process verification.

Ravindra W. Tejwani was trained as a pharmacist and has worked in the pharmaceutical industry for more than two decades. He earned his Master of Science in pharmaceutical sciences from the University of Mississippi and his PhD in pharmaceutical sciences from the University of Kentucky. He has been author or co-author of many publications, conference symposia, and patents. Tejwani maintains interest in computational modeling and simulation of the phenomena in pharmaceutical sciences. In this area, his recent works include molecular dynamics simulations of the lipid bilayer membranes, prediction of content uniformity, and biorelevance of content uniformity. At Bristol-Myers Squibb since 1997, Tejwani has held positions of increasing responsibility and led development, scale-up and technology transfer, and commercialization of new drug products.

ORGANIZATIONS

ASTM International

Standard Guide for Application of Continuous Processing in the Pharmaceutical Industry[1]

ASTM has released a new guide that introduces key concepts and principles to assist in the appropriate selection, development, and operation of continuous processing technologies for the manufacture of pharmaceutical products. Particular consideration is given to the development and application of the appropriate scientific understanding and engineering principles that differentiate continuous manufacturing from traditional batch manufacturing. Most of the underlying concepts and principles (for example, process dynamics and process control) outlined in this guide can be applied in both Drug Substance and Drug Product processes. However, it should be recognized that in Drug Substance production, the emphasis may be more on the chemical behavior and dynamics in a fluid phase, whereas for drug product manufacture there may be a greater emphasis on the physical behavior and dynamics in a solid/powder format. This guide is intended to apply in the development of a new process as well as the improvement/redesign of an existing one.

PIC/S

PIC/S Revises Annex 15 to PIC/S GMP Guide[2]

The PIC/S Committee has adopted, by written procedure, the revision of Annex 15 of the PIC/S GMP Guide, which will enter into force on 1 October 2015, simultaneously with the EU revision of Annex 15. The PIC/S revised Annex 15 can be downloaded at their website.

AFRICA

EAC Secretariat Hosts African Medicines Regulatory Harmonization Round Table[3]

The East African Community (EAC) Secretariat hosted the EAC-Africa Medicines Regulatory Harmonization Round Table Donors Conference at its headquarters in Arusha, Tanzania. The Round Table Donors Conference explored ways of financing the African Medicines Regulatory Harmonization Initiative at a time when many countries are struggling to streamline medicine registration processes and systems. The conference also looked at plans for the future and expansion into other Regional Economic Communities.

Ghana

Minister of Health: "Good Governance of Pharma Sector Critical to Sustain Health Insurance Scheme"[4]

Kwaku Agyeman-Mensah, Ghanaian Minister of Health, said that his government is committed to putting the necessary measures in place to ensure the sustainability of the National Health Insurance Scheme. Speaking at a forum organized by the Medicines Transparency Alliance, a United Kingdom Department for International Development-funded initiative to improve sustainable access to medicines through increased transparency in the pharmaceutical sector, the Minister said that the medicines component for the reimbursement is a burden and a key challenge and addressing it requires a multi-stakeholder approach.

Nigeria

NAFDAC's Drug Control Lab Gets International Accreditation[5]

Michael T. Harvey, the US Agency for International Development's Director in Nigeria, presented the International Organization for Standardization quality certificate to the National Agency for Food and Drug Administration and Control (NAFDAC) Central Drug Control Laboratory in Yaba, Lagos. NAFDAC becomes the third national quality control lab in Africa to achieve ISO 17025 accreditation with support from the Promoting the Quality of Medicines program.

AUSTRALIA

Consultations on Adoption of European Union Guidelines in Australia[6]

Following consultation within the Therapeutic Goods Administration (TGA) and relevant external stakeholders, including industry and consumer groups, ending 22 May 2015, several European Union/ICH guidelines have been adopted by the TGA, effective 25 May 2015. More information on these guidelines can be found at TGA's website.

Australia Publishes TGA Reforms: A Blueprint for TGA's Future — Progress Report[7]

TGA Reforms: A Blueprint for TGA's Future: Progress Report as at 31 December 2014 is a six-month progress report on reforms to the Therapeutic Goods Administration (TGA) to ensure that it remains adaptable to community and industry expectations. The report outlines the TGA's progress in addressing reforms recommended in *TGA Reforms: A Blueprint for TGA's Future (the Blueprint)*. The report provides an overview of the TGA's progress in responding to the blueprint recommendations, including:

- Progress to 31 December 2014 (recommendations completed, in progress, and those with potential delays)
- Expected benefits from the blueprint reforms
- Major outputs delivered to 31 December 2014 and outputs to be delivered in the six months to 30 June 2015, for each blueprint recommendation

TGA Makes GMP Clearance Application Process Improvements[8]

The Therapeutic Goods Administration (TGA) has experienced a significant increase in the total number of GMP Clearance Applications, from approximately 2,500 in 2010 to more than 4,000 in 2014/2015. This has placed significant pressure on the TGA's existing resources; as a result, it is currently not able to consistently meet target timelines. To improve its ability to meet demand, the TGA is reforming some processes, including the collection of performance data, which will enable it to better understand inefficiencies. This information will be used to inform consultation with stakeholders.

ASIA

China

CFDA Issues 90 Industry Standards for Medical Devices[9]

The China Food and Drug Administration (CFDA) recently issued Announcement Number 8 of 2015, which released 90 industry standards for medical devices, such

as "Water for Hemodialysis and Related Therapies." These standards contain 14 mandatory industry standards and 76 recommended industry standards, including implants for surgery, medical electrical equipment, in vitro diagnostic reagents, and dentistry. The issuance of these standards will further improve the medical device standards system of China, help improve the quality of medical devices, and promote the sound development of the medical device industry.

India

Bar Coding of Drugs Becomes Mandatory [10]

The government has mandated the bar coding of mono cartons of drugs shipped out of India beginning in July as an additional measure to ensure that medicines manufactured illicitly in other countries are not passed off as made in India. The bar coding of mono cartons, which hold primary packs of drugs, will enable them to be traced back to the source. Drugmakers will also have to maintain evidence in a central portal controlled by the Indian government.

India Considers Joining PIC/S [11]

The Indian Commerce Ministry called a meeting with small- and medium-sized pharmaceutical companies to decide whether India should become part of multinational regulatory regime PIC/S. Many fear that stricter standards necessitated by membership could drive up costs and make them uncompetitive, but being a part of the new system could make it easier for Indian firms to access lucrative export markets.

South Korea

Kim Seung-hee to Lead Food and Drug Safety Ministry [12]

Cheong Wa Dae appointed Kim Seung-hee as the new minister for food and drug safety. Prior to this appointment, Kim, 61, served as vice minister.

EUROPE

European Union

Preventing Medication Errors in the European Union [13]

The European Medicines Agency, on behalf of the European Union (EU) Regulatory Network, has released two draft good-practice guides that aim to improve the reporting, evaluation, and prevention of medication errors by regulatory authorities and the pharmaceutical industry throughout the EU.

New EU Rules on Human Tissues and Cells Increase Patient Safety [14]

The European Commission has adopted two sets of rules for human tissues and cells to protect patients in the European Union (EU) by ensuring high-quality and safety standards. The first sets out technical requirements that facilitate the tracing of all tissues and cells from donor to recipient and vice versa. This will happen via a Single European Code and EU Commission-hosted IT platform that will guarantee the uniform labeling of all tissues and cells distributed in the EU. In the case of a safety alert, this label will ensure that all those who received tissues and cells from the same donor can be traced and treated as needed. It will also allow for unused tissues and cells to be discarded. The second directive covers imports and sets out procedures for making sure that tissues and cells from emerging economy countries meet the same safety and quality standards as those procured, processed, and distributed in the EU. The implementation of these rules will ensure that, regardless of their origin, these tissues and cells are safe for EU recipients.

EMA Issues Reflection on Chemical Structure and Properties to Be Considered for the Evaluation of New Active Substance Status [15]

The European Medicines Agency (EMA) has released a draft reflection paper that outlines the chemical structure and properties criteria to be considered by its Committee for Medicinal Products for Human Use for the evaluation of a new active substance status. The paper also outlines the elements that applicants are required to include in their marketing authorization applications in support of their new active substance status claims. Stakeholders have until 24 July 2015 to provide their comments to qwp@ema.europa.eu.

EMA Publishes 2014 Annual Report: Progress in Science, Medicines, Health [16]

The annual report published by the European Medicines Agency (EMA) focuses on its key priorities, including the evaluation of medicines and supporting the research and development of new and innovative medicines. In 2014, the EMA recommended 102 new medicines for marketing authorization, both for human (82) and animal (20) use. The number of applications for orphan designation increased by 63 percent and requests for scientific advice for human medicines by 16 percent compared to 2013. Developers of medicines are making more and better use of the EMA's tools aimed at helping patients get access to effective and safe medicines more quickly.

New Service Will Improve Safety Monitoring of Medicines and Simplify Pharmacovigilance Activities for Companies [17]

The European Medicines Agency has published a list of active substances and a reference to the journals that will be covered by its new medical-literature monitoring service. This service will start with a limited number of active substances on 1 July 2015 and be fully rolled out in September 2015. A guide, a training video, and a document detailing the inclusion and exclusion criteria to be used when screening the literature are also available on a dedicated website.

EU Publishes Inspection of Tissue and Cell Procurement and Tissue Establishments: Operational Manual for Competent Authorities [18]

This manual is intended to support member states that are establishing such regulatory systems for the first time. It should also promote standardization of regulatory systems that are already well established in the European Union (EU). The scope of this manual reflects these related directives on the quality and safety of human tissues and cells used for transplantation or in assisted conception. This manual has been established for information purposes only. It has not been adopted or in any way approved by the European Commission. It is not legally binding.

EMA Solicits Comments on Concept Paper on New Guidance for Importers of Medicinal Products [19]

The increased complexity of supply chains and the observation that most GMP non-compliance statements uploaded to EudraGMDP pertain to third-country manufacturers have created new areas where further guidance is desired by both the regulators and the industry; this includes, in particular, the requirements applicable to importers of medicinal products and concerning the application of GMP requirements, which are traditionally oriented to activities performed at true manufacturing sites. In response, the GMP/GDP IWG agreed to draft a specific guidance for import authorization holders. This document most likely would take the form of a new annex (Annex 21). The scope of the project will be focused on importation activities not addressed in detail in the GMP guide and annexes, taking into consideration recent changes in GMP chapters and annexes as well as changes in other regulatory documents.

Finland

Fimea Presents Opinion on Interchangeability of Biosimilars [20]

Finnish Medicines Agency (Fimea) has presented its position on interchangeability of biosimilars licensed in the European Union. The position is a recommendation to the local health care system. It has been argued that a switch from an original biological medicinal product (reference product) to its biosimilar copy is risky. The recommendation of Fimea concludes that:

- Switches between biological products are common and usually not problematic (in the context of hospital tendering processes, for example).
- For the time being, there is no evidence of adverse effects due to the switch from a reference product to a biosimilar.
- The theoretical basis of such adverse effects is weak.
- The risk of adverse effects can be expected to be similar to the risk associated with changes in the manufacturing process of any biological product.
- Automatic substitution at the pharmacy level is not within the scope of this recommendation.

Therefore, the current position of Fimea is that biosimilars are interchangeable with their reference products under the supervision of a health-care person.

NORTH AMERICA

Canada

Health Canada and US Food and Drug Administration Joint Public Consultation on International Conference on Harmonisation Guidelines for Registration of Pharmaceuticals for Human Use [21]

Prime Minister Stephen Harper and US President Barack Obama announced the creation of the Canada-United States Regulatory Cooperation Council (RCC) to better align the two countries' regulatory approaches, where possible. Under the RCC initiative, Health Canada and the US Food and Drug Administration (FDA) are holding joint public consultation meetings on International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines currently under development. The aim of this initiative is to hold public consultation meetings prior to each biannual ICH face-to-face meeting in order to seek input on areas of current regulatory disharmony and where harmonized ICH guidelines would be beneficial. Stakeholder input received through this initiative will be considered in current or future guideline development. Health Canada also intends to use these opportunities to better understand areas where Canadian requirements may differ from those in place in the United States, with a view to minimizing these differences.

Guidance Document on the Application for a Certificate of a Pharmaceutical Product [22]

Health Canada has issued a document that clarifies the requirements to be met for the issuance of a Certificate of a Pharmaceutical Product (CPP) and describes the procedure for the request of a CPP. A CPP is issued for human drugs (pharmaceutical, biological, and radiopharmaceutical) as well as veterinary drugs (food-producing animals and non-food-producing animals). Since the Food and Drugs Act and Regulations apply also to veterinary pharmaceuticals intended for non-food-producing animals, they must be fabricated according to GMP requirements, and, consequently, Health Canada chooses to issue CPPs for these pharmaceutical products. Products falling under the Natural Health Products (NHP) framework are excluded from the scope of this document.

Minister Ambrose Launches New Drug and Health Product Inspections Database, Underlines Commitment to Transparency [23]

Health Minister Rona Ambrose today launched the Drug and Health Product Inspections Database, a new online resource designed to provide ready access to information on inspections of companies that manufacture and sell drug products for the Canadian market. Canadians can search the site for information on inspection findings, including which companies have a good history of meeting safety and quality standards and which do not. The tool provides centralized access to plain-language, timely information on inspections. Canadians can use this information to have a better understanding of how Health Canada is enforcing – and how companies are meeting – Canada's high standards for drug safety and quality.

Health Canada Updates Guidance on Medical Device Compliance and Enforcement [24]

Health Canada has updated its Guidance on Medical Device Compliance and Enforcement. This document outlines the strategy and provides guidance for the medical-device industry on Health Canada's compliance and enforcement activities. This version of the document includes updated Web links and the incorporation of changes to the establishment of licensing provisions, which recently occurred due to the cost-recovery initiative.

United States

Risk Evaluation and Mitigation Strategies: Modifications and Revisions Guidance for Industry [25]

The US Food and Drug Administration (FDA) has issued a guidance document that provides information on how it will define and process submissions from appli-

cation holders for modifications and revisions to approved risk evaluation and mitigation strategies (REMS). Specifically, this document provides information on what types of changes will be considered modifications and what types of changes will be considered revisions. There are different procedures for the submission of REMS modifications and revisions to the FDA, as well as different time frames for FDA review and action on such changes. This document provides information on how modifications and revisions should be submitted to the FDA and the FDA's process for reviewing and acting on these submissions. The definitions of REMS modifications and revisions set forth in this document apply to all types of REMS. This document does not address additional procedures that may apply to application holders proposing changes that are part of a single shared system. The FDA intends to address these procedures in future guidance documents.

FDA Launches Pharmaceutical Quality Oversight Office[26]

The launch of the Center for Drug Evaluation and Research (CDER) Office of Pharmaceutical Quality (OPQ) is a milestone in the US Food and Drug Administration's (FDA's) efforts to ensure that quality medicines are available to the American public. As a new super-office within CDER, OPQ is strategically organized to streamline regulatory processes, advance regulatory standards, align areas of expertise, and originate surveillance of drug quality. Supporting these objectives will be an innovative and systematic approach to product quality knowledge management and informatics. Concerted strategies will bring parity to the oversight of innovator and generic drugs as well as domestic and international facilities. OPQ will promote and encourage the adoption of emerging pharmaceutical technology to enhance pharmaceutical quality and potentially reinvigorate the pharmaceutical manufacturing sector in the United States. With a motto of "One Quality Voice," OPQ embodies the closer integration of review, inspection, surveillance, policy, and research for the purpose of strengthening pharmaceutical quality on a global scale.

The FDA Releases "Assessing CDER's Drug Safety-Related Regulatory Science Needs and Identifying Priorities"27
The US Food and Drug Administration's (FDA's) new document aims to communicate priority drug safety-related regulatory science research projects and explore external collaboration ideas and possibilities. There are seven areas highlighted in the report that the FDA believes would benefit from internal and/or external collaboration:

1. Improve access to post-market data sources and explore the feasibility of their use in safety signal analyses.
2. Improve risk assessment and management strategies to reinforce the safe use of drugs.
3. Evaluate the effectiveness of risk communications of drug safety information to health-care providers and the public.
4. Improve product quality and design, manufacturing processes, and product performance relating to safety.

5. Develop and improve predictive models of safety in humans, including nonclinical biomarkers.
6. Improve clinical-trial statistical analyses for safety, including benefit-risk assessment.
7. Investigate clinical biomarkers of safety, including standards for qualification.

The Federal Register notice requests that interested parties submit descriptions of their ongoing research and initiatives related to the seven areas of need, especially the identified priority projects, and indicate their interest in working with the FDA to address these needs. Comments can be submitted to the docket and this email address: CDER_Science_Needs@fda.hhs.gov.

FDA Releases New Biosimilar Guidance to Help Manufacturers Develop More Treatment Options[28]

The US Food and Drug Administration (FDA) released four guidance documents for industry – useful tools to help manufacturers navigate the new terrain of biosimilar development. "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" assists companies in demonstrating that a proposed product is indeed biosimilar to an existing biologic product and intended to provide clarity to manufacturers about the expectations for a biosimilar development program. "Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product" focuses on the analytical studies that demonstrate that the product is "highly similar" to an existing biological product, which supports the demonstration of biosimilarity. "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009" answers common questions about the biosimilar development and application process and contains information intended to provide a better understanding of the law that allows biosimilar development. A fourth, still in draft form, "Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009," answers a variety of additional questions that have arisen regarding the biosimilar development process.

FDA Withdraws 37 Guidance Docs that Were Never Finalized[29]

The US Food and Drug Administration (FDA) is announcing the withdrawal of 47 draft guidance documents that published before 31 December 2013, and have never been finalized. The FDA is taking this action to improve the efficiency and transparency of the guidance development process. The names of the withdrawn guidance documents can be found in the Federal Register notice announcing this action.

Revised Recommendations for Reducing the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products: Draft Guidance for Industry[30]

This guidance document provides the US Food and Drug Administration's (FDA's) revised donor deferral recommendations for individuals with increased risk for transmitting human immunodeficiency virus (HIV) infection. The FDA is also recommending that organizations make corresponding revisions to donor education materials, donor history questionnaires, and accompanying materials, along with revisions to donor requalification and product management procedures. This document also incorporates certain other recommendations related to donor education materials and testing contained in the memorandum to blood establishments entitled "Revised Recommendations for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products," dated 23 April 1992. When finalized, it will supersede the 1992 blood memo. The recommendations contained in this document apply to the collection of blood and blood components, including source plasma.

Updated Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use[31]

The US Food and Drug Administration (FDA) is amending the regulations applicable to blood and blood components, including source plasma, to make the donor eligibility and testing requirements more consistent with current practices in the blood industry, to more closely align the regulations with current FDA recommendations, and to provide flexibility to accommodate advancing technology. In order to better ensure the safety of the nation's blood supply and to help protect donor health, the FDA is revising the requirements for blood establishments to test donors for infectious disease and to determine that donors are eligible to donate and that donations are suitable for transfusion or further manufacture. The FDA is also requiring establishments to evaluate donors for factors that may adversely affect the safety, purity, and potency of blood and blood components or the health of a donor during the donation process. Accordingly, these regulations establish requirements for donor education, donor history, and donor testing. These regulations also implement a flexible framework to help both the FDA and industry to more effectively respond to new or emerging infectious agents that may affect blood-product safety.

FDA issues "Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products: Guidance for Industry"[32]

The US Food and Drug Administration (FDA) has developed a guidance document to address the lack of clarity with respect to what chemistry, manufacturing, and controls (CMC) information in a marketing application constitutes an established condition or a "regulatory commitment" that, if changed following approval, requires reporting to the FDA. Clarification regarding which elements of the CMC information constitute established conditions and where in an application these elements are generally expected to be described should lead to a better understanding that certain CMC changes can be made solely under the Pharmaceutical Quality System (PQS) without the need to report to the FDA. For those changes that do require reporting, a better understanding of established conditions could allow for a more effective post-approval submission strategy by the regulated industry. Specifically, this guidance document describes those sections in a common technical document (CTD): a formatted application that typically contains information that meets

the definition of established conditions and provides considerations for managing and communicating changes to the approved established conditions over the life cycle of an approved product.

SOUTH AMERICA

Venezuela New Program Unveiled to Combat Medicine Shortages in Venezuela[33]

Venezuelan Health Minister Henry Ventura announced a new program to improve consumer access to medicines through the coordinated participation of over 7,000 pharmacies nationwide. The denominated Integral System for Access to Medicines (SIAMED) prioritizes patients who have illnesses that require regular treatment, such as heart disease, diabetes, and neurological disorders.

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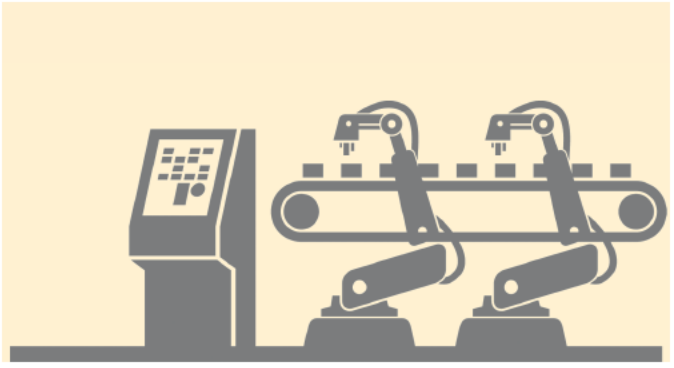
SINGLE-USE FREEZE-THAW SYSTEMS: A PROCESS IN TRANSITION FOR THE PHARMACEUTICAL INDUSTRY

Adam Goldstein and Pietro Perrone, P.E.

The next area of development and innovation: bulk drug substance containers for the transportation/ storage of APIs.



Abstract

Single-use systems are becoming a well-established technology in the pharmaceutical industry. One can easily find single-use filters, mixers, and bioreactors in a biopharmaceutical operation. In addition, tangential flow filtration (TFF) steps, ultrafiltration/diafiltration (UF/DF) steps, and chromatography steps now include single-use products. Single-use products are routinely employed in cell-culture processes of up to 2,000 liters. And there are complete process operations made up entirely of single-use equipment. This article highlights the next area of development and innovation: bulk drug substance (BDS) containers for the transportation and storage of active pharmaceutical ingredients (APIs). In this area, single-use products are being applied in bulk freeze-thaw operations and are forging their way into clinical manufacturing. These single-use products offer several advantages over the industry's current standard stainless steel components. The single-use freeze-thaw operation can:

- Reduce the risk of contamination events
- Decrease cleaning and steaming validation efforts
- Streamline logistics
- Reduce infrastructure (eliminate the management of stainless steel assets)
- Reduce resources and staff (eliminate the maintenance of a fleet of stainless steel tanks)

However, the use and fit of the technology have to be carefully considered and critically reviewed. In this analysis, one must consider:

- Domestic and international shipping standards
- Temperature control within shipping containers
- Compatibility of the film with operation at low temperatures

This article focuses on the shipping and supply chain aspects of the freeze-thaw operation; it specifically highlights the logistics and related cost benefits for on-boarding single-use equipment compared to traditional stainless steel bulk freeze-thaw tanks.

The Drivers for Change

Reduced financial risk and reduced product cross-contamination risk have been the main drivers for the implementation of single-use or disposable technologies in numerous operations. What started with filtration cartridges and small bags for storage now includes complete systems for mixing, bioreactors, TFF, and chromatography. Recent advances in technology have resulted in a wide range of opportunities for single-use systems to be beneficial in the areas of upstream and downstream applications. Developments include cell-culture bioreactors, formulation and filling applications, new mixing technology, and the disposable depth filters used in harvesting processes. These developments have prompted the industry to move toward a completely disposable system paradigm for smaller-scale operations.

Single-use bioprocess containers (BPCs) are increasingly being welcomed into the bulk freeze-thaw applications of biotech facilities. Bulk freeze, transfer, and storage are important steps because they ensure that the final product is safely handled, stored, and promptly delivered to fill-finish sites and eventually to patients. As with other traditional manufacturing processes, current bulk freeze-thaw practices predominantly use stainless steel systems. However, stainless steel bulk freeze-thaw systems have several disadvantages. Difficulties in the passivation and integrity testing of systems, the shipping validation, and the continued upkeep of stainless steel systems require dedicated support teams to spend many man-hours sustaining the operation. These challenges have prompted investigation and acceptance of disposable bulk freeze-thaw systems. Similar to the conversion of other steps in therapeutics production, disposable bulk freeze-thaw systems are following the overall trend of single-use products moving into mainstream manufacturing.

Traditional Bulk Freeze-Thaw Operation

The ever-competitive manufacturing of biologics requires vigilance with regard to opportunities for cost savings. Decoupling the production of biologics BDS from the final drug product can provide flexibility and cost savings in the manufacturing process. This method of operation requires the production of biologics in campaigns that produce large amounts of biologics that must be stored for lengthy periods until needed for further processing into the final drug product.

Once the BDS is purified from the fermentation broth through subsequent protein purification steps, the liquid is stored in vessels/containers. Storing the liquid in a typical temperature range of 2ºC to 8ºC for long periods can be a problem for maintaining product quality. While the cold temperatures help stabilize product quality, the liquid phase is not ideal for long-term storage. At these temperatures, the protein can still be easily affected by the environment and time. Aggregation, precipitation, and oxidation can significantly impact the quality of the liquid product. Therefore, most monoclonal antibody (mAb) processes store the BDS in a frozen state. The solid phase of the frozen-state BDS is a more stable environment for the protein. A typical operation may include multiple transitions between the liquid and solid phases. To benefit from the frozen state, these transitions must be closely controlled. During the process development phase, the temperature ranges and gradients that allow for the best control in the freeze-thaw process are identified. These conditions are then transferred to the manufacturing operations to yield a reliable and consistent freeze-thaw operation that provides the required stability for the protein.

While stainless steel systems have a proven track record of capabilities at this critical step in the process, they are resource intensive. Extensive resources are needed for maintenance, cleaning, validation, and life-cycle management. The process also creates a complexity in logistics that results in an inflexible schedule and requires tight control of time and activities. The types of issues that arise in this process include:

1. Use of a complex vessel-tracking system
2. Need for a large facility to maintain, clean, and store empty vessels
3. High potential for bioburden contamination due to the long-term storage of empty vessels
4. Preparing vessels for use (CIP and SIP, for example) is labor intensive and costly
5. High operating cost for the annual cleaning validation
6. High capital expense for stainless steel vessels
7. Long lead times for stainless steel vessel fabrication
8. Inconsistent validation potential for vessels that are older or configured differently
9. Safety concerns due to ergonomic vessel handling (size and weight)

The tank process flow shown in Figure 1 highlights the steps and the sequence of events that a stainless steel tank typically goes through.[1]

When multiple tanks and multiple locations are involved, it becomes a very complex logistical operation that requires tight control of time and activities. Typical vessel transport paths are shown in Figure 2.

Figure 1 Example of a freeze-thaw tank process flow; this diagram excludes validation and potential reprocessing activities

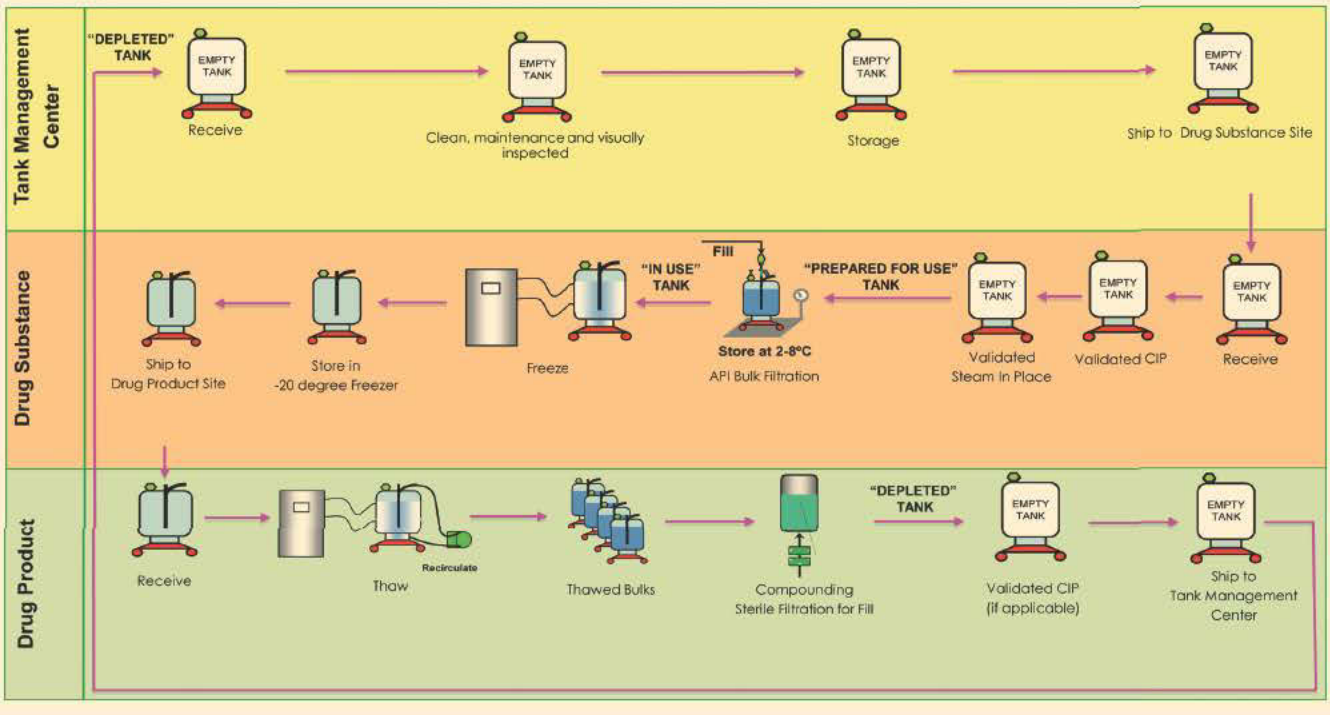
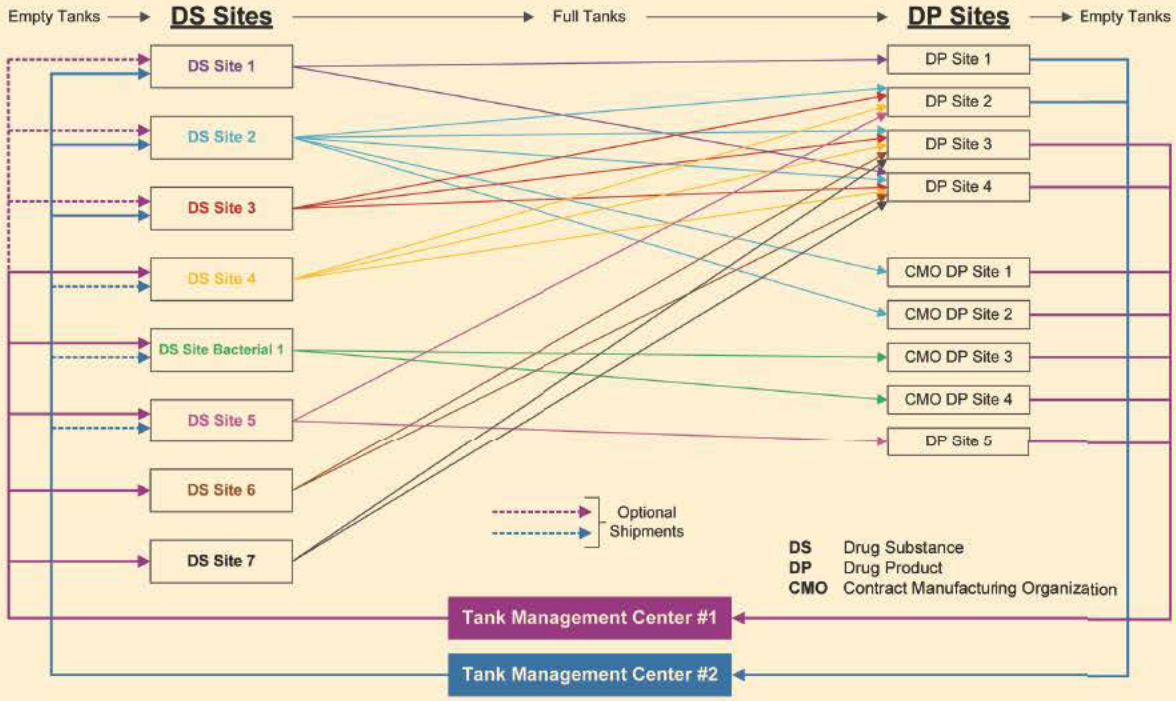


Figure 2 Example of a global freeze-thaw tank process flow; this diagram is a case-study example showing the transfer paths for stainless steel storage/transport vessels between multiple locations



The decision to incorporate the complex and time-sensitive freeze-thaw activities into the production of therapeutics needs to be supported by significant benefits for the process to be feasible and acceptable in an efficient operation. While each operation would have its own justification, common benefits of freeze-thaw include:

1. Products can be held for a longer time.
2. Frozen products are safer to transport between contract manufacturing operations (CMOs) for specific functions.
3. Each operation can handle multiple products without the need of vessel CIP/SIP.
4. The process is well suited for handling mAbs and recombinant proteins.

It's preferable to store product that is frozen rather than liquid because proteins are less likely to aggregate. The effects of oxidation are more prevalent in liquid form. Oxidation and any subsequent reactions can degrade the product over time. Minimizing the complexity of a freeze-thaw process is an important consideration for an existing process or one that is being evaluated for implementation. The cold chain logistics shown in Figure 2 can be simplified by using a process based on single-use disposable components.

Single-Use Disposable Bulk Freeze Operation

The complex routing inherent with the stainless steel tank freeze-thaw process can significantly impact supply chains that have a focus on just-in-time operations. A small delay in one section of the route can have a significant impact on the entire operation, and, of course, the delays will occur at the most inopportune times. These unpredictable conditions with the potential to have a wide impact raise serious concerns for the lean operation that relies on just-in-time manufacturing concepts. These concerns prompted investigations into the use of single-use disposable products. There are prior positive experiences with single-use technologies that have resulted in the implementation of disposable freeze-thaw processes at small volumes.2, 3 Eliminating the cleaning and preventive maintenance loop of stainless steel tanks changes the operation significantly when the single-use disposable method is adopted.

Utilizing the single-use disposable approach to bulk freezing can simplify the process with freeze-thaw steps in a number of ways. The typical single-use disposable process features:

1. Simple vessel tracking system by incorporating one-way logistics
2. Minimal space required to maintain secondary containers
3. No vessel storage needed; BPCs are closed systems and gamma sterilized by manufacturer

4. Bulk freeze BPCs can be ordered quickly with short lead times compared to those of stainless steel
5. Relatively lightweight BPC components

Operations that are based on single-use disposable freeze-thaw containers will benefit from:

- Reduced risk of contamination due to a closed system and irradiation
- Reduced labor due to the elimination of washing and autoclaving tanks
- Streamlined standard operating procedures
- Reduced gowning requirements
- Easier scheduling of product changeover (PCO)
- Quicker return to service (RTS) due to reduced preventive maintenance and calibration activities

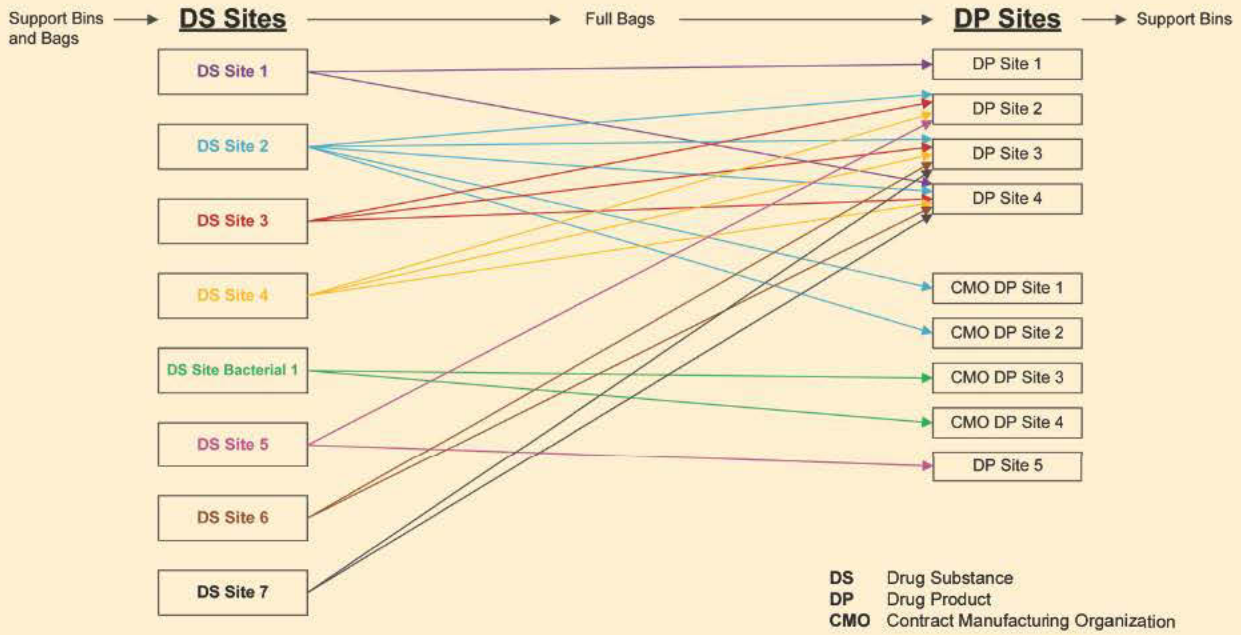
The freeze-thaw process is complicated, but it adds a level of security to the quality of the therapeutic products. If the freeze-thaw process is operated properly and the frozen substance is produced under tightly controlled conditions, the product can retain better quality for a longer period of time. This provides the manufacturer with more flexibility and usable therapeutic product available on demand. The details of how this is achieved are extensive and will be covered in a future article.

Table A compares the stainless steel vessel route with the single-use route. Simplification is the key factor to improving performance while controlling costs. The single-use equipment streamlines the operation and provides flexibility.

A qualitative list of benefits that can result from implementing single-use technology in the freeze-thaw process is shown in Table B. While quantifying these benefits is contingent on the specific operation, a guide for the estimated labor or cost improvements is given here:

1. Significant reduction in, or elimination of, work for tank setup, inspection, and cleaning; the work savings is estimated at 50 percent
2. Elimination of CIP and SIP along with associated documentation, deviations, and investigations; on average, the steps to set up and break down each stainless steel tank require 15 hours
3. Large reduction in water requirement, yielding economic and environmental benefits

Figure 3 **Example of a proposed global freeze-thaw tank process flow; this diagram shows transfer paths for single-use storage/transport vessels between multiple locations**



- Moving to disposable bags removes coordination and return of stainless steel tanks to DS sites.
- The greatest benefits are realized in shipping, handling and cleaning.

Table A Comparison between stainless steel vessel and single-use freeze-thaw operations

Traditional Bulk Freeze Operation	Criteria	Single-use Bulk Freeze Operation
Complex vessel tracking system	Logistics	Simpler vessel tracking system by incorporating one-way logistics
Bioburden potential in long term storage of empty vessels	Sterility	BPCs are gamma sterilized by manufacturer and only stored until use
Space requirements for the long term storage of empty vessels	Space	Space for carriers and inventory of packaged BPCs prior to use
Extensive labor with preparation of vessel for use (CIP, SIP, etc.)	Operating cost	Labor with preparation of carriers and installation of BPCs at use time
Expense and long lead times for purchasing stainless steel vessels	Capital cost	Carriers for holding the BPCs have relatively shorter lead times and lower costs
Utility systems to clean and steam in addition to the process water	Capital cost	Utility system for process water
Energy and cleaning chemicals	Operating cost	Maintain inventory of packaged BPCs prior to use
Treatment or disposal of cleaning chemical solutions	Operating cost	Disposal of used BPCs
Vessel validation can be inconsistent for older vessels	Quality/change control	Change control process for material improvements or manufacturing changes in single-use components and BPCs
Safety concern with vessel handling (size and weight)	Safety	Relatively lightweight BPC components

Table B Benefits that can be realized from the use of single-use BPCs

	Economic	Process	Utilities/Waste	Validation	Other
Advantage	▸ Less Capital ▸ Less Materials ▸ Less Labor ▸ Less Space ▸ Faster builds / mods	▸ Reduced down time ▸ Quicker set-up time ▸ Quicker batch turn ▸ Increased flexibility ▸ Closed systems ▸ Rapid configuration ▸ Development of integrated systems	▸ Less water used ▸ No steam used ▸ Reduced electrical ▸ Reduced waste water	▸ No CIP ▸ No SIP	▸ High level of innovation ▸ Large potential for improvements ▸ Amenable to Lean
Disadvantages	Consumables	Scalability	Waste treatment – Neutral	E / L studies	Supply chain

4. Mitigation of batch losses due to particulates, foreign objects, leaks from gaskets, or valves on tanks
5. Elimination or reduction of tank management activities globally
6. Inventory of single-use containers at drug substance warehouse, resulting in local and quick availability for storage and transport
7. Reduction of lead times for purchase of single-use containers related to fabrication and the installation qualification/ operational qualification (IQ/OQ) of stainless steel tanks

As with the implementation of any new technology, there are precautionary measures that should be considered in order to minimize the risks and gain the advantages. Possible concerns are:

- How is the sterility of the single-use BPC achieved and maintained?

  Single-use BPCs are often manufactured as part of a closed-system assembly. Many assemblies are gamma sterilized. Once sterilized, the closed system will remain sterile unless it is opened. Since the assemblies typically need to be

connected to other process equipment, they include sterile connectors that allow one to make these connections and retain the sterility at the connection and therefore for the entire assembly.

- Will exposure to the freeze-thaw conditions cause the BPC to develop leaks that compromise sterility?

  Validation of single-use containers is required to confirm the applicability of components under operating conditions. While components in single-use systems may seem more limited under extreme conditions, stainless steel systems often contain gaskets and elastomers with different heating/cooling characteristics. The expansion/contraction coefficients of steel/plastic interfaces can lead to leaks and sterility issues. Testing of final packaging vs. established ATSM International and Department of Transportation standards is recommended.

- Will the validation of the film and other components of the BPC delay projects?

  Validation is an important factor that applies in all situations where single-use components are integrated into a process. Validation of components that are applied in freeze-thaw processes needs to follow similar protocols. A well-planned implementation program should address the validation issues for material compatibility and applicability of single-use components under the extreme conditions of the freeze-thaw operation. Extra care and planning should be taken to study any effects of light, elastomers, or pH changes that occur during storage and shipping in single-use containers.

- What temperatures can BPCs handle?

  This is highly dependent on the film type. Most of the single-use films available today are multilayered. The glass transition temperature (Tg) state of the film varies depending on the makeup of the multilayered film. Typical single-use systems are validated for operation at the normal biopharmaceutical operating temperatures ranging anywhere from 4ºC to 40ºC. Since many freeze processes need the product to be at -80ºC, it is important to select components that are compliant and tested at this lower temperature. The polymers that make up the film and other single-use components are recommended to have cold crack temperatures that reach at least -80ºC. BPCs made from films that can handle these temperatures are starting to become available for commercial use in these applications. These criteria can be confirmed in handling tests where the assemblies go through several 48-hour cyclic processes at temperature cycles ranging from -85ºC to +40ºC.

- What pressures can BPCs handle?

  The film that makes up the BPCs can typically handle only a few pounds per square inch (psi) of pressure. However, the reusable containment vessel for the film is designed to support the film and handle the pressure requirements of the process. When these two components are properly designed to work with each other, the pressure capability is met with ease and does not cause increased risk.

- Since gamma irradiated assemblies/BPCs have a specific shelf life, how can the risk of having to dispose of unused but expired products be eliminated?

  Normally the shelf life is several times longer than the delivery time for the assembly. The inventory kept on hand in today's just-in-time environment is usually well within the shelf-life limit. The critical factor in defining the level of inventory is how quickly the next order can be delivered. Having an established delivery time from your vendor, by agreement, experience, or both, is the best way to make sure you have enough (but not too much) single-use products for your operation's needs.

Conclusions

The freeze-thaw process entails complex operations that are time-sensitive and can be logistically challenging. However, the process provides flexibility that is increasingly important in today's versatile and fast-changing operational arenas. Incorporating a freeze-thaw process with multiple locations is an undertaking that requires experienced resources, capital, and a well-executed plan to manage all the interconnected disciplines. The routing and management of reusable stainless steel vessels in the traditional freeze-thaw process require a synchronized operation that is very sensitive to deviations. A deviation in one part of the cycle can propagate throughout the whole operation. This can quickly destabilize an operation and require immediate attention from multiple resources. Incorporating single-use disposable equipment helps break the chain of propagating deviations and reliance on sole-sourced tank manufactures. Having a source of ready-to-use single-use freeze-thaw vessels minimizes the risk of delays and contamination of the bulk freeze process. Use of single-use technology in the bulk freeze supply chain can lead to smooth and efficient operations while minimizing the costs associated with reusable stainless steel systems. ◂

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About the Authors

Adam Goldstein has been a member of the biotech community for 20+ years. His experience bridges early-stage research and development as well as large-scale late-stage development. Over the years, Goldstein has developed new novel chromatographic and downstream capture processes. Prior work includes bacterial, mammalian, adenovirus, yeast, and human-derived materials. Goldstein was a downstream lead for five significant biotech start-ups, including Genentech, Amgen, Biogen, Baxter, Life Technologies, and GenVec facilities. He has authored numerous publications and is the inventor for several patents utilizing downstream processing techniques to purify novel proteins. He has lectured on the professional chromatography circuit as well as at several colleges on chromatographic techniques and scale-up techniques. More recently, Goldstein's work has involved leadership for some of the largest commercial manufacturing facilities in the United States. He is a co-founder and Member of the ISPE Communities of Practice (COP) Disposables users' forum and a scientific adviser for the IBC BioProcess International Conference (IBC) series and the American Pharmaceutical Review. Goldstein earned his Bachelor of Science in immunology from Old Dominion University in Norfolk, Virginia, as well as a biochemical regulatory engineering certificate, cGMP practices, from the University of Maryland. He also holds a Master's degree in biomedical sciences/molecular biology from Hood College, in Frederick, Maryland. He can be reached by email at goldstein.adam@gene.com.

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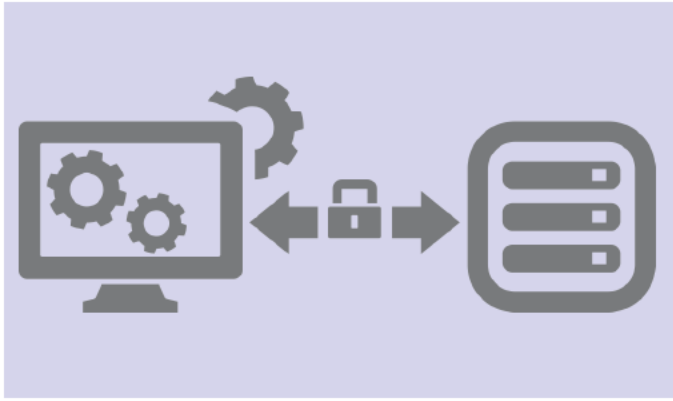
AN ELECTRONIC FORMAT FOR DATA EXCHANGE BETWEEN RAW-MATERIAL SUPPLIERS AND END USERS ENABLING SUPERIOR KNOWLEDGE MANAGEMENT

Ting Wang, Bryan Looze, Tony Wang, Duncan Low, and Cenk Undey

This article presents a standard format for electronic-data exchange between suppliers and end users in order to encourage superior knowledge management.



Abstract

Transferring data in electronic format between suppliers and end users greatly facilitates information exchange and enhances information usability. This article documents a standard format for electronic-data (eData) exchange between suppliers and end users. Initially, eData will operate with information available in Certificates of Analysis (CoA) or Certificates of Conformance (CoC), though it can be extended to handle in-process information from the supplier and its incoming raw materials, as appropriate. This information can complement information gathered using spectral inspection technology (such as near-infrared (NIR) and Raman) or key geometric or physical attributes (such as material strength). Exchanged information can be used to examine the impact of variability on process performance and product quality using multivariate analysis (MVA). However, the eData model is not initially intended as a replacement for formal CoA/CoC information. The project's long-term goals include developing predictive models for adaptive process control, implementation of process analytical technology (PAT), better specification development, and control of raw-material variation at the supplier. These advances will take place in multiple stages and affect multiple knowledge elements by effectively employing big data capture and analytics.

Introduction

It has long been recognized that raw materials (RMs) are an unpredictable variable that can affect process performance and product quality in pharmaceutical manufacturing. The definition of RM in the biopharmaceutical industry can be very broad and may include materials used in drug substance (DS) manufacturing, such as media, buffers, disposables, resins, and filters; excipients used in drug products (DP); as well as primary containers, such as syringes, vials, cappers, and stoppers.[1–2] Due to the complex nature of DS manufacturing, many media components, notably complex additives such as soy hydrolysate, pose variability challenges to cell-culture processes. Understanding relevant variability risks is crucial for optimal processing. The presence of particles, bioburden, and residual metals can result in rework, rejection, or quality investigations.[3–7] Primary container surfaces, air-liquid interfaces, and lubricants can mediate protein denaturation. Leachable plastics and latex rubber may contaminate a product by forming adducts with product materials, causing allergic reactions and immunogenicity.[8]

These are just a few of many examples, highlighting the fact that variability among RMs is a pressing concern. Thus, understanding and controlling variations among RMs is critical to protecting the robustness of biopharmaceutical processing and product quality. As processes become better understood and better controlled, the residual impact of RM variation will become more pronounced. This is a common concern across the whole pharmaceutical industry[1, 9] and the principles described in this paper are therefore broadly applicable.

There are several causes of RM variability: RMs can be derived from natural products, which makes them susceptible to seasonal as well as natural and man-made environmental changes. Variability among starting materials, in equipment used for manufacturing certain RMs, in the environment during the manufacturing process, or on the manufacturing site and among its personnel, can have an impact on material properties—even batch to batch within the same supplier. Additionally, unexplained variations in physical and chemical properties can also provoke some of the manufacturing problems that emerge unpredictably throughout the life cycle of a DP.[9,12]

To minimize and control the risk from RMs, therefore, it is necessary to identify and understand the sources of RM variability.

Sourcing Transparency

Supply-chain transparency is vitally important in an age of increasing globalization. The parties representing each link of the supply chain need to be open about, and appreciative of, their roles. A pharmaceutical company must be knowledgeable about their RM suppliers—offering information traceable through each level of sub-suppliers, as far as is necessary. This knowledge background is important to both ensuring supply continuity in the event of a local disaster and supply-chain integrity in the event of a deliberate attempt at adulteration.

Change Management

Transparency leads to increased predictability. For example, information about changes introduced to a material or conversion process helps predict which changes will occur in downstream manufacturing. Communicating such changes clearly allows for manufacturers to understand and control potential downstream impacts.

Material and Supplier Qualification

Current RM qualification practices require confirmation of identity for each batch of RMs on receipt, obliging the supplier to provide a Certificate of Quality or equivalent documentation. In addition, the supplier must pass audits of its facilities, provide analytical results that are confirmed reliable, and deliver a sampling plan for each incoming material.[1]

A common risk-mitigation practice for RMs is to conduct RM characterization and improve RM specifications beyond what is required according to applicable compendiums. In order to identify critical quality attributes of a material, we deploy RM risk-assessment tools, such as failure mode and effects analysis, which help predict the relationship between RM attributes and performance. Variability within specification can still affect product quality or processing performance; if a material or the process itself is found to be suspicious, the supplier can be asked to help. At that stage, additional testing, batch screening, and lot-to-lot blending are key procedures, employed either in-house or by the supplier.

The pharmaceutical industry is starting to call upon best practices initiated by other industries in order to develop a deep and holistic technical understanding of key RMs, their manufacture, their use, and their common interactions. Such approaches involve detailed technical engagement with suppliers, through initiatives such as supplier-relationship programs, technical visits, and effective audit programs. All these approaches are intended to advance and share knowledge, as opposed to ensuring compliance through a more traditional audit-style approach.

An important element in advancing knowledge about RM variability is the exchange of data between suppliers and users. At the end of the chain of data being exchanged, end users (pharmaceutical companies) transmitting their findings from variability analyses back to suppliers can, in effect, close the loop. Such an approach provides a holistic end-to-end map of all variability sources with the potential to affect process performance and product quality while permitting the implementation of adaptive control strategies to minimize the impact of those variables. For example, reporting and tracking the content of trace metal ions in cell-culture media can be correlated to product-quality attributes and adjusted accordingly if a relationship is established.

We have piloted this concept with success at several suppliers. Through the Supplier Relationship Excellence program, we implemented an eData exchange using a standardized format. We then reviewed data-analysis results with suppliers to identify the root causes of RM variations and improve RM consistency, thereby enhancing manufacturing performance. This article describes and discusses an electronic format for data exchange between suppliers and end users. Our objective is to achieve a pharmaceutical-industry-wide standard format that benefits both suppliers and end users, one made widely available through a standards organization such as the American Society for Testing and Materials (ASTM) for optimal end-to-end information flow. We envision the electronic transmission of CoA/CoC and other RM-related data becoming commonplace over the next few years. Having a standard will discourage unnecessary duplication of effort and lower the activation energy required between RM suppliers and users in establishing data exchange for trending information and data analysis for studying variability.

Basic Concept

Raw-material manufacturing processes provide rich data from incoming materials, in-process controls, and final-release testing. However, it has historically been a challenge to access the whole picture. (See Figure 1.) The most commonly used/available data is

Figure 1 Example of a raw material data set (S-1 Data: 2nd tier supplier; S-2: 3rd tier supplier)

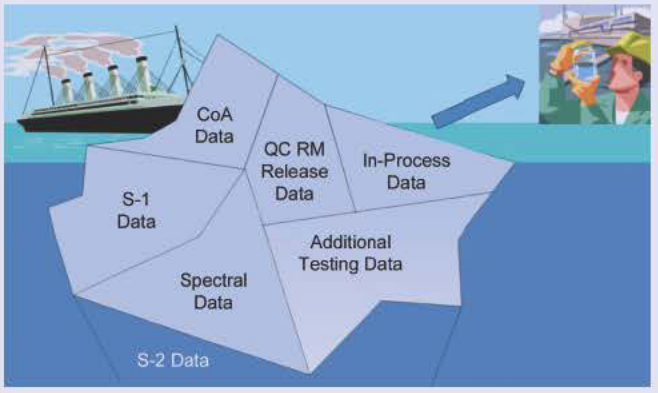


Figure 2 RMIS system design and process flow diagram

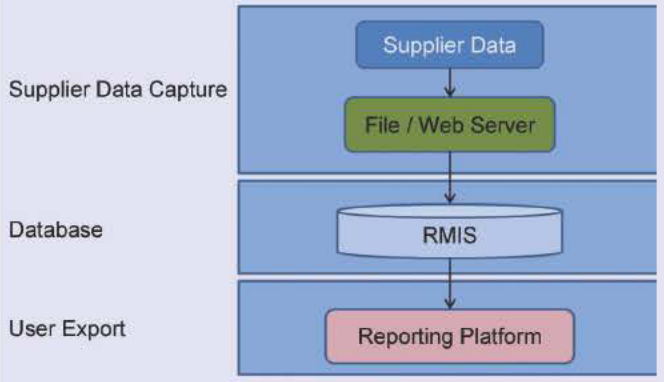
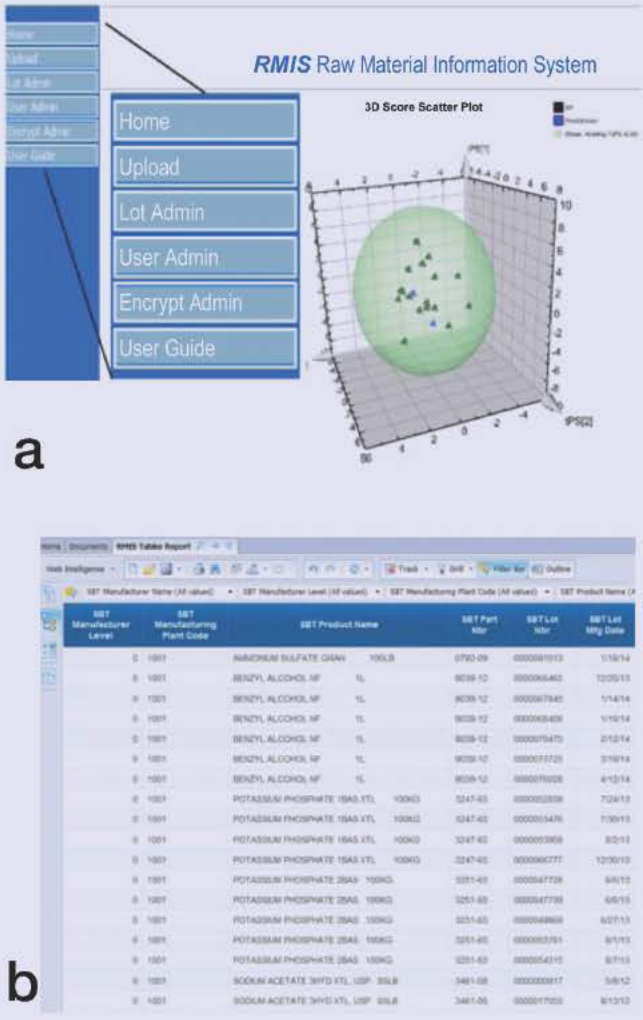


Figure 3 Representative view of RMIS
(a) Web form; (b) Reporting tool



provided in the CoA/CoC, which offers only a small portion of the comprehensive data set fully describing the RM. Additional data sets depend on the materials. They may include QC RM release data, in-process data (i.e., in-process testing results, control data, or process-monitoring data), data from tier 2 or tier 3 suppliers, spectral data, dimensional and functionality data, as well as additional information. Compared to these, CoA/CoC data is simply the tip of the iceberg. To improve our understanding of RM variability, we must understand the iceberg in its entirety, including relevant RM-related variables and data ranges appropriate to studying variability. Collaboration with suppliers through the exchange of key RM data beyond CoA/CoC information provides many opportunities to improve our knowledge and understanding of specific manufacturing processes. As the first logistical step to establishing robust data capture and management systems, we have developed a standardized, scalable, and validated Raw Material Information System (RMIS).

RMIS was designed to ensure that data is readily retrievable and verified in a format easy to analyze. Figure 2 shows an overview of the database components and its process flow diagram. As a Web-based application, the front end of RMIS is built for data exchange with suppliers, who provide information about RMs in standard file formats through a secured file transfer protocol (sFTP). In addition, the Web application has an on-demand upload page and a user administration page (Figure 3a) that allows entry of additional data coming from manufacturing sites until the transfer of such files can be automated. The RMIS back end is a Relational Database Management System, for exporting and reporting data through a reporting platform. Figure 3b is an example of a tabular report generated by that platform. The reporting platform can be used to select RMIS data from the database and connect it to data outside of RMIS but still within the end user's data universe, providing additional information pertaining to batches and material use, and to engage all parties with knowledge-management systems.

Another important step is to define and prioritize the scope of the data exchange and the format it will take with suppliers. In general, technical information such as prior knowledge and material/process characterization provides information to identify key parameters. RM data to be exchanged electronically may include data from CoAs/CoCs and other sources, such as the supplier's manufacturing process and in-process controls. In-process controls provide information about operational parameters measured in real time as well as process parameters such as temperature, moisture, other process set points, and performance parameters captured in Batch Records. Additionally, in-process controls may also deliver information about product quality attributes (such as dimensional and functional measurements) and rapid identification data (such as RM spectra generated from handheld spectral analyzers). The only limit to the data-exchange process is the capability of suppliers to provide data and of end users to define what information demands are reasonable and meaningful. In order to account for confidentiality and intellectual property concerns, we have developed a transformation formula and applied it successfully to data retrieved from some suppliers without losing key data-distribution characteristics.

To enable automated data transfer and data integrity, certain file formats are required, such as Extensible Markup Language (XML) and MS Excel files. (The XML format is more flexible than, and preferable to, the Excel format. A scheduled process auto-loads XML data files into an sFTP folder. Excel-based data files are converted to XML format for submission to the auto-load process on the RMIS Web server.) These formats allow for system parsing and information capture in certain fields and can be applied to multiple suppliers and various RMs in a scalable and sustainable fashion. The layouts of the XML and Excel files contain fields for entry of three major pieces of information: file/doc metadata, sample information, and measurement results. (See Figure 4.)

Figure 4 XML file layout

- Manufacturer Level: Manufacturing level relative to the customer (i.e., direct supplier = 0, supplier's component supplier = 1), with the default setting to direct supplier
- Manufacturing Plant Code: Code for (or name of) the plant at which this material was manufactured
- Manufacturing Facility: Code for (or name of) the facility at which this material was manufactured
- Container Number
- Product Name
- Part Number
- Lot Manufacture Date: Date upon which the lot was manufactured
- Lot Expiration Date
- Lot Number

File information includes document version, document date, and document time. These values apply to all of the supplier items listed in the document:

- Document Version: Document version number for suppliers. When the format of this XML document changes, this number will increase.
- Customer Version: Document version number for customers, used by customers who wish to track how this document has been processed
- File Contact Email: Email address for any questions related to the timing and format of the document
- Data Contact Email: Email address for questions related to eData results
- File Generation Date: Date upon which the data file was generated
- File Generation Time: Time at which the data file was generated (Eastern time)

Each supplier item maps to a supplier batch and contains the following elements:

- Manufacturer Name: Name of the manufacturer of this material
- Parent Manufacturer Name: If Manufacturer Level > 0 (indicating a position other than a direct manufacturer), this is the Manufacturer Name in which this material was actually manufactured.
- Parent Lot Number: If Manufacturer Level > 0 (indicating a position other than a direct manufacturer), this is the Lot Number of the material at the parent manufacturer.

Each measurement result maps to a Supplier Batch result or analysis and contains the following elements:

- Short Name: Short name for test/assay
- Long Description: Long description of test/assay
- Measurement Component: Used for multi-component materials to differentiate between similar tests on different components
- Measurement Attribute: Test result or attribute of a material or component (such as pH, purity, or outside diameter)
- Measurement Variable: Variable measured to differentiate between multiple variables measured according to the same attribute (such as minimum, maximum, or mean)
- Unit of Measure
- Measurement Number: Measurement number as documented by the supplier
- Measurement Type: One of five possible values: equal to (EQ), less than (LT), less than and equal to (LTE), greater than (GT), or greater than and equal to (GTE); used in conjunction with the Measurement Value field

- Measurement Value: Measurement value of test. Will be one of three possible values: PASS, FAIL, or a numeric value
- Measurement Text: Measured value with symbols as it appears on the CoA or data result
- Specification Number: Specification number related to the material (if available)
- Specification: Specifications with symbols as they appear on the CoA, since the "<" symbol may be used in this field
- Sample Location: If more than one measurement of the same type occurs, this field can be used to specify where in the process the measurement occurred.

Supplier data types, data-exchange standards, and current transfer technologies can be incorporated into a supplier quality agreement (SQA) to facilitate RMIS implementation.

A typical SQA would read:

End user shall provide the list of RM-related data (towards studying identification, monitoring, understanding, and control of RM variability) for applying eData transfer file-format standards and reserves the right to revise the list as needed. Suppliers shall provide the verified data related to raw materials electronically, in accordance with end user's data file-format standards.

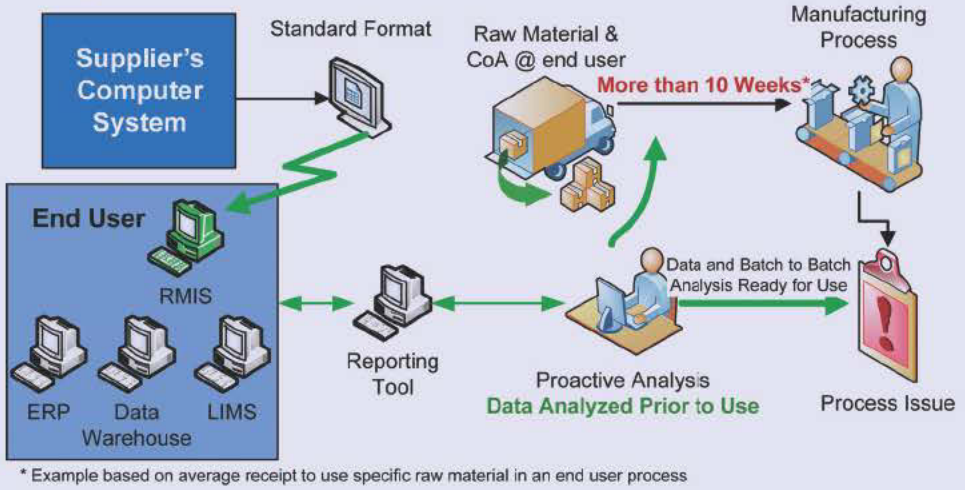
Once the basic infrastructure of the database has been created, and an agreement has been reached between the pharmaceutical company and suppliers, RMIS can be implemented and populated with supplier data at an agreed-upon update frequency.

Significance

Successful implementation of eData exchange allows a pharmaceutical company to share large data sets with suppliers, not limited to data about quality, and integrate those data into its internal information systems and knowledge-management tools. These activities allow better monitoring of RM variability throughout the supply chain, which is a foundation of PAT, providing improved understanding, control, and ultimately mutual economic benefits to both suppliers and pharmaceutical companies. For example, features such as fast data transfer and prevention of data recapture reduce cycle time and human interaction (and thus transcription errors), enabling a more streamlined business process. Through online access to supplier data offering custom sets of RM information, engineers and scientists can increase their efficiency on several levels while also expanding their potential to understand and reduce RM-related variability.

RM suppliers who understand sources of variability within their own production processes can thereby produce higher-quality products with science-based specifications, which may allow them to sell their products at a premium to customers. The intent of RMIS is not to increase quality burden or requirements on RM suppliers but rather increase knowledge about RMs among both suppliers and their clients. Having good process control and an improved understanding of how changes to processing

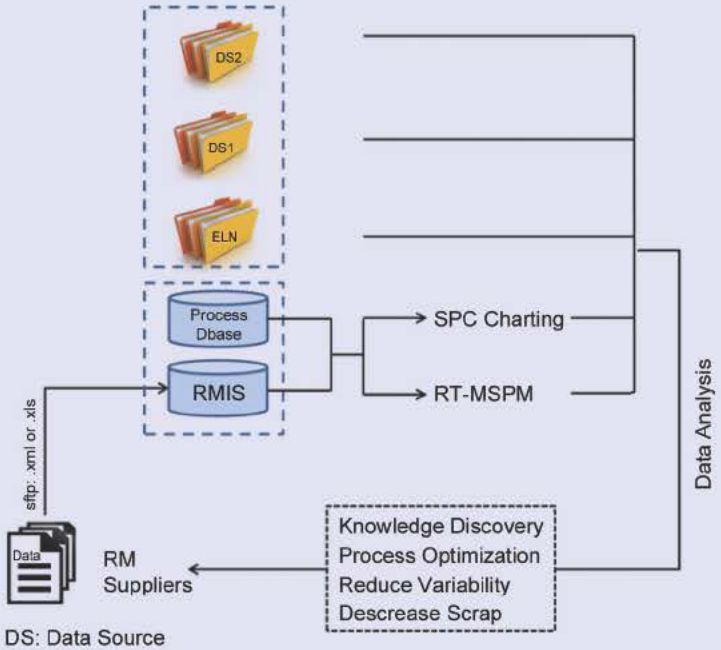
Figure 5 Proactive data analysis enabled by eData transfer process



* Example based on average receipt to use specific raw material in an end user process

RMIS: Raw Material Information System
ERP: Enterprise Resource Planning
LIMS: Laboratory Information Management System

Figure 6 Integrated view of data analytical tools and technologies utilized for mitigating RM variability



DS: Data Source
Dbase: Database
ELN: Electronic Lab Notebook
SPC: Statistical Process Control
RT-MSPM: Real-Time Multivariate Statistical Process Monitoring

affect suppliers' downstream partners will also increase RM suppliers' reputations, potentially decreasing the number of audit requests from their existing customers, and eventually attracting new clients. In addition, the ability to transfer large packages of information in close to real time can provide suppliers with a significant competitive advantage.

For a pharmaceutical company, eData exchange with suppliers is not only a change to data format but a paradigm shift from traditional in-house quality systems with a pure transactional-purchase approach to an integrated upstream-supplier extended-quality system and integrated partnership. Incorporation of information into the end user's system allows for proactive data analysis before RMs are used in production. Figure 5 demonstrates how the system works. In the existing process, the CoA/CoC and invoice are typically sent when the materials are shipped. An average total time from receipt to use for a particular cell-culture media component could be more than 10 weeks. With eData transfer, RM quality data can be made automatically available to the end user's RM database even before the materials arrive. Online access to supplier data allows the end user to take advantage of the 10 weeks of shipping time to analyze the data for trends. RM variability may be monitored by comparing incoming batches with historical RM batches considered representative of the desired performance and inherent material variability. Any weak signals indicating RM inadequacy or atypical trends can be identified prior to new batches being used in production.

In addition, supplier data can be integrated with data generated from the end user's other information systems, such as production data, lab data, and purchase, distribution, and usage (ERP) systems.[10] Data-driven investigation, such as multivariate analysis (MVA) based on integrated data, generates insights into RM attributes and their impact on process performance and product quality, which expands knowledge about processes and helps to prevent undesired impacts on process performance and product quality. In the event of unexpected deviations, the data-driven approach allows for rapid troubleshooting. The impact of RM lot-to-lot variability on process parameters and quality attributes is rarely fully documented and accounted for during processing and product development, due to the limited number of RM batches typically used at the development stage. Once at a commercial scale, production inevitably encounters the effects of unforeseen RM variations. Another challenge is that RM properties are complex and interrelated, and traditional statistical methods are less suitable than MVA, which can effectively decipher these types of relationships.[11–12] Therefore, data-driven approaches with MVA of integrated commercial manufacturing data will provide insights into the understanding and control of RM. Customized RM information would complement process data and enable PAT-based manufacturing, therefore enhancing continued process verification as elaborated upon in a previous article written by our group.[10]

Online access to RM data and integrated information provides opportunities to employ powerful data-analytical tools and technologies to analyze and study RM variability. As shown in Figure 6, data from suppliers can be fed into existing information and data-management systems for statistical process control (SPC) charting and real-time multivariate statistical process monitoring (RT-MSPM). Such ease of analysis builds towards a future of MSPM-guided feedback loops between pharmaceutical companies and suppliers effectively managing the transmission of variation in RMs. Additionally, widespread RM data presents a prospective array of benefits in areas of inventory management, transportation, and distribution. Other state-of-the-art tools, such as visualization systems, can be employed to improve end-user interaction. For example, analytical results can be made available on large touch-screen displays and through handheld tablets accessible on the manufacturing floor.[10] To that end, holistic monitoring encourages a connection among manufacturers' cross-functional teams, including those responsible for operations, quality control, quality assurance, manufacturing science, and purchasing. Making relevant information highly accessible allows for better and more efficient decision making and easier dissemination of lessons learned regarding product quality and product-life-cycle management.

An integrated electronic system also reduces the handling costs associated with sorting, distributing, organizing, and searching through paper documents for RM data to be used in analysis. One challenge posed by the adoption of eData exchange is the initial set-up cost of making arrangements with suppliers and establishing the basic information system infrastructure. However, a standard format for eData exchange being adopted broadly across the pharmaceutical industry would effectively lower the activation energy required to implement the methodology in relationships between suppliers and pharmaceutical companies.

Summary

An important element in advancing the understanding of RM variability is the ease of data exchange between suppliers and users. An electronic framework greatly facilitates this exchange of information while also enhancing the usability of data. This article documents a standard format for eData exchange between suppliers and end users. Initial eData will cover information available in CoAs or CoCs and can be extended to in-process information from suppliers and their incoming RMs, as appropriate. This information can complement information gathered using spectral inspection technology or key geometric or physical attributes. A wider and more accessible array of information about RMs can be used to examine the impact of variability on process performance and product quality, particularly by using multivariate analysis to improve understanding of processes. Long-term goals of this initiative include developing predictive models for adaptive process control, improving specification

development, and controlling RM variation at the supplier. These interventions will take place in multiple stages and affect multiple knowledge elements by effectively employing big data capturing and analytics.

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Ting Wang, PhD, is a senior engineer in Process Development at Amgen. She is responsible for implementing an internal raw-material information system to enable automated capture of supplier data as part of the knowledge-management system for Amgen products' life-cycle management. Collaborating with cross-functional teams, she provides scientific and technical input in the areas of multivariate analysis and predictive modeling towards understanding and mitigating raw-material variations and risk. Dr. Wang's background is in pharmaceutical sciences; she holds a Doctorate from the University of Maryland at Baltimore. Her research in pharmaceutical excipient variability has been recognized through several awards and projects, including US Pharmacopeia (USP) fellowships (in 2011 and 2012), an Outstanding Contributed Paper Award (Regulatory Science, AAPS, 2010), and an International Pharmaceutical Excipient Council (IPEC) foundation award (2012). Dr. Wang is a member of the International Society for Pharmaceutical Engineering (ISPE) and of the American Association of Pharmaceutical Scientists (AAPS).

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Tony Wang is currently a senior engineer in the Digital Integration and Predictive Technologies group at Amgen. He is responsible for multivariate data analysis, raw-material process and method optimization, computer model development, including model predictive control, and furthering PAT with Raman and NIR technologies. Previously, he worked as a cell-culture engineer in Process Development and as a process engineer in Facility Engineering at Amgen. Wang is a chemical engineer by training and a licensed Professional Engineer (PE) with APEGA. He holds a Bachelor of Science in chemical engineering and a Master of Science in biomedical engineering from the University of Calgary in Canada.

Duncan Low, PhD, is scientific executive director in Materials Science, Operations Technology. He joined Amgen in 2003 and is an active member of several industry groups and scientific advisory boards, including the ISPE Executive Committee for PAT, the ASTM E55 Executive Committee developing consensus standards for the Manufacture of Pharmaceutical Products, and the Extractables and Leachables Safety Information Exchange (ELSIE). Dr. Low is co-author of the *Parenteral Drug Association Technical Report 66: Application of Single Use Systems in Pharmaceutical Manufacturing*. He holds a Master's degree in biochemistry from the University of Cambridge and a Doctorate in microbiology from the University of Glasgow.

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TESTS ON ROUGING AND EXPERIENCES DEALING WITH ROUGING IN PHARMACEUTICAL PRODUCTION

Thomas Blitz, Ernst Felber, Robert Haas, Birgit Lorsbach, Andreas Marjoram, Roland Merkofer, Tobias Mueller, Nathalie Schuleit, Marc Vernier and Thomas Wellauer

The present technical article (in 3 parts) discusses the current body of knowledge on the subject of rouging. It is based on insights from tests and operating experiences of companies that manufacture pharmaceutical medicinal products.

By means of a generic risk-based approach and a test setup derived from this, it is shown that the danger resulting from rouging for products and patients may be regarded as slight. As regards products, however, a conclusive appraisal may be obtained only by means of specific risk analyses. The risks resulting from derouging actions must also be considered in the overall assessment.

Part 1 of this article described the background on rouging, rouging formation, derouging and a risk overview. Part 2 of this article described tests and practical experiences in rouging formation and the influence of rouge coatings on cleaning efficiency.

Part 3 of this article describes test and practical experiences using different cleaning methods, discusses the influence of different derouging chemicals on stainless steel surfaces and gives a summary of the results and assessment (Part 1 to 3).

Tests and Practical Experiences

Cleaning Methods

To permit appraisal of the possible effects of an acid-based derouging solution on the surface of process equipment, a test tank (material 1.4435, mechanically polished; $R_a \leq 0.8$ µm), which has been exposed to rouge-forming conditions (see part 2 section 2.3), was cleaned by means of acid derouging (mixture of sulfuric, phosphoric and citric acids; see section 2.2, solution C). The following results were found:

- The rouge coatings present were completely removed from the tank surface (see Figure 1c).
- After derouging, the tank surface had a matt appearance (see Figure 1c).
- The measurement of the arithmetic average height Ra by means of profilometry did not reveal any increase in roughness compared with the initial condition.
- Compared with the initial condition, faster redevelopment of rouging was observed (see Figure 1d).

After the acid derouging, the tank was exposed once again to rouging-promoting conditions as part of the test procedure, then at the end of the test was subjected to pH-neutral derouging

(mixture of sodium dithionite, phosphonic acid and potassium hydroxide; see section 2.2, solution D). The following results were found in this case:

- The rouge coatings present were completely removed from the tank surface (see Figure 1f).
- The time needed for pH-neutral derouging was very much shorter than the time required for acid derouging.
- The tank surface did not exhibit any visible differences compared with the surface condition after acid derouging (see Figure 1f).
- The dark discolorations that the hot sodium hydroxide solution caused on the tank surface in the zone of the liquid level were clearly visible after derouging (see Figure 1f).

The comparison of the two derouging methods can be summarized as follows:

- Significantly shorter time consumption for the pH-neutral derouging variant
- No change of the tank surface by the pH-neutral derouging solution
- High selectivity of the pH-neutral derouging solution toward rouge coatings (see also section on determination of specific surface loads due to rouging)

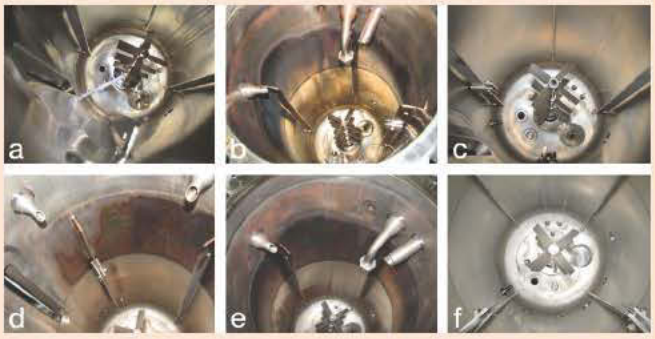
The surface conditions of the test tank before and after the respective derouging method used are illustrated in Figure 1.

The derouging solutions used in derouging were quantitatively analyzed as regards their metal concentration in order to determine specific surface loads due to rouging, i.e. the amount of corrosion products (rouge) formed per unit time and surface area under the CIP and SIP conditions employed here.

The specific surface loads due to rouging permit an estimate of which amounts of rouge will be formed under the given conditions within a specified time on a defined surface.

The rouge formed on the tank surface (material 1.4435) was completely removed and transferred into solution by both derouging methods. It was possible to determine specific surface loads due to rouging on the basis of the metal concentrations of the derouging solutions used as well as the known tank surface area and the times of exposure to cleaning and sanitizing operations.

Figure 1



(a) Test tank in the initial condition, (b) test tank before the acid derouging after 545 combined cleaning/sanitizing cycles, (c) test tank after the acid derouging; the slightly orange color can be attributed to the illumination of the tank, (d) derouged test tank after 48 combined cleaning/sanitizing cycles, (e) test tank before the pH-neutral derouging after 545 combined cleaning/sanitizing cycles and (f) test tank after the pH-neutral derouging

The calculated specific surface loads were $5.01*10^{-3}$ kg/(a*m²) (kilograms per year * square meter) for the acid derouging and $3.56*10^{-4}$ kg/(a*m²) for the pH-neutral derouging. The specific surface load determined for acid derouging therefore represents a worst-case value for any calculations of rouge ingress that may be carried out.

The value for the pH-neutral derouging is lower approximately by a factor of ten, thus confirming the higher selectivity (iron selectivity) of this derouging method. Because of the etching effect of acid derouging solutions, material is removed not only from the rouge layer but also from the base metal itself. The metal concentrations listed in Table A illustrate this circumstance.

To check the resistance of materials 1.4404, 1.4435 and 1.4539 to an acid derouging solution, test plates of these materials were mounted in the test tank while it was undergoing acid derouging and were then investigated as regards their weight change.

The resistance of the test plates to an acid derouging solution based on a mixture of sulfuric, phosphoric and citric acids (see solution C) is illustrated in Figure 2 on the basis of the measured weight losses. The material surface of material 1.4404 underwent the greatest change toward a matt surface and also exhibited the most pronounced weight loss due to the derouging solution. Material 1.4435 also exhibited clearly discernible surface changes, right up to a likewise matt appearance, and also suffered a significant weight, albeit to a smaller extent than material 1.4404. In contrast, material 1.4539 did not exhibit any significant weight loss or visually perceptible changes of the material surface (surface condition illustrated in Figure 7 in part 2).

The surface changes as well as the weight losses of material samples 1.4404 and 1.4435 can be attributed with high certainty to etching attack caused by the acid derouging chemicals.

Above and beyond the derouging of the test tank with acid and pH-neutral derouging solutions, a test was carried out to improve the understanding of the chemical and physical mechanisms during cleaning with phosphoric acid or a combination of phosphoric acid and sodium hydroxide solution. A particular goal was to investigate acid CIP in order to appraise its suitability for removing rouge coatings. Furthermore, it was planned to investigate the extent to which phosphates are formed on the rouged material surface due to such a treatment.

Two rouged test places of material 1.4435 from test 2.3 in part 2, "Rouge Formation due to Alternating stress of materials by cleaning and sanitizing Processes", were used as starting material in this test. In this test, one test plate was subjected to combined cleaning by means of phosphoric acid and sodium hydroxide solution and a further test plate was used as the rouged reference sample. Furthermore, an intact (non-rouged) test plate was used as an additional reference. This permitted a direct comparison between a rouged non-cleaned, a rouged cleaned and an intact non-cleaned material surface.

The cleaning with phosphoric acid comprises the following treatment steps:

Table A Metal concentrations of spent and fresh acid and pH-neutral derouging solutions

Element	Metal Concentrations (mg/L)			
	Acid-based, spent	Acid-based, reference sample	pH-neutral, spent	pH-neutral, reference sample
Chromium	364.06	0.54	1.28	0.06
Iron	1535.90	2.68	12.90	0.60
Molybdenum	46.65	1.08	0.09	0.07
Nickel	250.29	0.21	2.50	0.09
Manganese	27.30	0.07	0.13	0.06
Total	2224.20	4.58	16.90	0.88

Figure 2 Weight variation of the test plates exposed to CIP/SIP and additionally subjected to acid derouging after 325 CIP/SIP cycles

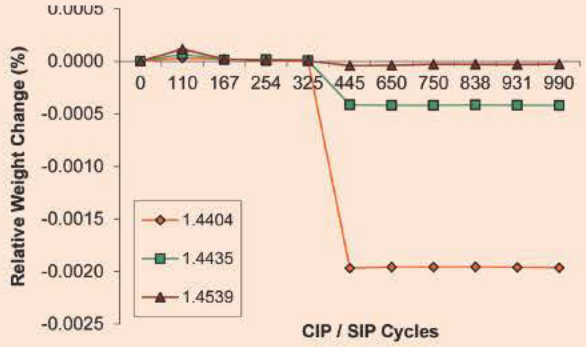
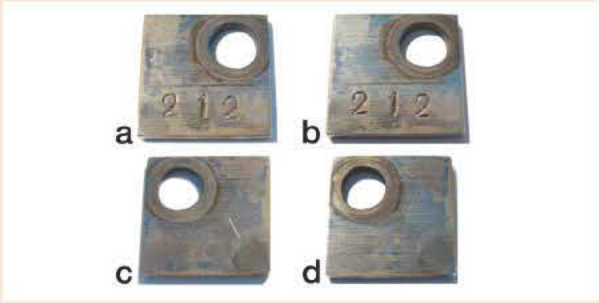


Figure 3



(a) Front side of the material sample (1.4435) before cleaning, (b) front side of the material sample (1.4435) after cleaning, (c) back side of the material sample (1.4435) before cleaning and (d) back side of the material sample (1.4435) after cleaning

1. Rinsing for 4 hours with 10% phosphoric acid at 60 ± 1°C
2. Intermediate rinsing with PW at room temperature
3. Rinsing for 15 minutes with 1% sodium hydroxide solution at 80 ± 1°C
4. Final rinsing with PW at room temperature

After the cleaning with phosphoric acid, only small, visually perceptible surface changes could be observed on the rouged test plates in comparison with the non-cleaned test plates (see Table B and Figure 3).

From the comparison of the two ESCA profiles of the cleaned and non-cleaned test plates (see Figures 4a and 4b), it was particularly obvious that the iron oxide content in the cleaned test plate is much smaller than that of the non-cleaned test plate in the near-surface layers (down to approximately 20 nm). A significant difference in the content of metallic iron can also be observed down to a depth of 90 nm.

The chromium oxide peak of the cleaned test plate is much broader than that of the non-cleaned test plate. In both test plates, the oxygen content is bound mainly in the form of chromium oxides (main content at 0 to 40 nm). From a depth of approximately 90 nm on, the elements of both samples again approach a distribution corresponding to the alloy composition.

Phosphating of the cleaned test plate was discernible only on the basis of the general ESCA spectrum. Thus as much as 1% phosphate (P2p) is bound at the surface of the cleaned test plate, but even at small sputter depth it was no longer detectable (Figure 4d).

Furthermore, the comparison of the ESCA profile of the sample after cleaning with phosphoric acid with that of the intact, non-rouged reference sample (see Figure 4c) made it obvious that the initial condition could not be restored by cleaning with phosphoric acid.

Judging by experience, acid CIP with phosphoric acid may have a positive effect on the visual appearance of stainless-steel surfaces with light rouge coatings. On the other hand, this method is hardly suitable for removal of heavier rouge layers. Nevertheless, neither can any detrimental effect be observed by such a treatment. In particular, it is noteworthy here that only slight traces of phosphorus bound to the material surface are present (see Figure 4d).

Influence of Different Derouging Chemicals on Stainless Steel Surfaces

In the following studies, the influences of different derouging solutions on the surface of steel alloy 1.4435 are investigated. It is often asserted that derouging of pharmaceutical systems does not cause any change of the electropolished surface condition.

Two independent approaches were followed to check this thesis. The first approach relates to investigation of the influence of different derouging solutions on non-rouged surfaces, while the second approach considers the influence of different derouging solutions on already rouged surfaces.

Part 1: Non-rouged Test Plates

The test plates are made from stainless steel 1.4435, ground and electropolished. No rouge is present on the test pates.

Positions to be used for repeated investigation by means of the scanning electron microscope and the optical profilometer (FRT Microprof) were defined for all test plates. The investigations were carried out respectively at the beginning of the test and after completion of 15 derouging cycles with the different derouging solutions. No repassivation is carried out between two cycles.

Table C lists the derouging solutions used. These correspond to the various state-of-the-art derouging solutions currently used in the pharmaceutical industry. One derouging cycle includes the steps listed below:

Table B	Change of weight of material sample 212 treated with phosphoric acid and sodium hydroxide solution
Weight before cleaning (mg)	5349.15
Weight after cleaning (mg)	5348.87
Weight decrease (mg)	0.28
Relative weight decrease (%)	0.000052

Table D	Composition and concentration of the investigated solutions
Solution ingredients	
20% Nitric acid (HNO_3) + 5% hydrofluoric acid (HF)	
3% Citric acid	
5% Phosphoric acid (H_3PO_4)	
5% Nitric acid (HNO_3)	

1. Cleaning (degreasing) with isopropyl alcohol/water (70/30)
2. Complete immersion in the derouging solution at the temperature indicated in Table C for six hours
3. Rinsing with demineralized water
4. Drying in air

The corrosion rate was calculated after 15 cycles (Figure 5). For all derouging solutions it is smaller than 0.004 mm/a, except for solution E, which has a corrosion rate of 0.3 mm/a. Neutral solution D exhibits the smallest corrosion rate, of slightly over 0.001 mm/a.

The small corrosion rate of neutral solution D compared with the acid derouging solutions is therefore consistent with the results of the derouging tests on a test tank (see part 2, section on "Influence of Rouge Coatings on Cleaning Efficiency"). This means that the neutral solution has higher selectivity and derouging efficiency while at the same time causing less material removal.

The metal surfaces before and after the 15 derouging cycles are illustrated in Figure 6 to Figure 10. For the most part, the electropolished surface was changed only slightly by the treatment: defects and grain boundaries are still clearly discernible. In the case of solution B, which is based on citric acid, oxalic acid and sulfuric acid, the grain boundaries are attacked but no further attack of the grains themselves is observed in the investigated zone.

In the case of solution E, which is based on hydrofluoric acid, the grains are attacked so intensively that it was no longer possible to relocate the same site after the 15 derouging cycles. Locally grains are completely removed (Figure 10b). The surface exhibits matting.

After the treatment with solutions B and D, isolated stains are present on the metal surfaces.

A significant change of surface roughness as represented by the Ra value could not be observed after the treatment, even in the case of the sample most severely attacked by solution E (Figure 11).

With the exception of solution E, the electropolished surface was not significantly influenced by the other investigated derouging solutions.

Part 2: Rouged Steel Samples

The cleaning ability, the influence on surface roughness and the corrosion rate or rate of material removal at various temperatures is investigated by means of various acid solutions. Pipe samples of stainless steel 1.4404 are used as the material. The pipe samples are taken from a sterilization process using pure steam. Because of the regular contact with this medium, they exhibit light rouging. The acids or acid mixtures that were used are shown in Table D.

The pipeline to be investigated was cut apart longitudinally and samples of approximately 2.5 × 5.5 cm were prepared from the half shells. The exposure time, the temperature and the calculated corrosion rate are listed in Table E. The derouging efficiency (cleaning ability) was estimated from an optical comparison with the untreated sample.

An attempt was made to determine the cleaning ability by means of Raman spectroscopy. Because of the inhomogeneous signals and the rouging distribution on the surfaces, it was not possible to evaluate the obtained spectra quantitatively. The cleaning ability was therefore estimated only visually.

At room temperature, the rouge coating could be completely removed only by 30 minutes of "etching" (20% HNO_3 + 5% HF). The corrosion rate under these conditions was 13.4 mm/a.

Table C	Ingredients, pH values and temperatures of the investigated derouging solutions		
	Solution Ingredients	pH Values	Temperature
A	Phosphoric acid; citric acid	pH < 1	approx. 70°C
B	Citric acid; oxalic acid, sulfuric acid	pH < 1	approx. 70°C
C	Sulfuric acid; phosphoric acid; citric acid	pH < 1	approx. 70°C
D	Sodium dithionite, phosphoric acid and potassium hydroxide	pH = 7	approx. 70°C
E	Sulfuric acid, hydrofluoric acid, hydrochloric acid	pH < 1	approx. 30°C

Passivation at a temperature of 60°C with 5% nitric acid for an exposure time of 24 hours also led to almost complete removal of the rouge coating. In this case also, even shorter exposure times would be sufficient. The corrosion rate was lower than 0.1 mm/a.

Even three hours of treatment with 5% phosphoric acid at a temperature of 80°C was able to remove the rouge coating almost completely, although the corrosion rate in this case was approximately 0.1 mm/a. At room temperature, on the other hand, 5% phosphoric acid was not sufficient for removal of the rouge coating.

A treatment with 3% citric acid during an exposure time of 3 hours at 80°C led to only a slight reduction of the rouge coating. In contrast, the treatment with an exposure time of 6 hours at room temperature had no effect as regards removal of rouge coatings.

A significant change of surface roughness could not be observed after the various acid treatments. For all samples the Ra values ranged from 0.2 to 0.6 µm (untreated sample 0.2 to 0.5 µm).

The conducted investigations show that only hydrofluoric acid should not be used as a derouging solution, because of the severe material removal that it causes. All other chemicals exhibited slight material removal during the derouging process.

Because the changes of surface roughness due to the different treatments were only small, the Ra measurement has very limited or no suitability for a meaningful assessment of the possible surface changes due to derouging solutions.

Test to Determine the Degree of Rouging by Color Measurement

At present, rouging is usually noted and appraised by visual inspections. Because of the individual color perception of the appraising person, this method proves to be highly subjective. An objective measuring technique would have the advantage of being able to express the subjective color perception by defined parameters, on the basis of which an assessment scale for rouged surfaces could be defined. The assessment scale is intended to permit an objective estimate of the degree of rouging and therefore of the success of derouging actions. In two production tanks, zones exhibiting rouging of different intensity were scanned using the CM-700D mobile spectrophotometer of Konica Minolta.

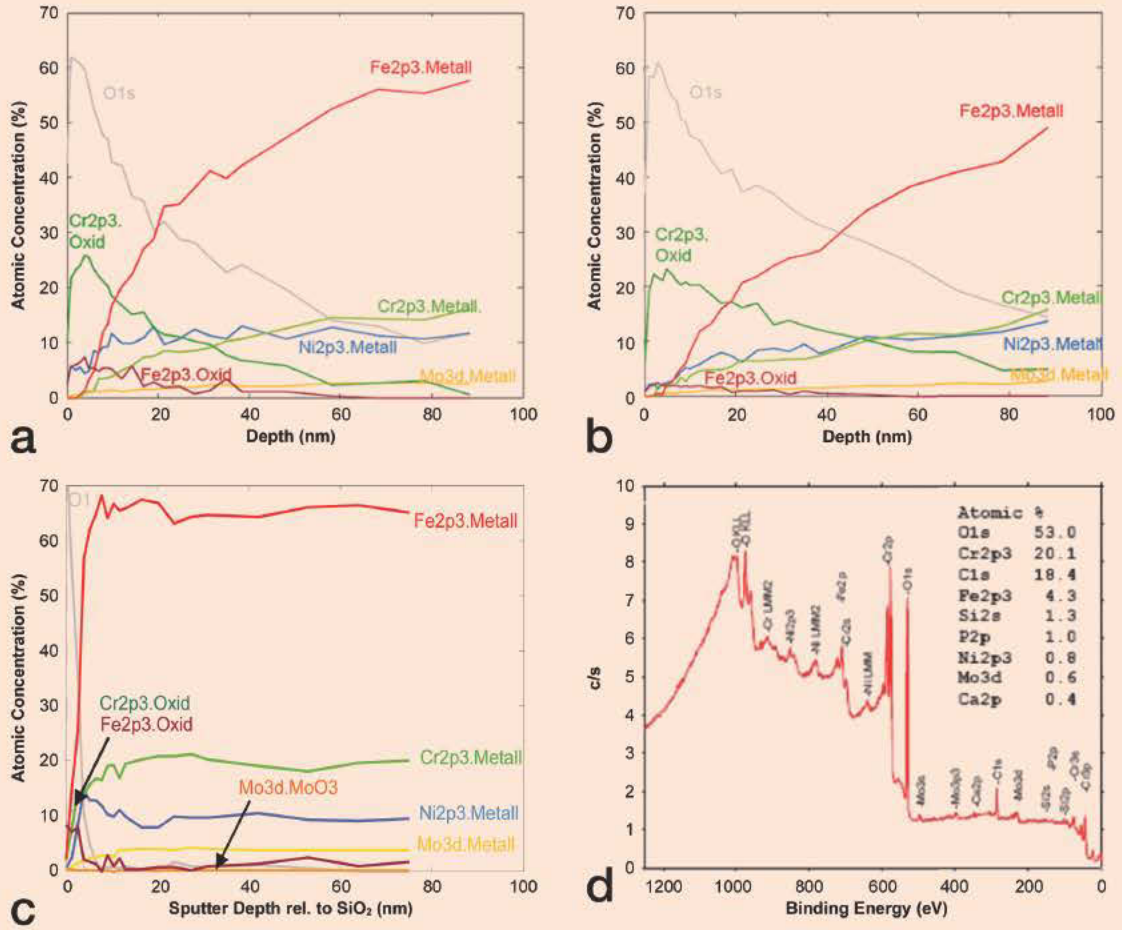
The color measurement was carried out in the Lab color model. This model covers all visually perceptible colors. This Lab model assigns each color a color location with coordinates L (luminance or brightness axis), a (red-green axis) and b (blue-yellow axis), thus spanning a Cartesian coordinate system in three-dimensional space. From these three color coordinates it is possible to calculate the color distance ΔE, which is used to describe the differences between two color values.

A triplicate measurement was made for each measuring point. Starting from the metallically bright surface, the color proceeded with increasing rouging through dark-gray and yellow to an intensive red hue.

Even though the L-value, which shows a decreasing trend with increasing degree of rouging, correlates with the visual color impression, the following reasons show that this instrumental technique is not suitable for a completely objective appraisal of the degree of rouging:

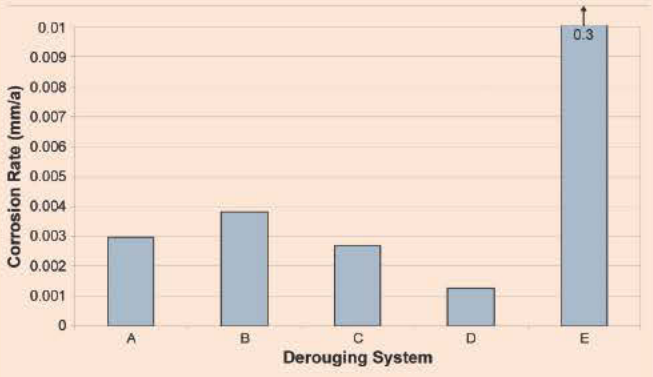
On the one hand, the problem exists that different combinations

Figure 4



(a) Rouged reference sample of material 1.4435; ESCA depth profile, (b) rouged and cleaned sample of material 1.4435; ESCA depth profile, (c) intact reference sample of material 1.4435; ESCA depth profile and (d) rouged and cleaned sample of material 1.4435; general ESCA spectrum

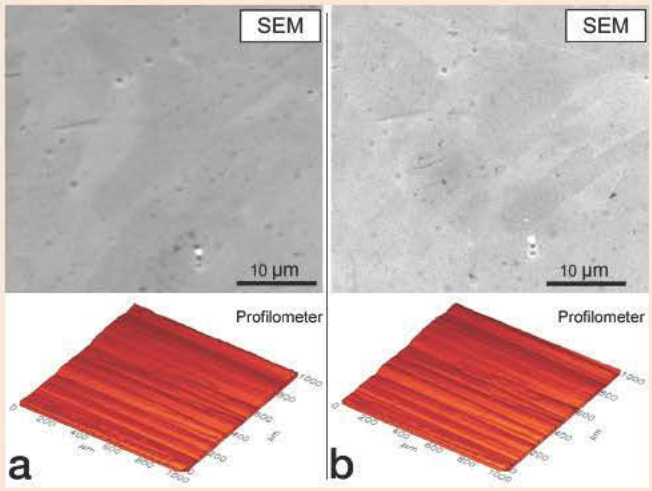
Figure 5 Corrosion rate determined after 15 derouging cycles for the solutions used



of luminance L as well as of the color values a and b can lead to identical ΔE values. Thus the color distance ΔE can have identical values for surfaces in the initial condition and for surfaces with different rouging intensity, even when the color perceptions are different.

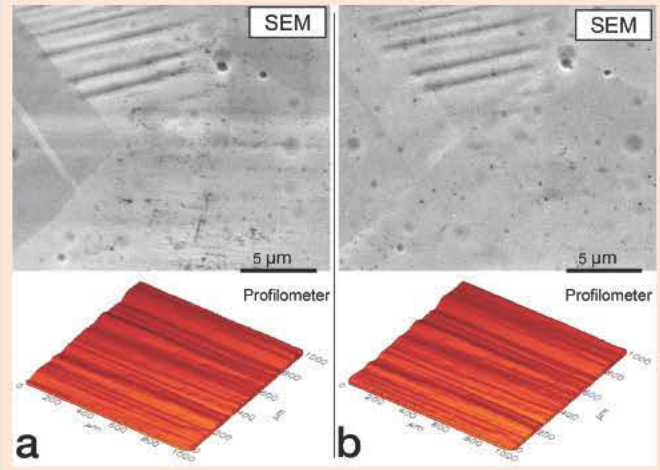
Furthermore, if the discolorations developed in the production equipment are not uniform, the problem arises of deciding which of the discolorations should be measured.

Figure 6 Derouging solution A



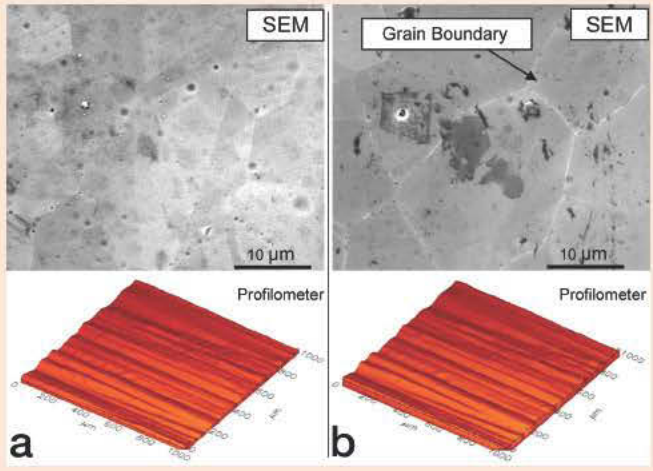
(a) surface before derouging and (b) surface after 15 derouging cycles

Figure 8 Derouging solution C



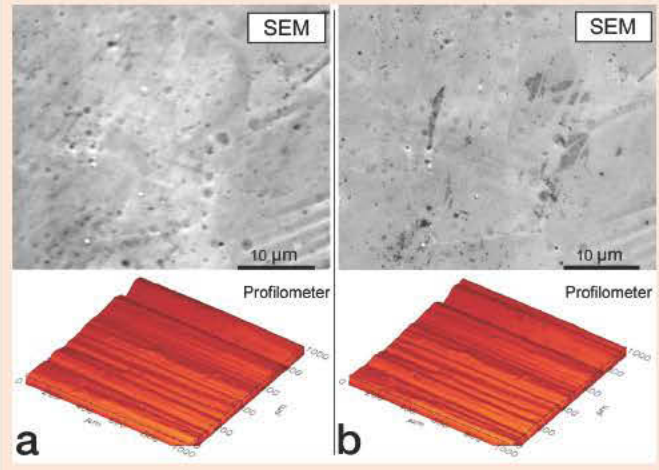
(a) surface before derouging and (b) surface after 15 derouging cycles.

Figure 7 Derouging solution B



(a) surface before derouging and (b) surface after 15 derouging cycles; stains and slight grain boundary attack

Figure 9 Derouging solution D



(a) surface before derouging and (b) surface after 15 derouging cycles; stains

Summary of the Results and Assessment

The results from the "Tests and Practical Experiences" section of Part 2 and the "Tests and Practical Experiences" section in this part are summarized and assessed below on the basis of the risks listed in Table 7 from Part 1.

Conclusion

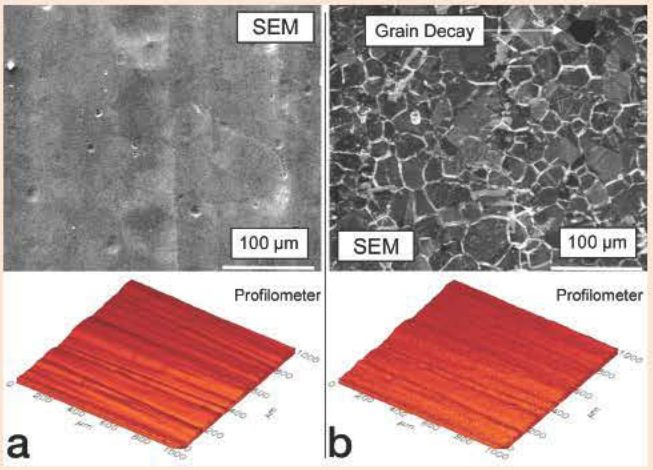
The tests conducted on the risks considered in part 1, table G show that rouging does not cause any risk to product safety.

No evidence was found that the water quality in a WFI system is negatively influenced by rouging. This is also the finding after many years of study. The requirements of the pharmacopeias were always safely complied with.

On the basis of this knowledge, the following recommendations can be made for dealing with rouging in pharmaceutical production:

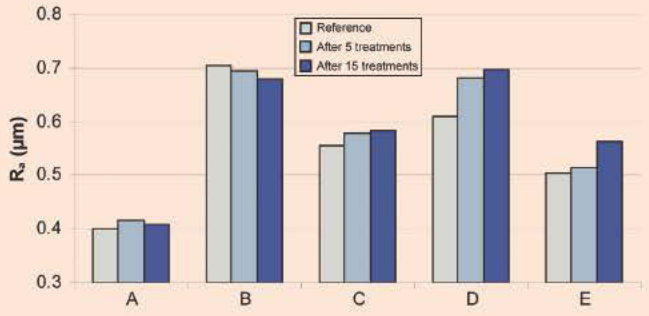
- Rouging within pharmaceutical production should be monitored. In particular, it must be ensured that the discolorations are due to rouging and not to other kinds of surface changes.

Figure 10 Derouging solution E



(a) surface before derouging and (b) surface after 15 derouging cycles; severe grain boundary attack and grain decay

Figure 11 Surface roughness Ra determined by means of profilometer after 5 and 15 derouging cycles for the solutions used



- In the case of rouging in systems having direct contact with product, the following rule applies: Derouging must be considered if any signs appear of a reduction of cleaning efficiency or if impurities due to rouging can no longer be detected with certainty.
- Derouging always necessitates a risk analysis, which should be undertaken in cooperation with specialized firms. In particular, risks to occupational safety as well as product and GMP risks must be assessed here. It must be ensured that the surface quality is not negatively impaired by derouging.
- The derouging procedure should be set forth in local instructions.
- In order to keep the influence on the material surfaces as small as possible, pH-neutral derouging methods are preferred over acid-based solutions.
- The success of derouging should be demonstrated on the basis of methods agreed beforehand, such as wipe samples and/or visual investigations.

Glossary

API	Active Pharmaceutical Ingredient (pharmaceutical, active substance)
CIP	Cleaning in Place (usually with hot NaOH solution)
Carry Over	Entrainment of impurities into the next batch or into a subsequently manufactured product
EDX	Energy dispersive X-ray spectroscopy
el.pol.	Electrolytically polished, electropolished
EMEA	European Medicines Agency
ESCA	Electron Spectroscopy for Chemical Analysis (also known as XPS, or x-ray photoelectron spectroscopy)
ICP-MS	Inductively Coupled Plasma-Mass Spectrometry
mm/a	Millimeters per year
PW	Purified Water (as defined in the European Pharmacopoeia)
RD	German abbreviation for Clean Steam (Reinstdampf)
REM	German abbreviation for Scanning Electron Microscope (Raster Elektronenmikroskop)
Rouging	Denotes both the surface color change due to oxidative corrosion products of corrosion-resistant steel alloys as well as the process by which these corrosion products are formed
RT	Room Temperature

Table E Results for the cleaning ability of the investigated solutions

Medium	Exposure Time (h)	Temperature (°C)	Corrosion Rate (mm/a)	Cleaning Ability (derouging) (%)
20% HNO_3 + 5%HF	0.5	24.0	13.4	95
3% Citric acid	6.0 3.0	24.0 80.0	0.02 0.06	0 40
5% H_3PO_4	6.0 3.0	24.0 80.0	0.02 0.09	30 95
5% HNO_3	24	60.0	0.02	95

Figure 12 Results of the action of various chemicals on the pipe samples

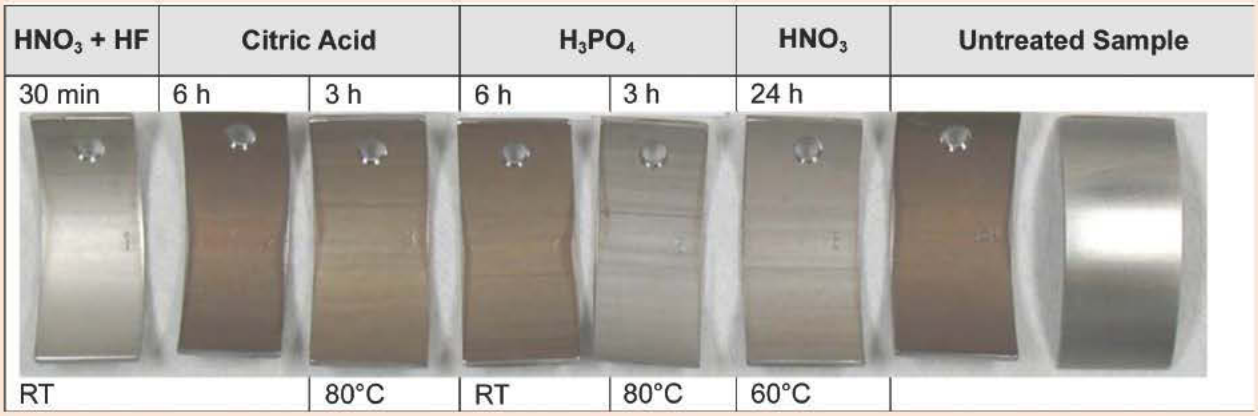


Table F	Summary of the results
Risk	**Summary of the Results**
Rouge ingress into the final product	▸ By virtue of the very small weight changes of the test plates, the tests for gravimetric determination of a material-specific corrosion rate (see part 2) yielded the knowledge that the rouging-related corrosion rate for systems having contact with clean steam and alkaline solution and subject to alternating stresses (CIP / SIP) is very much lower than the corrosion rate of $3.4*10^{-3}$ mm/a cited in the literature[9] and is also lower than the values of $4*10^{-4}$ mm/a (1.4435) to $1.8*10^{-3}$ mm/a (1.4301) determined in part 2 section on "Investigations by Surface Analysis". ▸ Analyses performed on WFI samples from rouging-stressed distribution systems in part 2, section on "Heavy Metal Concentrations" revealed an increased content of nickel only after prolonged circulation times without media replacement. Under normal operating conditions, no elevated concentrations of heavy metals were detectable, and the water quality therefore conformed with the legislative requirements. ▸ During the heavy-metal investigations of various APIs (see part 2, section on "Heavy Metal Concentrations"), an increased heavy-metal content was not detected in any of the investigated active substances.In this connection, no relationship between system age or potentially existing rouging and the heavy-metal content is perceptible. ▸ The investigated color-measurement method is not suitable for determining the degree of rouging of a surface (see part 3, section on "Rouge Formation").
Influence of rouge coatings on efficiency of cleaning of the process equipment	▸ Despite the adjusted worst-case conditions, the test of the influence of rouge coatings on the efficiency of cleaning (see part 2, section "Influence on Rouge Coatings") did not reveal any violation of the specified protein limit values for the test duration of 545 combined CIP/SIP cycles.
Derouging	▸ Acid CIP with phosphoric acid (see part 3, section on "Cleaning Methods") may have a positive effect on the visual appearance of stainless-steel surfaces with light rouge coatings. On the other hand, this method is less suitable for removal of heavier rouge layers. The tests on derouging of the test tank and determination of the specific surface load of rouge from derouging solutions (see part 3, section "Cleaning Methods") showed that the pH-neutral derouging method used selectively removes iron oxides (rouge), whereas acid derouging may also remove base metal in addition to the rouge coatings (etching attack), thus causing micro-roughening of the treated surfaces. Furthermore, the experience with acid-based derouging solutions in the first derouging action on the test stand showed that rouging proceeds much more rapidly after acid-based derouging than was the case in the initial condition of the test tank. ▸ In accordance with the investigations in part 3, sections on "Cleaning Methods" and "Influence of Different Derouging Chemicals" measurements of the surface roughness before and after a derouging operation are not suitable for appraising the surface condition.

SE	Secondary Electrons
SEM	Scanning Electron Microscope
SIP	Sanitization/Sterilization in Place
Specific surface load	Defined as the amount of rouge formed in a certain time unit per unit surface area The specific surface load is expressed in units of kg/(a*m²) (kilograms per year * square meter)
Swab	Polyester fabric cloth
TOC	Total Organic Carbon
VE-Wasser	German abbreviation for Demineralized water (Vollentsalztes Wasser)
WFI	Water For Injection

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A STRUCTURED TOOL FOR SUT IMPLEMENTATION

Carl Carlson

This article presents a tool for proactive single-use technology (SUT) design review and implementation. The tool utilizes a failure mode and effects analysis and a single-use design template for systematic review and risk assessment of SUT biotechnology facilities.

Abstract

Evaluation for the implementation of single-use technology (SUT) can be accomplished by utilizing a structured analysis by linking a single-use design (SUD) template with a failure mode and effects analysis (FMEA) template. The SUD template, coupled with FMEA, has been developed as a tool to document process steps and parameters. This enables the correlation of process steps and parameters with a risk assessment for the use of single-use systems (SUS) and SUT. The many facets of SUT implementation will be reviewed, and the use of the structured tool will be applied. Fixed stainless steel systems have the benefit of a fully scrutinized Installation Qualification/Operational Qualification (IQ/OQ) prior to use in manufacturing. SUT performing operations would benefit from having an abbreviated IQ/OQ applied every time a SUS/SUT is used. Process documentation via the SUD template is coupled with a risk-based evaluation of design approach via an FMEA template that could help to document process risks. This numerical evaluation also allows for sensitivity analysis to be performed so that key risk assumptions can be evaluated in a proactive way to support decision making.

Introduction

This article presents a structured approach for evaluating SUS/SUT that can be used to partially or completely replace traditional stainless steel systems. Regardless of what the motivation is to implement SUT (such as reduce cost, increase speed to market, and reduce non-recoverable investment), the discussions of its merits have been well documented.[1-3] Successful implementation requires a complete understanding of the process design space and the quality structure that will be applied to maintain control. A life-cycle approach for product process design and production shall be assumed.

In general, the tool for SUT implementation evaluation follows this sequence:

1. Establish the quality system.
2. Define the design space (DS).
3. Document the DS with the SUD template.
4. Perform risk-based analysis with the FMEA template.
5. Perform sensitivity analysis on the risk data.
6. Conclusion: finalize the design approach.

Establish the Quality System

There are many quality systems that can be employed to implement and document a manufacturing process. In addition, standards for equipment design, such as ASME BPE and ASTM E2500[6], have been developed to aid in designing production facilities with lessons learned for stainless steel systems that require cleaning and steam sterilization. Guidelines for SUT have not yet been well established; however, a Quality by Design (QbD) life-cycle approach can be utilized as the quality system framework[4] for SUT implementation.

One such quality system can be found in the International Conference on Harmonisation (ICH). ICH has guidelines that are broken down into four categories

Q – Quality Guidelines

S – Safety Guidelines

E – Efficacy Guidelines

M – Multidiscipline Guidelines

Of particular interest are ICH Q8(R2) QbD, Q9 Risk Management, and Q10 Quality System. ICH Q11, "Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)," illustrates the life-cycle approach described in ICH Q8(R2), Q9, and Q10.

The ISPE Product Quality Lifecycle Implementation (PQLI®) Guides, parts 3 and 4, has details on how to utilize this quality system.[5]

Define the Design Space

A key aspect of the ICH Q8(R2) QbD system is the definition of the design space and the life-cycle approach to design. The use and effect of stainless steel systems on process design space has been well established over the years for food, dairy, pharmaceutical, and biological processes. Many aspects that have an impact on product quality and efficacy can mostly be confined to within the facility, with a few exceptions being outsourced materials (media, filter membranes, and chromatography resin, for example).

With SUT, biopharmaceutical manufacturers are outsourcing a great deal more of the process design space. Not only does a quality attribute have to be met within the facility but the manufacture of the SUT has a dynamic process of its own. Leachables, modified leachables, leachable by-products, and mechanical stability are slowly being identified and the effects characterized by both vendors and manufacturing organizations. With SUT being used more throughout the process, there will be some process development testing required within the

design space to ensure that there are no adverse effects or additive adverse effects by leachables/leachable by-products that could alter the process or product. Adverse leachable by-product effects have already been demonstrated.13 Vendor collaboration and agreements could help, but they are still only just beginning.14 The discovery of the effect of some leachable by-product compounds on manufacturing and, more specifically, the product or the cell making the product has serious implications. In addition, documentation of the reproducible performance of activities such as mixing, temperature control, sparging, pH control, and mechanical stability will provide confidence in the manufacturing process.

A certificate from the SUT supplier indicating the quality control points and conditions of manufacture could be a communication tool for the operators setting up and utilizing the SUT. SUT testing by the manufacturing QC organization could become commonplace to ensure consistent supply. Standard testing involves physical testing (see Table C) as well as chemical testing. In summary, this new approach for production could add to the complexity of defining the design space. One view of the manufacturing design space could be represented as shown in Figure 1.

Process and system validation is changing from an object-based qualification to a design space qualification. The term "design space" in this article is used to include all parameters that may affect final product quality. It is important to consider what the boundaries of the primary design space, secondary design space, and remote design space parameters are and how they are linked. The potential impact of SUT on processing warrants a closer communication of the SUT manufacturing parameters and makes the SUT vendor design space integral to the biological manufacturing design space.

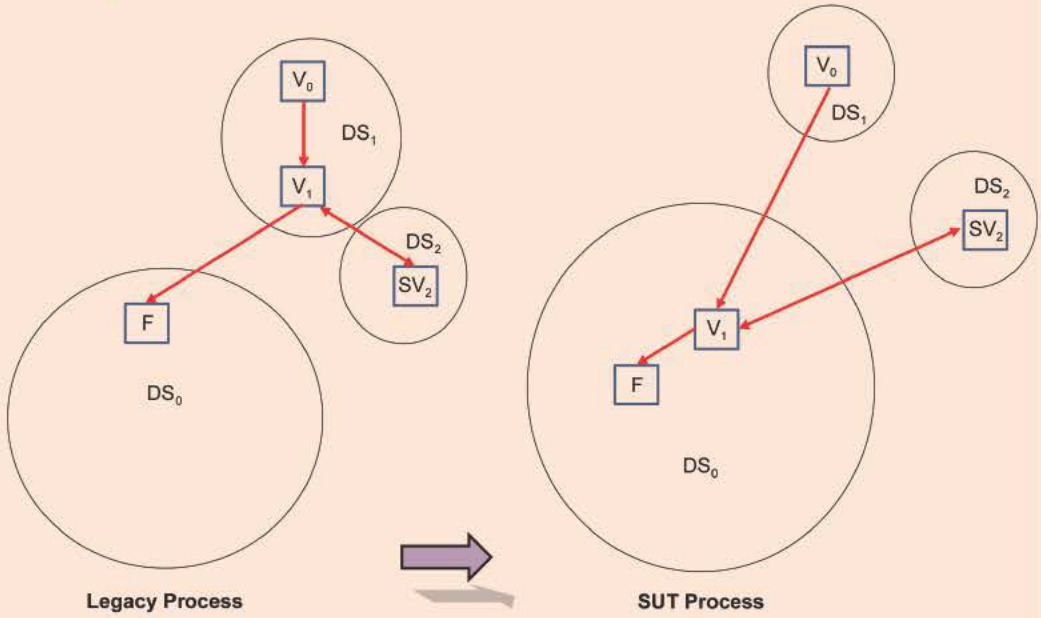
Document the Design Space

Effective methods of establishing the process needs and critical areas where design space ranges would be established are required. A process flow diagram (PFD) can facilitate discussion and documentation of the testing and studies required to define the product design space. In addition, engaging in discussions with SUT manufacturers to understand their production process and product design space may now become as important to include in the biopharmaceutical production design space.

Process Flow Diagram (PFD)

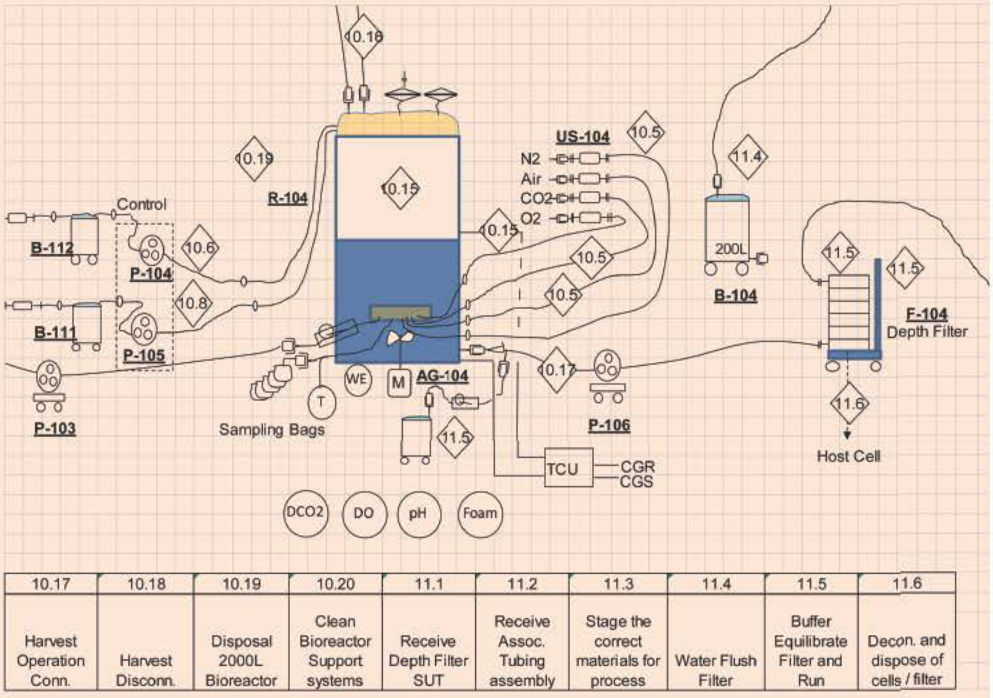
The PFD combined with the SUD template has the following attributes that are of most value in documenting the design space:

Figure 1 One view of the manufacturing design space



DS_0	Primary Design Space is that space in direct control by the cGMP Biopharmaceutical facility. Knowledge and performance of systems and the ranges for which they are effective are known by the Biopharmaceutical Manufacturer. Air classifications for open systems, temperature, product temperature, concentration, conductivity, pH, etc. are typically established with maximum and minimum values.
DS_1	Secondary Design Space is the space within a primary vendor of a cGMP regulated product. This is the sterile container made of virgin plastic, or the sterile filter, tubing manifold, with integrity test or quality certificate information for use in the cGMP facility.
DS_2	Remote Design Space is one where raw materials that are used in the manufacture of systems for cGMP regulated products such as Virgin Resin for product contact plastics. These are controlled by remote vendors and seldom scrutinized by the Biopharmaceutical Manufacturer. A level of quality is established and tested lot by lot. Change of processing notification may be employed by biological manufacturers to maintain a level of control.
F	cGMP Manufacturing Facility is the facility where the cGMP regulated product is made.
V_0	Remote Vendor primarily creates raw material for cGMP regulated processes (virgin plastics, column resins, etc.).
V_1	Primary vendor is the provider of assemblies, bags, and components with significant product contact used in manufacture of cGMP regulated products.
SV_2	Sterilization provider is an organization that may be separate from the Primary vendor that provides a sterilization or bioreduction service for the cGMP components.

Figure 2 PFD excerpt



10.17	10.18	10.19	10.20	11.1	11.2	11.3	11.4	11.5	11.6
Harvest Operation Conn.	Harvest Disconn.	Disposal 2000L Bioreactor	Clean Bioreactor Support systems	Receive Depth Filter SUT	Receive Assoc. Tubing assembly	Stage the correct materials for process	Water Flush Filter	Buffer Equilibrate Filter and Run	Decon. and dispose of cells / filter

1. Pictorially represent the process or model process and support functions that affect product quality (such as transfer methodology, sampling points, sterile boundaries, cleaning, and sanitization). The model process is a combination of all processing capabilities in one PFD.
2. Identify all process streams to document process and utility flows (maximum, minimum, and average). Ideally, these are kept together for updates and review.
3. Unit operation or step timing. This can be of great importance when switching to SUT where transfer times will probably increase based on connection limitations.
4. Documentation of key parameters, which may have an effect on SUT (such as temperature, pressure, and reactivity).

The PFD would be specific enough to establish all critical transfers within the facility. (See Figure 2.) It will help facilitate discussions of key operational steps captured in the SUD template as well as support steps further evaluated within the FMEA template.

For this tool, the requirement of the PFD in building the SUD template is a beginning to facilitate discussions around all the critical steps and operations that pose a risk within the process. Then more specific actions, such as heat up, cool down, reactions, transfers, and changeover, would be captured in the SUD step identifications so that the operation can be evaluated within the SUD template and FMEA analysis. The SUD will capture the sub-steps or sub-sub-steps for the process to completely describe the process. For example, the bioreactor operation (10.15) can break down further to bioreactor venting (10.15.1) bioreactor agitation (10.15.2) and sampling (10.15.3).

The stream table in the PFD can be used to preliminarily identify risk factors, as indicated in Figure 3. The Step Risk column can be reassigned to process components for material balance after the SUT evaluations are complete in support of the Conceptual Design.

A very crude volume and mass balance can be tracked so that facility capacity and material handling information can be evaluated. (See Table A.) Large quantities of buffer salts can be identified here if buffer-salt materials are included in the material balance. The purpose for the material balance would be to evaluate operator safety and ergonomics as opposed to cost or productivity.

Once the model process has been determined and it is represented in the PFD, it is time to document the design via the SUD template.

Collection of Information for the SUD Template

Ideally, a User Requirement Specification (URS) for the facility or Basis of Design (BOD) document would be generated for the planned facility. This information could also be summarized within the SUD template.

Figure 4 indicates many of the areas that impact the design space and are important to document or have inputted on the SUD template.

The steps of the process are walked through while details are added to the steps identified in the SUD. The steps, sub-steps, and sub-sub-steps will cover all areas of risk for the inventory, setup, run, and retirement of the process(s). The process is followed from raw materials through final vial fill/packaging/shipment or bulk fill/storage/freeze-thaw/shipment. Following the product all the way through shipment is suggested and can be considered part of the design space. SUT final bulk storage bags and freezer storage bags have been used for some time, and the bag performances (i.e., gas permeability) as well as sturdiness are well known.[15]

Preventing health and safety issues when switching to SUT is also a concern and could be considered and documented in the SUD template. The walk-through of the process and documentation of operations provide an ideal opportunity for documentation of EH&S issues arising from SUT use.

Although not yet identified as an issue, development of carpal tunnel syndrome (CTS) can be associated with repetitive hand motions, awkward hand positions, strong gripping, mechanical stress on the palm, and vibration, according to literature [16]. Knowledge of these potential causes of CTS can be of value when planning the SUT setups and interconnections.

The SUD template is used to document all critical attributes of the facility and process. After the initial understanding of the processes and processing needs is achieved, there would be a review of the SUS/SUT available to fit the design needs. There would be a match between process needs and system availability/design. Note that it is also advisable to have backup SUT components and system suppliers for components so that manufacturing interruptions will not be due to lack of inventory. In many cases, this may be accomplished by using connector adaptors, although redundant SUS/SUT (if required) may prove to be impractical in some cases.

SUT Components and Systems

Major Systems and SUT Equipment Review[17-27]

The major systems include bags for product and support solutions, bioreactors, mixing bags for product and support solutions, filters for depth filtration and cross-flow filtration and disposable membranes, chromatography systems, membrane chromatography systems and disposable chromatography columns, centrifugation, freeze/thaw system bags and product storage bags, bulk fill assemblies, and vial fill flow .

IIt is advisable to invest in at least one item for each of the SUT components considered for use. In this way, the interaction with other components and the ergonomics of setup and use can be evaluated while completing the SUT evaluation. Careful consideration to SUS/SUT and setup requirements (minimized connections on SUT manifolds) could be important. This author recommends that a batch record IQ/OQ checklist be developed

Figure 3 PFD step risk excerpt

Stream No.			10.15	10.16	10.17	10.18	10.19	10.20	11.1	11.2	11.3	11.4	11.5	11.6
Mass Balance (Kg) **Step RISK**	Molec. WT	Density	Run 2000L Production	Provide Feed Media	Harvest Operation Connection	Harvest Disconnect	Disposal 2000L Bioreactor	Clean Bioreactor Support systems	Receive Depth Filter SUT	Receive Associated Tubing assemblies	Stage the correct materials for process	Water Flush Filter	Buffer Equilibrate Filter and Run	Decon. and dispose of cells / filter
Operator Error														
Leachable														
Reactable														
System Failure														
System Fragile														
Temperature Limit														
Pressure Limit														
pH limit														
Connector														
Disconnector														
Tube Weld														
Tube Assembly														
Tube Field Fit														
Adapt to SS System														
Autoclave / SIP required														
Training														
Open System / Closed System														
Vol. turn-down and mixing														
Center of gravity														
Spill containment / handling														
Time / Duration														
CRITICALITY REVIEW														
Critical Impact														
Impact														
Requires Consideration														
Minimal Impact														
Max Media 1	g													
Max Buffer 1	g													
Cells / ml														
Product	g													
% Yield														
Product Concentration	g/L													
Temperature	degC													
Total Volume	L													
Total Weight	kg													
Density	g/ml													

Table A	PFD material balance excerpt
Max Media 1	g
Max Buffer 1	g
Cells/ml	
Product	g
% Yield	
Product Concentration	g/L
Temperature	°C
Total Volume	L
Total Weight	Kg
Density	g/ml

to capture all the important attributes of system setup, operation, and shutdown. Approaches for integrity testing system setups[33, 34] as well as vendor agreements[14] that are recommended to maintain control would be documented as required. Integrity testing may be employed, but risk analysis and potential benefits would be weighed against potential bag damage and failure.

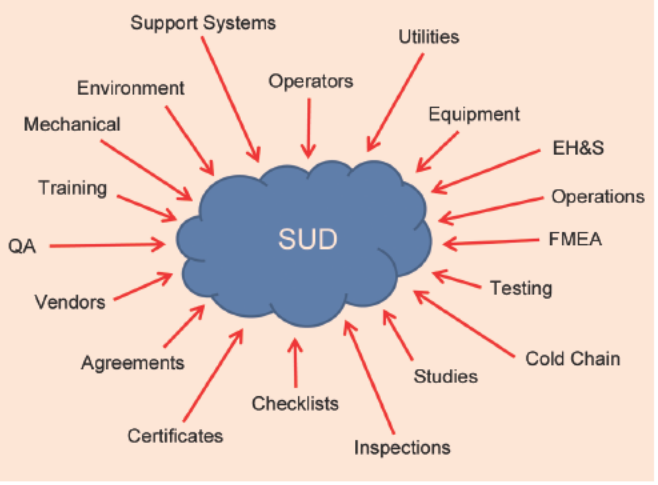
IQ/OQ checklist: This author recommends that they be inserted into every batch record with step sign-offs.

1. Verify components (i.e., a picture, indicate size, materials of construction, and capacity)
2. Install SUS/SUT: Installation instructions with sign-off on critical setup items.
3. Design space function: Operational check of system to verify design space operation

There are critical parameters that affect the manufacture of SUT bags that can very easily be overlooked. An audit of the SUT supplier and paying particular attention to its understanding and communication of the process design space and critical parameters is important. The design parameters and the ability to notify customers when manufacturing of the bags have gone to the extremes of the design space may be addressed to fully encompass the reach of the potential risk.

It is suggested that a manufacturing certificate be developed that communicates critical parameters (indicating that they are in range) from vendors of SUT manufacturing. The certificate would identify the manufacturing time and ideally be specific to each SUT manufacture. The use of this certificate as a design control that mitigates risk would be a valid control to list when filling out the FMEA. The system validation and ongoing control are dependent on the controls put in place.[35-39] See QC testing below for testing data that may be important to track and include in the manufacturing database.

Figure 4 SUD inputs



Single Use Design (SUD) Template

The SUD template is a tool for documenting all relevant information for the processes and provides a common document to review process parameters and risk. This list is presented in Microsoft Excel so that risk evaluations can be ordered by degree of importance or risk priority number (RPN) value. The SUD can also be utilized to document ongoing mitigation of risks found during the evaluations.

The first four columns have listed the PFD step, the first sub step, a second sub step is reserved, and the final step, which is actually the failure mode as taken from the FMEA. (See discussion below.) These steps are broken down into individual columns so that there is maximum flexibility in sorting, filtering, and prioritizing the steps/sub steps and failure modes during evaluations.

The columns are used to document the process parameters as well as the critical risk items. The number of columns used to document the design space is not limited. Where applicable, a range could be indicated for the design space parameters. The following is a generic list of the types of items documented within the SUD template after the FMEA RPN import as started in Figure 5:

1. Process Step (four columns indicated, including failure mode)
2. Area (Location)
3. System Name
4. System Step Description
5. RPN (linked to FMEA template)
6. System Capacity
7. Biosafety Level/Area Classification
8. Step Open vs. Closed
9. Connection type and size (can also identify, for example, type of connector, number of steps to make connection, thermal welder, and time to connect)

10. Connection adapter required primarily for backup vendor for SUT
11. Product Contact Material (multi-layer bags should have layer material identified and purpose and testing that can confirm function of layers)
12. Working Volume
13. Product Concentration
14. System Total Volume
15. System Capacity
16. Comments
17. Process Flow
18. Process Pressure
19. Process Temperature
20. Process Dissolved O_2
21. Process pH
22. Process Conductivity
23. System Turn Down
24. Mixing (such as kLa, Torque, Pumping Capacity, and Power Requirement)
25. System Portable In-Use
26. Center of Gravity (portable equipment)
27. Step Time
28. Shelf Life (new product at vendor site pre-sterilization, post-sterilization, at manufacturer site)
29. Shipping Time
30. SUT Temperature Range (shelf)
31. SUT Temperature Range (component manufacturing)
32. Connection – Hybrid (CIP/SIP/Flush)
33. Utility Load (list) – Purified Water, WFI, CS, PS, Contained Drain, O_2, CO_2, N_2, CA, CGS, CGR
34. Leachable/Extractable (Identified/Amount)
35. Standard Physical Testing (See Table C)
36. Reactivity Testing
37. Vendor
38. Alt Vendor 1
39. Alt Vendor 2
40. Cost SUT
41. Cost SUS
42. Cost S.S.
43. SUT Y/N
44. Required Lot Size
45. Scalable Y/N

After completing the SUD template column headers (more columns of critical items can be added as information develops), a detailed walk-through of process steps, sub-steps, and sub-sub-steps would be added.

The list is populated with all process data that is associated with the process step. The list will then be expanded to fit all failure modes per step/sub-step. Then, the list is ready to expand and populate with the FMEA template RPN values. The two list item numbers should match line for line prior to linking the RPN cells between sheets. All critical aspects of the facility would be included in this review.

If steps or sub-steps are added, care should be taken to preserve the order of the list and agreement between lists (SUD template and FMEA template). Once linked, the SUD template becomes the repository of all process information by which failure modes, degrees of risk, and all associated process parameters are compared. Data ranges could be included to define the process parameters within the design space.

Figure 5 **SUD template excerpt**

PFD St	Sub St	Sub Sub Step	Failure Mode	Area	System	System Step Description	FMEA RPN
10	1	0	1	Cell Culture	Production Bioreactor	Receive SUT for 2000L Bioreactor Operation	8
10	1	0	2	Cell Culture	Production Bioreactor	Receive SUT for 2000L Bioreactor Operation	24

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Failure Mode and Effects Analysis (FMEA)

Failure mode and effects analysis evaluations have been performed for many years on a wide range of subjects. The author believes that this tool provides an ideal format to compare process parameters identified within the SUD template with associated risks identified in the FMEA analysis. The generation of a numerical evaluation of risk with cross-references to process details can provide a more open review of the potential issues.

The FMEA template columns are as follows:

1. PFD/SUD Template Step Numbers: All process streams as represented via PFDs are identified via a numbering system (i.e., PFD step, sub-step, sub-sub-step, failure mode)
2. Item/Function: The sequential steps or operations
3. Potential Failure Mode: The failure modes selected for evaluation on each step or operation; seven failure modes have been indicated in Figure 6 and are detailed below
4. Potential Effect of Failure: The severity of the effect is evaluated (value 5 is very severe with no warning; value 1 means no effect and safe operation)
5. Potential Cause of Failure: The probability of the failure is evaluated (value 5 means that failure is a high probability; value 1 means that failure is unlikely to occur and a low probability)
6. Current Design Controls: The current design controls in place to detect failure and the likelihood of detecting the failure (value 5 means that the design control cannot detect the failure; value 1 means that the failure will be detected by design control)
7. RPN: This is the product of the estimated severity, probability, and detectability
8. Recommended Actions: In many cases, these are corrective actions for defining the design controls that are put in place to safeguard the design and improve the RPN value
9. Responsibility and Due Date: This column is used to identify responsible individuals and due dates to address the potential issues
10. Action Results and Re-evaluation: The action results are followed up on, and a new RPN is calculated if improvements have been identified

One important consideration to a successful FMEA is the selection of the failure modes and consistent, fair evaluation of each of the tasks or functions. It is highly recommended that the group used to evaluate the risk will be involved in brainstorming the failure modes. This will add to the understanding of the FMEA template prior to filling out the risk evaluation.

Seven failure modes that have been used are as follows:

1. Power loss: Evaluate in the context of the step function and how the failure could affect the step.
2. Operator error: Evaluate in the context of the step function and how the failure could affect the step.
3. Adverse leachable: Review data and evaluate spiking studies.
4. Bag tear/leak: Evaluate in the context of the step function and how the failure could affect the step. Establish if there is a shelf life associated with this failure.
5. Tube or fitting wear or leak: Establish vendor and in-house data to provide statistical information.
6. Over pressure: Evaluate in the context of the step function and how the failure could affect the step.
7. Material compatibility: Review data and evaluate spiking studies.

While it may not be possible to always ensure fully consistent findings, a five-point system has been selected to help minimize the guessing between hazard ratings. In addition, preparing a listing of the types of failures considered from value 5 down to 1 for severity, probability, and detectability will help to normalize the evaluations. (See Table B.)

Try to keep evaluation simple by first addressing if the risk "is", "is not," or "may be." By starting here with a 5, 3, or 1, the degrees can be determined (4 or 2 leaning in one direction or another). It is best to filter the list to independently review each of the failure modes. This helps to minimize the occurrence of mind wandering and changing point of reference during the evaluation process.

The RPN is established by multiplying the severity by the probability by the detectability.

RPN = SEV x PROB x DET

The maximum RPN value of 125 can be obtained.

Note that the severity (SEV) is the most difficult parameter of RPN to improve. Probability (PROB) may be improved, although typically this parameter has already been optimized. Detectability is the most likely parameter to improve through testing or Process Analytical Technology (PAT)[7-12] integration.

PAT provides a means to improve definition and monitor the design space identified for manufacture. Use of PAT to monitor processing in SUT manufacturing could improve the confidence for the implementation of SUT.

FMEA Data Sensitivity Analysis

Once the FMEA evaluation is completed, the SUD template is expanded with failure modes per step and then updated with the FMEA RPN values.

The product of SEV and PROB form a fairly firm value of risk.

Ideally, the manufacturing management would be able to define a very distinct cutoff between acceptable risk and unacceptable risk.

Table B Failure mode ranking

Potential Effect or Severity (SEV)

Effect	Severity of Effect	Ranking
Hazardous without Warning	Affects safe system operation with no warning	5
Hazardous with Warning	Affects safe system operation with some warning	4
Moderate	System inoperable with minor damage	3
Minor	System is operable with some degradation of performance	2
None	No Effect	1

Potential Cause or Probability of Failure (PROB)

Probability of Failure	Failure Probability	Ranking
Very High, Failure is inevitable	> 1 in 2	5
Repeated Failures		4
Occasional Failure	> 1 in 100	3
Few Failures		2
Failure is Unlikely	> 1 in 1,000,000	1

Current Design Controls and Likelihood of Detection (DET)

Detection	Likelihood of Detection by Design Controls	Ranking
Uncertain	Design Control cannot detect potential mechanism and resulting failure	5
Remote	Remote chance that design control will detect potential failure	4
Moderate	Even change of detection by design control	3
Minor	Good chance that design control will detect potential failure	2
Almost Certain	Design Control will detect potential failure	1

Table C Standard testing examples

Test	Units	References
Tensile Property	N (kg·m/s2)	ASTM D412, ASTM D638, ASTM D882, ISO 37, ISO527.5
Toughness	$kN \cdot m/m^{-3}$	ASTM 2794, ASTM D1709, BS2782 Part 3 Method 352E
Elastic Modulus at 2% elongation	psi	ASTM E111, ISO 17025
Puncture Resistance	N (kg·m/s2)	ASTM F1306, ASTM D3787, ASTM D4833
Tear Resistance	kN/m	ASTM D1004, ASTM D1922, ISO 6383-2, BS2782:3
Flex Durability	WVTR – g/m2·24hr	ASTM D392, BS 3177AEA

1.00 $N \cdot m/m^{-3} \simeq 0.000145$ $in \cdot lb_F \cdot in^{-3}$ and 1.00 $in \cdot lb_F \cdot in^{-3} \simeq 6.89$ $kN \cdot m/m^{-3}$

Once the RPN values have been linked to the SUD template, the design can be investigated by using the sorting and filtering function within the FMEA template.

1. Investigate high RPN with the goal of reducing the value through PAT or operational factors. The results will indicate those items where there is too much risk to perform the operation as planned and a decision to go with a system or equipment with acceptable risk is required.
2. Investigate the middle region to move items in the acceptable risk range as agreed upon in a corporate directive (selected acceptable risk) or consider this a member of the high RPN.
3. Accept low RPN results for design as these items evaluated are within risk tolerance.

Results Tabulation and Evaluation

Group the failure modes and establish the reproducibility around the FMEA results.

Evaluation tables can be developed by filtering the failure modes and tabulating the individual FMEA results. By using Microsoft Excel functions, one can then investigate RPNs with wide deviation. For example (Figure 8), with 10 individuals ranking the risks, Step 10.3.0.7 has only seven matching RPN values. Looking back, the SUD template will provide all process data related to that specific step and that particular failure mode. The other RPN values matching this step can quickly be found by sorting on the specific step and including all RPN values in the filter.

Further Considerations

Leachables/Extractables

The SUT is evaluated on its stand-alone merits. The issues of leachables can become very subjective. This tool provides a means to document the issue and to identify potential courses of action to minimize the risk to the product. The BioPhorum Operations Group (BPOG) is developing a protocol for working with SUT vendors to determine what Leachable/Extractables may exist and how to detect them. The goal is to open dialog with vendors to improve our understanding of the SUT material processing and to provide a proactive way to anticipate the effects on processing based on these known leachables.40-43 This author believes it is no longer acceptable to just look at Class

Figure 6 FMEA template excerpt

System: Single Use Technology Implementation
Subsystem:
Component:
Design Lead: CJC
Core Team:

Potential Failure Mode and Effects Analysis (Design FMEA)
Key Date: 6/29/2014

FMEA Number:
Prepared By: CJC
FMEA Date:
Revision Date:
Page: of

Process Step				Item / Function	Potential Failure Mode(s)	Potential Effect(s) of Failure	S e v	Potential Cause(s)/ Mechanism(s) of Failure	P r o b	Current Design Controls	D e t	R P N	Recommended Action(s)	Responsibility & Target Completion Date	Action Results				
PID Step	Sub St	Sub Sub Step	Failure Mode												Actions Taken	New Sev	New Occ	New Det	New RPN
10	1	0	1	Receive SUT for 2000L Bioreactor Operation	Power Loss	SUT on loading dock or warehouse exceed design space	2	Unknown shipment delivered late on Friday	2	Vendor agreements, Inventory control procedures, 24/7	1	4							
10	1	0	2	Receive SUT for 2000L Bioreactor Operation	Operator Error	Checked product in without review of certificate change notice	3	New employee not aware of practices	3	Certificate is issued with materials for a batch (shelving)	2	18							
10	1	0	3	Receive SUT for 2000L Bioreactor Operation	Adverse Leachable	Change (missed in certificate) to SUT introduces a new adverse leachable	4	New employee not aware of practices	2	Certificate is issued with materials for a batch (shelving)	2	16							
10	1	0	4	Receive SUT for 2000L Bioreactor Operation	Bag Tear	Unseen shipping damage	3	Damage occured prior to shipment	3	Vendor agreements, Certificate of inspection provided	2	18							
					Tube or Filling Lock /	Unseen damage				Vendor									

Figure 7 Sensitivity analysis

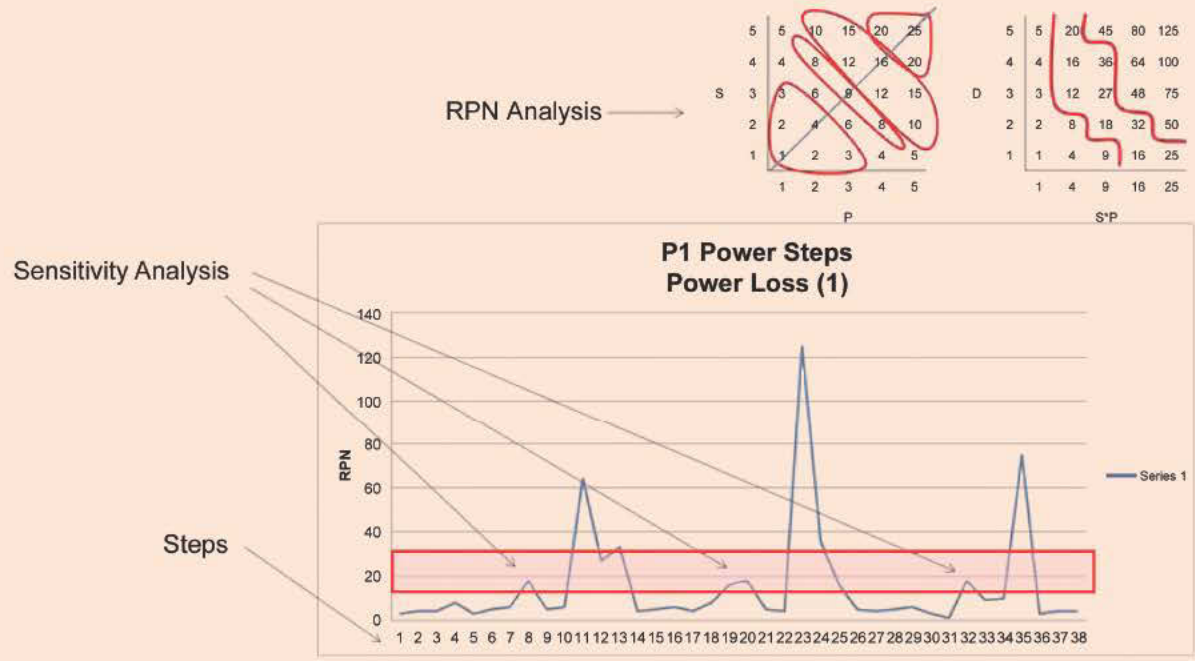

Figure 8 Evaluation reproducibility excerpt

Step	Sub Ste	Sub Sub Step	Failure Mode	Match RPN	# Matc	High	Low	Outlie	Total	Comments
10	1	0	7	32	10	0	0	0	10	
10	2	0	7	32	8	1	1		10	
10	3	0	7	60	7	1	1	1	10	
10	4	0	7	18	9			1	10	

VI testing data and say that a plastic is acceptable. Because of the increased surface area, increased temperature, and knowledge that is being developed around plastics and SUT materials, the ability to better predict the performance of various plastics used in SUT is increasing. There has been a history of SUT in, for example, freezer bags, cell culture seed components, and buffer and media support, and there are lessons learned. With the desire to get to 100-percent SUT use, there is now a constant exposure

of product from the beginning to the end of processing, and this author believes it is important to determine if there is an additive nature to plastic's effect on processing.

QC Testing

Consideration for increasing the in-house QC testing to include destructive testing on SUT may help to clarify the performance of SUT in the manufacturing setting in the case where failures have become routine. Tests have been developed to measure the properties of plastics. A few of the following tests may provide useful data to evaluate or track shelf life, performance degradation, and failure when tested over time on storage and use samples. This data can provide a benchmark to evaluate the SUT and confirm the performance in the design space in the future.

Some useful characterization tests and testing standards are shown in Table C.

IQ/OQ Considerations

Each manufacturing run with SUT is a new installation and operation. Providing a IQ/OQ checklist can help to ensure that every installation of SUT is done consistently and with the required documentation from in-house QC lab and vendor testing via test certificates. It could prove valuable to document that the correct tubing assemblies with required connectors, equipment components (with capacity), and programs are installed and that the system performs within the design space.

Integrity Testing

Integrity testing of bags, bioreactors, and tubing can be checked with integrity testers available in industry and sold separately from the SUS/SUT. The methodology and value of the test will be worked out by the user during the design and implementation of the SUT. The methodology and level of integrity assurance can vary greatly. Helium leak detectors and pressure decay are the two most common methods used at this time.

Waste Handling

The waste handling and decontamination of the SUT will require planning not just for the first process but for all processes planned for the maximum capacity of the facility. This can prove to be considerable space for a contract manufacturer with several processing trains in operation. The space required for inventory, staging, decontamination, and shipping of the waste would be considered. Cost of waste disposal and potential take-back programs from vendors could be investigated prior to committing to the manufacturing platform.

SUT Vendor Communication

Change control and vendor audits can become an integral part of vendor agreements. SUT vendor certificates for each lot of material produced that records relevant data can be used as a communication tool to improve transparency and control between the operating company and SUT supplier. Vendors can identify and monitor the key parameters identified for their manufacturing processes.

Conclusion: Finalize Design Approach

The method presented provides a structured proactive walk-through of the process requirements, in addition to documentation of the process steps and risk. The numerical evaluation on the FMEA template when applied to the SUD template provides perspective around the process risk and the ability to review process parameters where risks may be misapplied or overestimated. The numerical sensitivity analysis gives a review of evaluations and the confidence limits associated with the individual RPNs.

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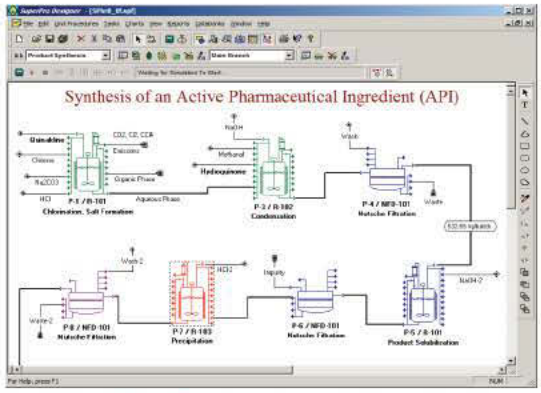

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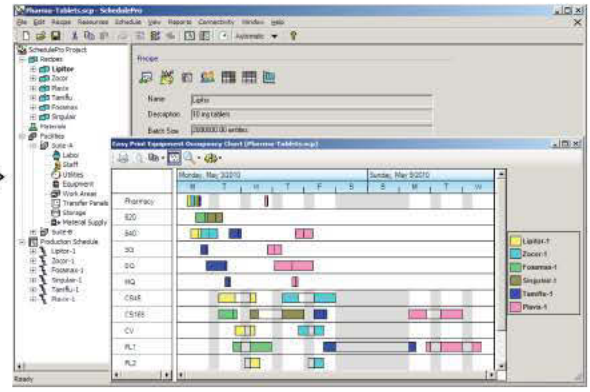

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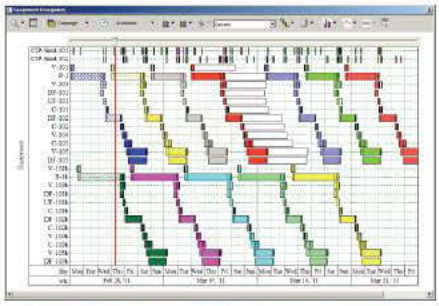

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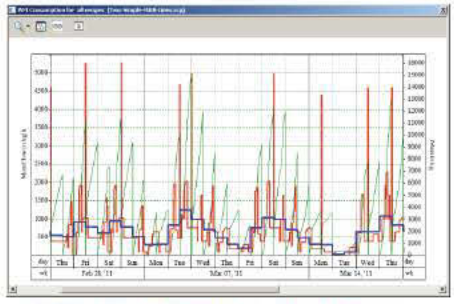
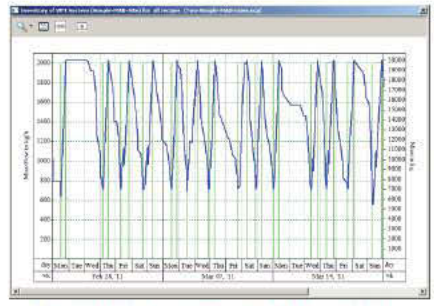


Tracking demand for resources (e.g., labor, materials, utilities, etc.)



Managing inventories for input, intermediate, and output materials

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Value of the SUD and FMEA Tool:

1. Evaluate the high-risk steps for the SUT design. Microsoft Excel-based filtering and sorting capabilities for evaluation reviews
2. Proactive evaluation of design and potential failures in an FMEA review linked to SUD summary of the process
3. Team alignment through group involvement
4. Thoughtful walk-through of process(es) and evaluation of failure and risk impacts
5. Evaluation and documentation of process design space

By linking the SUD template with the FMEA template, high-risk activities can be identified and evaluated as per operational activities. This proactive review provides a platform for facility design and risk mitigation. Ongoing use of the tool (SUD/FMEA templates) can document process improvements and risk mitigation for the life cycle of the facility processes.

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Carl Carlson has 30+ years of pharmaceutical and biotechnology "hands-on" processing, process engineering, and validation/qualification experience. He earned a Master of Science in biochemistry from Eastern New Mexico University and a Bachelor of Science degree in physical chemistry, with a minor in mathematics, from Northern Illinois University. He has been a principal officer for two biopharmaceutical engineering/validation consulting companies in addition to working for large- to medium-size A&E firms and is currently Senior Biotechnology Specialist at Middough Inc. Carlson developed operational experience when he was a chemist for DuPont performing protein purification, small molecule synthesis/modification, and protein conjugation scaled up from bench-scale to production-scale equipment and process unit operations. He has also developed a wide range of engineering and cGMP design experience with human and animal biologics, vaccines, biotherapeutics, nutraceuticals, and pharmaceuticals in addition to food additive and green-ethanol projects. His current project trends involve the integration and evaluation of single-use technology for appropriate applications. He is a member of ISPE, ACS, ISA, and AIC. He can be reached by email at carlsocj@middough.com.

UTILIZING A SCIENCE- AND TECHNOLOGY-BASED APPROACH WITH VOLTAGE OPTIMIZATION TO SAVE ENERGY AND PROTECT YOUR FACILITY

Dr. Alex Mardapittas and Sean O'Reilly

This article will explain how voltage optimization can significantly reduce energy costs, reduce electrical consumption (kWh), lower carbon emissions and extend the lifetime of equipment whilst at the same time protecting against harmful harmonics, transients and correct issues related to phase voltage imbalances.

Voltage Optimization (VO) is a proven and effective green technology that has been saving industry millions of dollars in wasted electrical energy since the beginning of the new millennium. It is well documented that in the USA voltage optimization can improve grid efficiency.[1] However voltage optimization in the commercial and industrial application is a relatively new technology.

UK studies carried out by the National Health Service (NHS) Sustainable Development Unit and St George's University, London in October 2013 identify VO as one of the three most worthwhile green technologies for the consumer to adopt. VO along with LED lighting and Variable Frequency Drives (VFDs) offer the highest energy savings as well as fastest payback across a range of different sized sites.2 It is a "fit and forget" solution that reduces energy at source and works alongside other energy-saving equipment such as photovoltaic panels and lighting controls.

Thousands of voltage optimization installations have been carried out across multiple market segments including life science, healthcare, manufacturing and retail over the last 15 years. The market-leading VO system delivers average annual electricity savings of 12% to 15%, extending to 17% on High Voltage side electronic variable optimization with correlating reductions in CO2 emissions. Typical return on investment is between two and three years depending on kWh cost. In some cases rebates are available from utility companies in both the US and the EU for voltage optimization, which provide companies with an even more attractive payback and return on investment.

The concept behind the technology is simple. On the whole, power is supplied at a higher voltage than is necessary. Although the ideal 3 phase voltage required for equipment in the US is 460 V, the average delivered is actually 493 V – voltage has actually been recorded in multiple USA cities at levels as high as 515 V. Figure 1 shows the voltage profile from a site in Baltimore, Maryland. The blue line is the current voltage profile and the green line is the voltage profile of the same site with voltage optimization

Figure 1 Voltage profile measurement (from 4/15/2014 to 4/21/2014)

The mismatch between voltage required and voltage delivered results in a waste of energy and of course money. VO corrects the over-voltage and brings it in line with the actual needs of the equipment on site through use of a device installed in series with the mains electricity supply. In this way, companies only pay for the electricity they actually need and use.

National Steady State Voltage Regulation Standards

The current national standard is ANSI C84.1 – American National Standard for Electric Power Systems and Equipment – Voltage Ratings (60 Hertz). This establishes the nominal voltage ratings for utilities to regulate the service delivery and establishes operating tolerances at the point of use.

The National Electrical Manufacturers Association (NEMA) recommends that all electrical appliances and motors should operate at nameplate plus or minus 10% satisfactorily.[3] Table A shows the nominal voltages supplied in the USA, whereas the equipment on site is designed to operate at the nameplate voltage so VO should be used to reduce the voltages as shown in Table B.

Why is voltage optimization required?

Voltage optimization is needed to correct the supply issues caused by the high voltage (HV) infrastructure. The voltage supplied to a site will generally be at a higher voltage than the equipment on site needs to run effectively. The extra voltage supplied is not needed but ultimately the consumer will be paying for this through the electricity bills.

Low Voltage Side Optimization

Low Voltage (LV) side optimization is connected to the low voltage side as shown in Figure 2. There are two variations of LV side optimization technology on the market: fixed and variable (also referred to as electronic-dynamic, electronic or intelligent VO). Fixed VO systems reduce the incoming voltage by a set amount to the optimum level for site operations. However; their output varies as the input voltage varies. Variable VO systems set the output voltage at the optimum level and maintain this by systematically managing the peaks and troughs in the power supplied – irrespective of the incoming voltage levels – to ensure that voltage is supplied at a constant, stable level.

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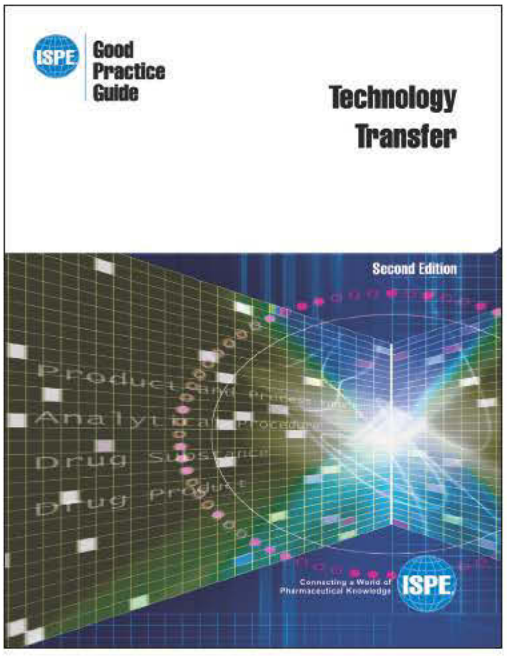

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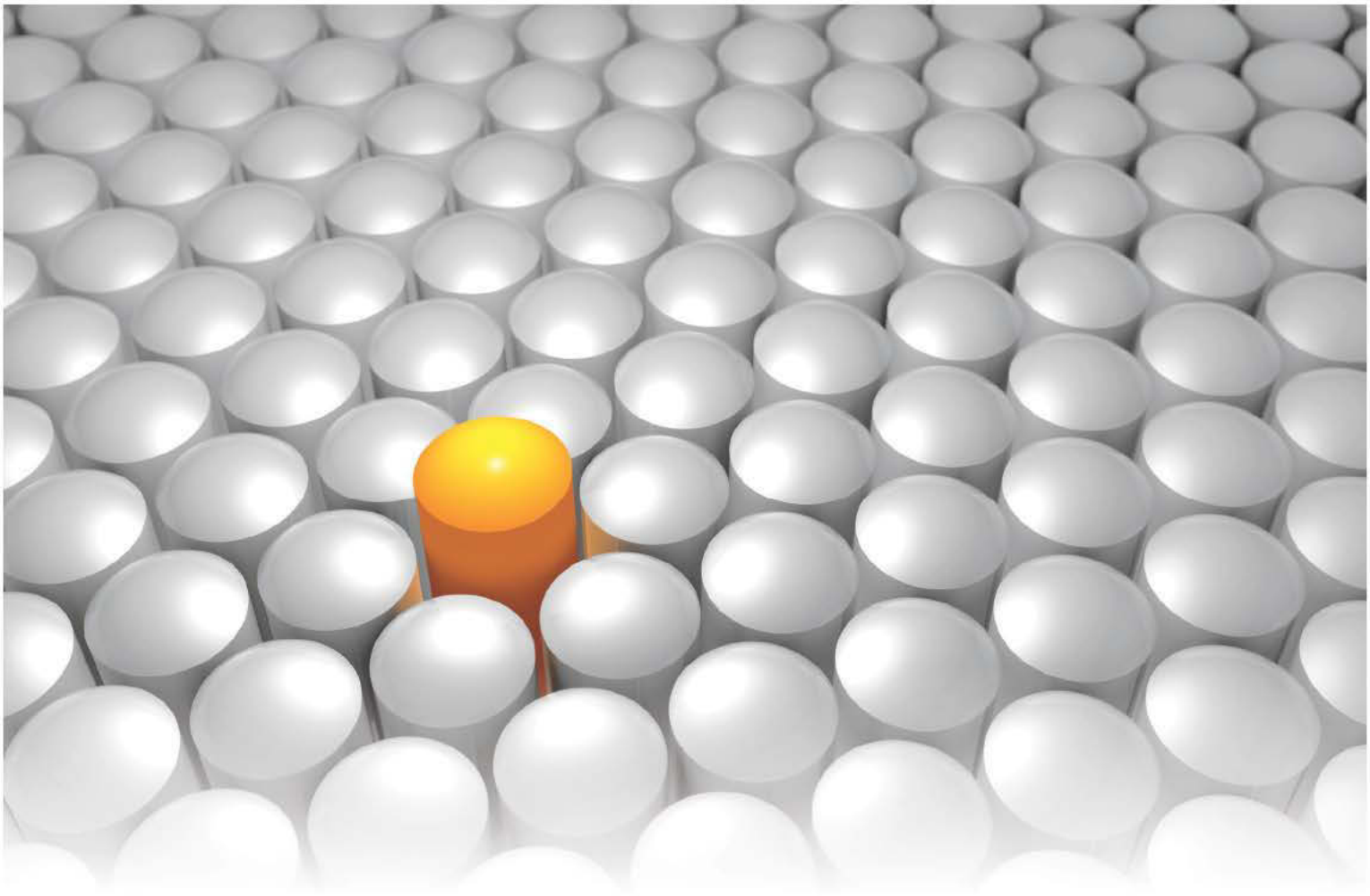

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Table A This table taken from ANSI C84.1 shows the present voltages in the USA with specific information on utilization and NEMA regulation

Nominal	Service	Utilization	Nameplate	NEMA
Standard	-5% +5%	-13% +6%	Motor	-10% +10%
120	114 – 126	104.4 – 127.2	115	103.5 – 126.5
208	197.6 – 218.4	181 – 220.5	200	180 – 220
240	228 – 252	208.9 – 254.4	230	207 – 253
277	263.2 – 290.9	241 – 293.6		
480	456 – 504	417.6 – 508.8	460	414 – 506
	Bandwidth 10%	Bandwidth 19%		Bandwidth 20%

This is beneficial for sites with fluctuating voltage, varying loads and sensitive equipment – particularly if they operate through the night when demand on the Grid drops, and voltage levels tend to rise further. The savings the LV systems achieve are based on the negative power (80%) and equipment efficiency improvements (20%) of the overall savings.

High Voltage Side Optimization

High Voltage (HV) side optimization technologies offer optimization solutions to sites that own their own transformers before power is distributed into the facility. Many technologies exist but there is only one system currently on the market, which provides HV, electronic variable voltage optimization. This is a combined solution, which could replace an on-site, inefficient HV transformer with an amorphous core super-low loss HV transformer, with an integrated electronic-dynamic VO technology.

A system can take up to 38,000 V input and provides a fully electronically regulated 460 V (or user-defined (from 380 V up to 690 V)) output. Technology also exists that will allow the user to alter the defined voltage locally through a Human Machine Interface (HMI) on site or remotely via the Internet. The HMI allows users to manage and monitor the system in real time to ensure maximum savings are being realized.

Depending on the age and type of the transformer that it replaces, an amorphous core transformer can provide between 1% to 5% savings simply because it is so much more efficient. In addition to savings on replacement of the transformer, the integrated voltage VO technology can be expected to provide 6% to 9% savings for more energy efficient sites that already have VFD's, LED lights and other energy saving technologies. Less energy efficient facilities can expect up to 9% to 12% savings. Therefore HV voltage optimization systems make savings from the negative power (75%), equipment efficiencies (15%) and improvement in transformer efficiencies (10%) of the overall savings.

Table B Optimum voltage levels

Nominal 3 Phase Supply Voltages	Design Equipment Voltage
480 V	460 V
240 V	220 V
208 V	190 V

How does voltage optimization save energy?

VO is a transformer-based system used to optimize the characteristics of the current supplied at the source (first current), according to current characteristics required at the load (second current). The first current is typically an alternating voltage in

Figure 2 Optimize your HV or LV supply

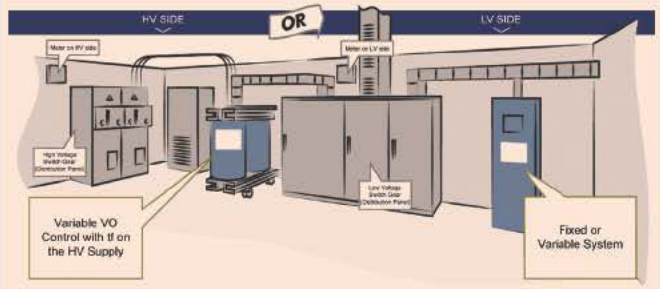
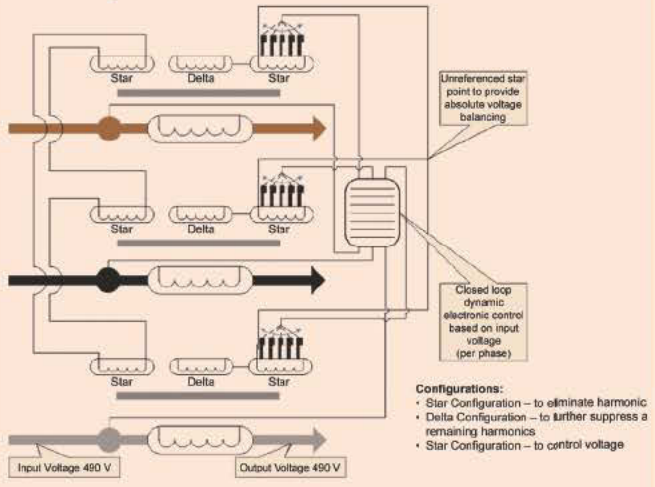


Figure 3 Typical LV VO electrical design



which case the resultant voltage is increased or decreased, this transformation routinely results in excess transformed voltage. The supply current flows from the first winding into the second winding of a VO system, wherein the magnetic flux causes the induction of a reverse current, which is a fraction of the supply current, typically 10%. This reverse current flows in the opposite direction to the supply current, wherein it is directed back to the electricity supply. Because this reverse current is real energy, which is distinct from apparent or reactive energy, there is a direct effect on the consumption of the load. This effect is a reduction of power consumed by a load, seen by actual kWh savings.

In simple terms, any excess voltage above the VO set-point, is chopped and returned back to the grid, generating induced negative power which flows towards the supply and is subtracted from the incoming power (the subtraction process occurs within the VO transformer). The negative power feedback accounts for 70% to 80% of VO savings with the remaining 20% to 30% savings coming from equipment efficiency improvements. The theory can be shown quite simply using a simple derivative of Ohm's law. By substituting into the basic equation:

From Ohm's law, $I = \frac{V}{R}$

Power (W) $= \frac{V \times V}{R}$ which is shortened to Power $(W) = \frac{V^2}{R}$

Example:

- A 10 kW load at 490 V input
- W = I x V, hence I = 10 kW / 490 V = 41.7 Amps
- V = I * R, hence R = 490 V / 41.7 Amps = 5.76 Ω

If we assume resistance to be a fixed property of the circuit, using the optimized supply Volts of 460 V, the optimized power will equate to:

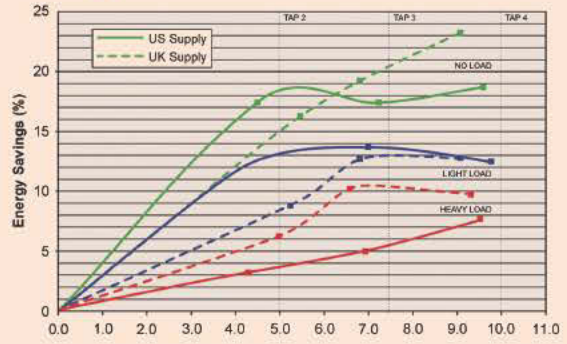
I (optimized) = V (optimized) / R = 460 V / 5.76 Ω = 38.2 Amps

Hence, Power W (Optimized) = 38.2 Amps x 460 V = 8.4 kW

Improving Equipment Performance

Optimizing the supply voltage for a building not only saves electricity, it can also prevent equipment and machinery from early burn out as well as reduce maintenance costs (Figure 4). Operating equipment at a higher voltage than it is designed for does not improve performance; on the contrary it has the effect of reducing its lifespan. For example a 460 V rated motor used at 500 V will achieve only 55% of its rated life. It will also take 4.3% more current and consume almost 9% more energy.[4] If you supply a motor with more voltage than it needs, it doesn't spin any faster, it just wastes the extra energy as heat. VO extends the life of motors by lowering their operating temperatures.

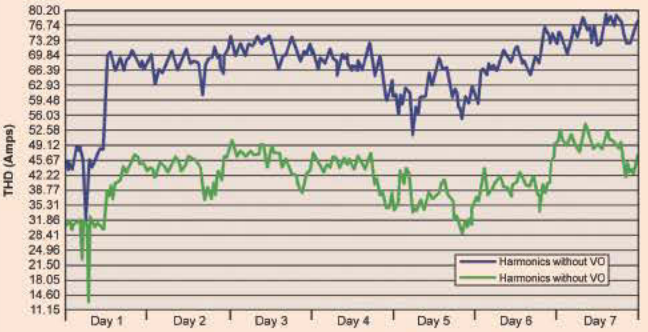
Figure 4 Savings of 3 Phase 30 kW motor with voltage optimization for US and UK supply



Improving Harmonics

In theory, most electricity is supplied as an Alternating Current (AC) sine wave, which rises, falls, and reverses direction smoothly around 50 to 60 times a second (the ordinary supply frequency). In practice, AC supplies can also include irregular, higher-frequency waveforms called harmonics. If the level of harmonics becomes too high, sensitive electronic equipment can be damaged.[5] The efficiency of electrical loads can be improved by attenuating harmonics at the supply, or by preventing their generation (Figure 5). Well-designed VO systems can complement electrical filters.

Figure 5 Effects of harmonics before and after installation of voltage optimization



Protection from Transient Events

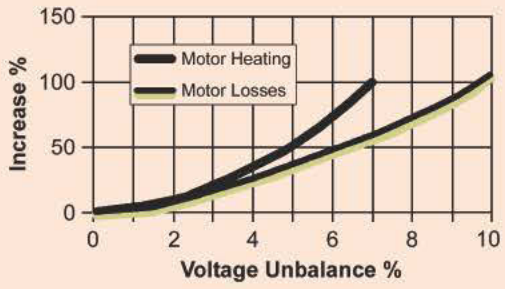
Transients are large, very brief and potentially destructive increases in voltage. They can be caused by lightning, switching of large electrical loads such as motors, transformers and electrical drives and by switching between power generation sources to balance supply and demand. The voltage that a building receives can rise and fall quite dramatically from hour to hour – even from minute to minute or second to second. Specific VO systems can protect a facility up to 25,000 V transient events.

Correcting Voltage Imbalance

Phase voltage imbalances can also be addressed by VO. Industrial and commercial sites are supplied with 3-phase electricity.

Imbalance between the phases causes problems such as heating in motors and existing wiring, leading to wasteful energy consumption (Figure 6).[6] Some VO devices are able to improve balance on the building's electrical supply, reducing losses and improving the longevity of three phase induction motors, typically used in a variety of equipment including refrigeration, pumps, air conditioning and conveyor drives.

Figure 6 Effects of voltage imbalance on a motor



Identifying How Voltage Optimization Can Help Specific Sites

The energy savings achieved by VO are an aggregation of the improved efficiency of all equipment across a site in response to the improvements in the power quality problems – typically 8% to 12% energy savings per annum using the market-leading VO system.

VO provides savings on a variety of loads but not all equipment will consume less energy. The greatest savings come from inductive loads such as lighting (Figure 7) and motors, especially if motors are not always loaded at 100% of their capacity. A building, which has fixed speed devices such as air-handling units, multi stage compressors (i.e. chillers), pumps and standard switch-start fluorescent fittings, will achieve high savings. Some loads such as variable frequency drives will also see savings but at reduced levels and some loads will yield zero savings but will benefit in other ways. It is important to understand the electrical loading characteristics of your site and to remember that no two sites are the same.

An alternative, although far less effective method of reducing electrical voltage, is through the use of step down transformers. These typically rely on the principle of magnetic induction between coils to convert voltage and/or current levels. A step-down transformer changes the entire power output from one specific voltage to another. The transformer's secondary winding that delivers the energy has less turns (coil) than the primary winding.

This type of transformer has many applications, such as enabling equipment from the US to operate in UK voltage conditions (i.e. 230 V to 120 V), and to transform for example 13,200 V to 480 V for HV distribution transformers in the USA. However, although these devices reduce the voltage, they also increase the current and as a result, do not save energy. In comparison, a VO transformer uses what is known as "negative voltage feedback". This specific design will reduce only the voltage required, and then subtracts this voltage from the input voltage.

For example, to reduce the voltage from 493 V to 460 V, only the 33 V are transformed and these are then subtracted from the input voltage by inducing a voltage in the opposite direction. This ensures that only around a tenth of the power is transformed which results in a reduction of voltage, and current, thus significantly saving a large amount of energy. By reducing the voltage by 5% using a step-down transformer you will expect to see savings of between 0.5% to 1.5%, while at the same time increasing the I^2R losses in the transformer system, therefore reducing these benefits further.

Figure 7 Savings comparison for lighting equipment

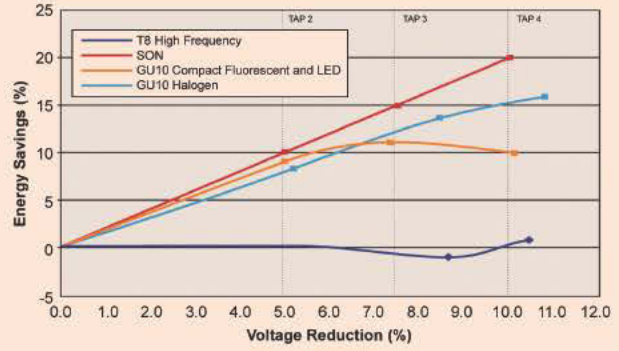
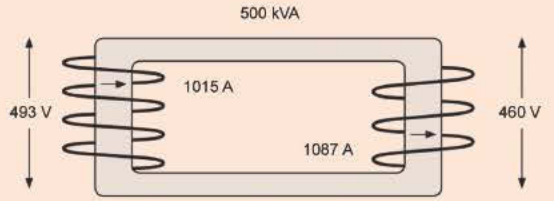


Figure 8 Traditional step-down transformer



Traditional Step-down Transformer

Figure 8 shows that with a traditional step-down transformer no savings are achieved from reducing the voltage. In a traditional step-down transformer (HV / LV – 13.2 KV / 480 V) or any other step-down transformer, the secondary side has less turns and the reducing the voltage increases the current. Therefore in a 500 KVA transformer, if the voltage on the primary side is 493 V, the current will be 500 KVA / 493 V = 1087 A. Not only are savings not made but actually the losses in the transformer will be increased as losses are I^2R. The power consumption is = voltage (3-phase) *current* Sqrt (3) * Cosφ.

Voltage Optimization Technology

Figure 9 shows savings can be achieved by reducing the voltage through voltage optimization due to negative power feedback. With this specific design, the transformation from one voltage to another occurs by only transmitting the voltage we need to subtract from the mains, which means only a fraction of the power is transformed. Therefore, in a 500 KVA transformer, if the voltage on the primary side is 493 V, the current will be 500 kVA / 493 V = 1015 A

If the voltage on the secondary side was to be reduced to 460 V, then the system will only transform the 33 V and subtract these from the primary voltage, resulting in the power affected being 33 V / 493 V * 500 kVA = 34 kVA. Therefore, the current on the 34 kVA and 460 V is – 34 kVA / 460 V = 74 A and which means the increase in current will be 74 A * 33 V / 493 V = 5 A.

Figure 9 Voltage optimization technology

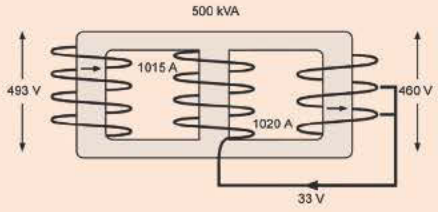


Figure 10 Average electricity consumption by half hourly periods pre and post installation of market-leading VO system

Savings

Analysis of a global life science facility pre and post installation of the market-leading VO product shows a reduction of 18,342 kWh, which gives savings of 8.3% per annum, equivalent to $48,715 per annum. This delivers a carbon dioxide reduction of 189.8 tonnes.[7]

Analysis was based on provided Half Hour Data (HHD) – data that is supplied by the electricity supplier – consumption data for the supply using a comparison of 14 days prior and 14 days post installation one year apart (Figure 10). The comparable periods were 4/11/2013 – 4/24/2013 and 4/11/2014 – 4/24/2014.

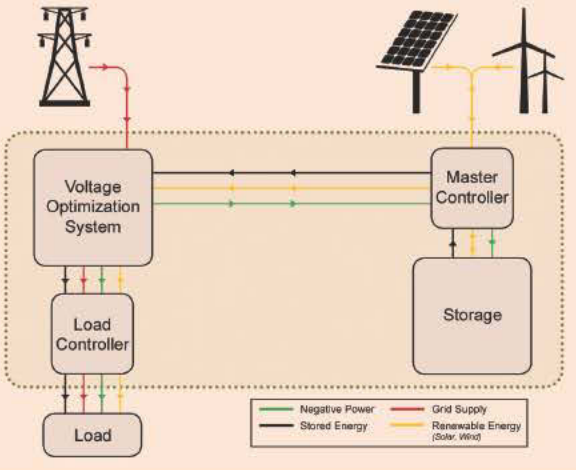
Conclusion

VO systems work to address the issue of wasted energy that exists as a result of an imbalance between a building's incoming supply and its usage. Voltage is generally supplied to a site at a considerably higher level than the optimal amount of 460 V required by modern electrical equipment. This is because utility companies cannot precisely target voltage over varying distances and simply transmit power in a way in which ensures that all sites receive between 440 V and 515 V.

There have been studies in the US of over 700 readings in 23 cities; the average voltage delivered in the US is actually 493 V. This excess energy is still factored into a building's energy bills despite the fact that it offers no benefit to the business and can actually be detrimental to equipment. VO technology ensures that companies only pay for the energy that they need. In addition, it filters out harmonics, transients and provides phase balanced voltages to give a smoother power supply and extend the life of equipment.

With no moving parts, a well-designed VO system requires no maintenance and will operate effectively for many years without replacement. The VO technology will contribute significantly to corporate sustainability goals by cutting energy consumption and thereby reducing greenhouse gas emissions. Continuous improvements and developments in VO technology has ensured that these systems will complement and enhance existing energy saving initiatives already installed by many major life science manufacturers.

Figure 11 Schematic of voltage optimization and energy storage



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New innovations in VO are seeing energy storage solutions that employ the VO technology to harness negative feedback to charge a storage medium and integrate it with renewable generation. With this users can confidently rely on the fact they will always have the optimal power during times of need (Figure 11).

The supplied electricity flows into the voltage optimization transformer and is optimized before it reaches the load, the load controller senses the amount of power being demanded by the facility and ensures the voltage is maintained at the optimum amount. The excess current not needed for the site is siphoned off to charge a storage medium. The stored energy can then be used when required. Renewable energy sources, such as wind and solar power, can be integrated into the energy storage systems to maximize the savings that can be achieved.

Figure 12 shows typical loads for a site. The green line indicates low tariff periods, the yellow line indicates medial tariff periods and the red line indicates high tariff periods. The direct effect of solar (purple line) on the load profile is quite substantial, reducing the stores overall consumption of electricity by 32.6%. However, the majority of this load reduction occurs during non-peak hours, with the solar only reducing the load requirement of the site during peak tariff times by 18%.

Figure 12 A typical load profile of a site fitted with 200 kW solar panels on a sunny summer's day

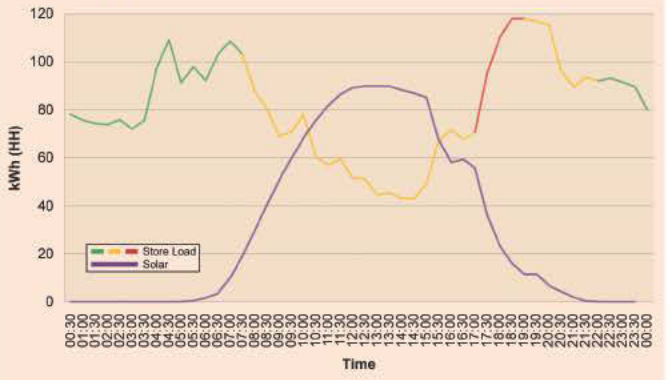


Figure 13 The same site with a voltage optimization and energy storage system installed.

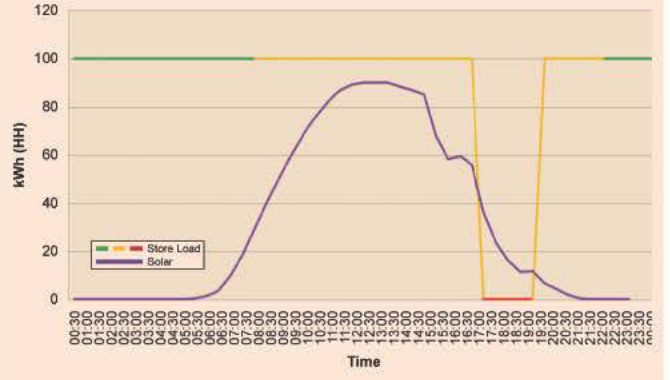


Figure 13 shows the same site with a VO and energy storage system installed utilizing both the negative power and the solar power in such a way as to prevent the site ever demanding more than 100kWh per half hour of energy from the grid, as well as removing the site completely from grid power during peak tariff.

The green shaded column on Figure 14 represents the optimum time for the site to come off grid to avoid the highest costs and inconsistent supply. In Figure 15 the high peak tariff period has been completely avoided by powering the site entirely from the energy storage medium. The rest of the load profile remains unaltered. This is because the storage medium has been charged using the induced negative power, not power from the grid. Therefore not only is the user saving money, but they are also directly reducing kWh usage, both for themselves and the grid.

The negative induced power generated by the VO systems is voltage and building load dependent and therefore a reliable source for charging (as long as the building power is on consistent amounts of energy can be harnessed). Consequently by combining the negative current and renewable energy generation on a site renewables can be made reliable.

Figure 14 A typical load profile for a site with no on-site renewable generation.

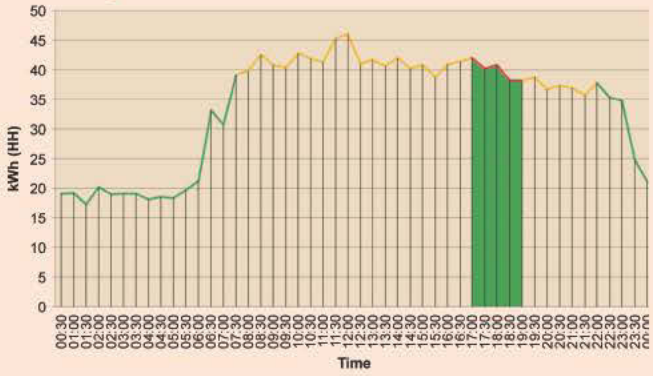
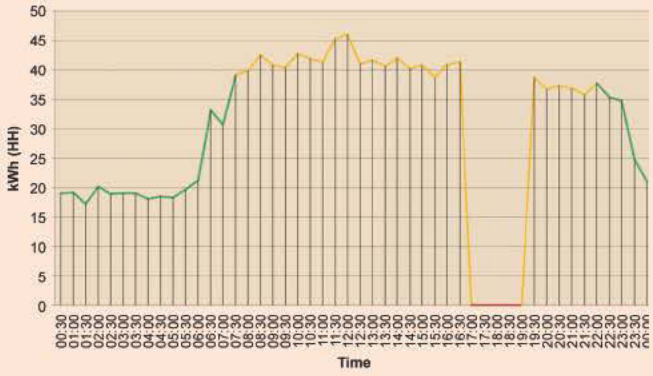


Figure 15 The same profile as Figure 14 with a VO and energy storage system installed.



Due to the exceptionally easy way of predicting available power at all times a VO energy storage system can act as a virtual power station (VPS) with the VPS capability the user can utilize the system as a full UPS as well as the stored energy during the high peak tariffs.

VO is firmly established as a proven, reliable and cost-effective method of reducing energy consumption and CO_2 emissions. A well-designed VO system will also protect your facility's plant and equipment by extending lifetime and decrease operating costs.

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About the Authors

Dr. Alex Mardapittas BEng, PhD, CEng, MIET, MEI is managing director of EMSc (UK) Limited. He has an extensive knowledge of software programming and innovative engineering design. In 2001 he set up EMSc (UK) Ltd to provide energy and environmental consultancy to UK organizations. The company has since become an engineering-led market leader, renowned for the innovative design of a range of energy saving products that is able to boast several blue chip companies and government departments amongst its clients. Powerstar®, devised by Dr. Mardapittas and his colleagues at EMSc (UK) Ltd, is a voltage optimization unit that works to reduce electricity consumption, and has been heralded as one of the most commercially viable energy saving solutions available in the marketplace. Dr. Mardapittas studied at Kings College London and then at Brunel University. On completing his research fellowship at the Brunel Centre for Manufacturing Metrology in 1993, he went on to work in professional computer software training and development. He has since built energy management systems and industrial automation systems for companies operating in leisure and tourism, manufacturing and the public sector.

Sean O'Reilly is President and owner of Intelligent Sustainable Solutions (ISS) LLC, the exclusive representative of the Powerstar® brand for the Life Science Segment and cleanroom industry. O'Reilly has extensive experience working within the Life Science and Microelectronic market segments primarily in cleanroom and air filtration applications. He has been historically focused on developing and promoting products that bring the lowest life cycle and long term sustainability. Before starting his own company as the exclusive representative for the Powerstar® Voltage Optimization brand in North America, O'Reilly was the Global Segment Manager for Camfil and held multiple sales and product development functions for over 30 years within Camfil Group first in Europe, then Asia and USA. O'Reilly has been an active member of ISPE since 1995. He has led the development of customized design and energy saving software for cleanroom applications, he holds multiple patents and has contributed and or written many technical papers and articles in the HVAC field. O'Reilly is recognized as an industry expert in the cleanroom market and is known for identifying and driving implementation of energy saving solutions focused specifically in the Life Science industry.

How VO Compliments CHP Applications

Approximately 9% of the US electricity-generating capacity is from combined heat and power (CHP). This represents about 82 gigawatts in capacity, 87% of which is installed in manufacturing facilities, including an increasing number of life sciences facilities. The opportunity to integrate voltage optimization (VO) on the HV or LV side also exists. (A majority of generation happens on the LV or 480 V side.)

Combining grid electricity and CHP can increase flexibility and reliability, as well as reduce the blended rate per Kwh. The supply normally serves the same distribution panels from the grid and CHP, so voltage must be tied on the same busbar. This not only ensures that the voltage is the same, but allows VO to further reduce consumption and deliver a minimum 7% savings due to the back EMF explained earlier in this article.

For new construction applications, the preference is to supply a well-designed VO system that can be installed on the HV and LV side. The system should be designed with specific impedances, magnetic flux densities, and voltage output (from HV to LV) to minimize losses and maximize savings. For retrofit applications, the end user should provide exact specifications of the installed HV transformer—including the Tesla value—to optimize efficiency savings and design on the LV side.

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Scott Fotheringham, PhD

▸ Orphan drug treatments have helped boost global pharmaceutical sales, which are expected to grow almost 5 percent annually and reach $1 trillion by 2020. ◂

Johann Kerlow and her family know the life-saving effects that an orphan drug can have. According to a Toronto Star story published 5 November 2015, the Toronto-area woman was diagnosed with atypical hemolytic uremic syndrome (aHUS), which quickly led to kidney failure that required weekly dialysis. She would no doubt die without Soliris (Alexion Pharmaceuticals), the only medication shown to treat aHUS. But with a price tag of well over US $500,000 annually—Soliris is the most expensive drug on the market—the mother of three could not afford the treatment.

Only about 1,000 people in North America suffer with aHUS, which makes it an "orphan disease" as defined in the US Rare Diseases Act of 2002. To qualify for this designation, a disease must affect fewer than 200,000 Americans. More than 6,000 of these conditions have been identified.

Prior to 1983, there was little hope of treatment for patients suffering from an orphan disease. Drug development and commercialization costs for new treatments were too high to allow manufacturers to recoup their research and development expenses.

The Orphan Drug Act (ODA) of 1983 changed the landscape. In concert with the Office of Orphan Products Development, operated by the US Food and Drug Administration (FDA), the act provides incentives for pharmaceutical companies to research, develop, and commercialize products to treat rare diseases. These include tax incentives (such as clinical-testing credits), waiving prescription drug user fees, reduced competition (usually no generic competition for seven years), and fast-tracked review and approval process during drug development.

Over the past 32 years, more than 400 orphan disease drugs and biologics have been developed and marketed, compared to fewer than 10 in the decade preceding passage of the ODA. In 2014 alone there were 440 FDA applications for orphan drug designation, with 48 approvals (up 53 percent from 2013).

This has not only improved patient treatment, but has also been a boon for the entire pharmaceutical industry, which historically depended on drug sales for the treatment of diseases and conditions that affect large numbers of people. Orphan drug treatments have helped boost global pharmaceutical sales, which are expected to grow almost 5 percent annually and reach $1 trillion by 2020.

According to the market research of EvaluatePharma, orphan drug sales alone are forecast to grow 11 percent annually to $176 billion in sales by 2020, when they will account for 19 percent of all prescription drug sales, excluding generics. Importantly, the expected return for orphan drugs in Phase III clinical trials is nearly double (1.89 times higher) that of other drugs.

What accounts for this phenomenal growth? The incentives provided by the ODA certainly help, as does a patient base that usually needs lifelong access to these breakthrough therapies. Most top sellers are oncology biologics, such as Revlimid (Celgene), Opdivo (Bristol-Myers Squibb), and Rituxan (Genentech). Add to this the reduced Phase III development costs (50 percent or lower) and prices that are on average more than six times higher than that of non-orphan drugs, and it is little wonder that orphan drugs appear to be the next big thing for the industry.

As big pharmaceutical companies acquire orphan drug developers to gain access to this lucrative market, these ailments could need a new name. They may be called "orphans," but they are being adopted at a record pace.

The bottom-line benefit of orphan drugs is paradoxical: While there were few treatment options for most orphan disease sufferers before 1983, now that treatments exist they may be too expensive for many to afford. Patients like Kerlow must rely on third-party payers—whether insurance companies or publicly fund ed insurers—who may be hesitant to pay the hefty bills. ◂

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