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September-October 2018 | Volume 38, Number 5

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THE JOURNEY TO DATE IN OUR NAVIGATION PLAN



John Bournas
CEO and President of ISPE

Welcome to the September-October issue of *Pharmaceutical Engineering!* This issue features a special preview of the ISPE 2018 Annual Meeting & Expo (ispe.org/AM18) in Philadelphia, Pennsylvania.

Annual Meeting is a good time to reflect on the work that ISPE is doing to update and improve our structure, delivery of services, and development and implementation of various programs and products. The direction we are following is driven by the ISPE Strategic Plan (https://ispe.org/sites/default/files/about-ispe/Strategic-Summary_2016.pdf). Our Strategic Plan, a composite of your collective views and input, guides our decision-making and contains our goals for a four- to five-year horizon.

The current Strategic Plan began in 2016 and concludes next year. ISPE's Board of Directors is already working to refresh the Strategic Plan. The Strategic Plan's strategic goals are rapid information delivery, driving efficient manufacturing operations, local and regional relevance, compelling member and industry value, and operational strength.

Great progress has been made in developing and implementing a range of projects to support these goals: we completed 15 projects in 2016 and 20 in 2017. Thirty projects are either complete or in progress for 2018.

Here are just a few of these achievements:

- **Create and implement the ISPE Foundation.** The foundation launched in June with three key initiatives to start. (Read more about the ISPE Foundation on page 12.)
- **ISPE collaborations with other associations, educational institutions, and foundations.** ISPE signed a memorandum of understanding with the Parenteral Drug Association for potential collaboration on quality metrics and quality culture topics, and engaged in other cooperative initiatives with organizations including Pew Charitable Trusts, University of St. Gallen, and a cross-industry association group.
- **The ISPE Guidance Document Portal is a new member benefit.** The portal offers 24 Good Practice Guides for free as part of your ISPE membership.
- **Redesigned ISPE web site.** The design and platform updates were completed last year with a fresh look and easier navigation.
- **New PE online site.** The new site will bring you a more accessible PE format plus new content.
- **A range of regulatory interactions since 2016.** These include:
 - More than 200 regulators from 20 countries participated as speakers, leaders, or panelists at ISPE events in Europe, Asia-Pacific, and the US.
 - ISPE presented at three invitation-only EMA workshops and meetings.

Developing the Strategic Plan and implementing toward its goals is a critical and crucial endeavor that the organization has in defining its remit. It's a collective responsibility that we all have as one ISPE. Your input in this sense is valued as all ISPE members play an important part in our achievements. Beyond this seminal task, your contributions to PE, guidance documents, conferences and training, committees, and communities of practice are necessary and appreciated in meeting ISPE's strategic goals.

I look forward to continuing our work together and I hope to see you in Philadelphia at the Annual Meeting & Expo. We will share more about our achievements to date and those that are on the way. ◊

John Bournas is the CEO and President of ISPE.



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Editorial Policy

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Pharmaceutical Engineering welcomes readers' comments. Letters must include the writer's full name, address, organization, and years of ISPE membership. If published, letters may be edited for length and clarity. Send correspondence to Susan Sandler, Editorial Director, at ssandler@ispe.org.

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A YEAR OF ACHIEVEMENTS

Tim Howard

I write my final “Message from the Chair” article full of a range of thoughts and emotions. Perhaps the best way to sum up my feelings is just to say, “Time flies when you’re having fun.”

As I started my year as Chair, I shared with you three areas of focus: chapters and affiliates, the ISPE Foundation, and continued execution of our Strategic Plan.

During my tenure, I have attended and spoken at chapter events in the Greater Los Angeles area and the Carolina–South Atlantic region, and at affiliate events in the Philippines and Singapore. I have attended face-to-face meetings of the European Affiliate Council and Asia–Pacific Affiliate Council. I also had the pleasure of meeting with representatives from the China Center for Food and Drug International Exchange office in Beijing, where we were hosted by Mr. Bin Xue. At each of these events and meetings I have relished the opportunity to connect with chapter and affiliate leadership and members and learn what is most important to them as ISPE members.

I established a work group in North America to identify and implement some quick wins that would benefit local chapters and strengthen their connections with our international committees, such as our Communities of Practice. I am highly encouraged by their progress and I look forward to sharing the output of this group at the Annual Meeting in November.

Our foundation board, under the leadership of Mike Arnold with strong support from our ISPE staff, has been very active this year in establishing the foundation. Fund-raising is well underway, and we expect to identify the recipients of scholarships for full attendance at and travel to the 2018 Annual Meeting. (See page 12 for more information on the ISPE Foundation.)

I have provided updates throughout the year on the progress of executing against our strategic plan. While we have achieved much success, we are always looking for areas to improve. Next year is the final year of our 2016–2019 plan, and as such we have started the process to update the plan for the next 3–5 years. We have engaged with many stakeholders to get a broad spectrum of input. We have connected with industry leaders who are at the forefront of leading innovation and change. We have reached out to constituents from our chapters, affiliates, committees, and communities. Our board, along with our ISPE staff, will meet in mid-September to assess the input from these channels. We expect to deliver a new strategic plan by the end of this year.

It has been a true honor and privilege to serve as Chair of ISPE this year. I have so many to thank for that I risk leaving some out—but here it goes: To our ISPE staff, you are dedicated, professional, and fun to work with. Thanks for all you do for our members and our society. To my fellow board members

(past and present), I hold all of you in such high regard. I’m humbled to sit among you, much less serve as your chair. I have learned much from each of you and look forward to staying connected with each of you for years to come. To all of the volunteer leaders throughout our organization, your commitment to the society and your passion for what you do is remarkable. ISPE would not exist without you. To Bob Chew and Commissioning Agents, who have supported me with time and treasure to serve on ISPE’s board for the last seven years, I am forever grateful for the unwavering support you have offered throughout my tenure.

Finally, to my wife Ashley and children Carson and Bradley, thank you for allowing me to be away on weekends, miss family events, and for doing so with genuine support and robust encouragement. <>

Timothy P. Howard, CPIP, PE, Vice President Asia Operations at Commissioning Agents, Inc., and President of its wholly owned subsidiary Coactive, Inc., is Chair of the ISPE International Board of Directors. He has been an ISPE member since 1993.



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MY TOP TIPS FOR YPS Attending Large Conferences and Navigating Exhibitor Halls

Caroline Rocks

In June I attended the ISPE Quality Manufacturing Conference and Continuous Manufacturing Workshop in Arlington, Virginia, followed byACHEMA, a large exhibition for the chemical and process industries held every three years in Frankfurt, Germany. After successfully navigating both of these conferences, I wanted to share my top tips for getting the most value out of these large events and their exhibitor halls with my fellow YPs.

PLAN YOUR AGENDA

Both ISPE andACHEMA have excellent apps that provide information on the conference; they also have a clever feature that allows you to create your own schedule. Larger conferences usually have multiple concurrent sessions, so it's a good idea to plan which ones you want to attend. At most conferences I try to sit in on one or two sessions covering areas of the industry that are not part of my current job, but that I want to learn about.



The ISPE conference app

The apps also allow you to map and bookmark individual exhibitors. This is helpful because exhibitor halls can be quite large; you need a plan so that you don't wander aimlessly, but instead navigate efficiently to booths that are of greatest value to you and your area of business.

Planning an agenda in advance also helps me determine at the outset if a conference is actually of value to me and my organization. If you are approaching your manager for approval to attend a particular conference, I've found that it can be easier to demonstrate its value to your role or your

organization's business priorities if you show a well-planned agenda that highlights the sessions you plan to attend and the exhibitors you plan to meet.

NAVIGATING THE EXHIBITOR HALL

It can seem a little daunting to approach an exhibitor booth, particularly if it is a service or technology that you know very little about. ISPE UK Chair Jon Youles, Managing Director of Ytron-Quadro and a regular at larger international exhibitions, says you don't need to be shy. The one thing exhibitors want more than anything is to talk about their products and services.

"Every exhibitor welcomes students and YPs," he told me. "Although they may not yet be in a position in their career to select equipment or services, they are potential users and buyers of the future!"

I asked Jon what type of questions he would recommend that students and YPs ask. He reassured me that with a lot of equipment on display, it isn't initially obvious what the application is for, so a good question is simply, "What is this equipment for?" or "Can you tell me more about this?"

He also recommends that if you want to spend a bit more time walking around a larger stand it might be beneficial to visit in the afternoon, when the exhibition hall is usually a little quieter and exhibitors will have more time.

— continued on page 10

Exhibitor Etiquette

- Don't just take something from a table without at least saying hello.
- Introduce yourself and your organization.
- Be honest if you know little or nothing about the company, but do indicate that you are interested in learning about the services they offer.
- Tell the vendor if you have a specific area of interest and ask if they offer anything that would be suitable for your company.
- Ask the vendor how they got started with their company. You never know who is manning the booth; it can be anyone from a YP to a director.
- Ask for a business card so you can follow up later. Top Tip: Write at least one fact shared during your conversation on the back of the card so you can add a personal touch in later communications.
- Remember your value as a YP: You are the buyer or user of the future.

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Caroline visits the Pall Biotech booth in theACHEMA Frankfurt exhibitor hall

NETWORKING

Some of the most enjoyable aspects of attending an international conference are the opportunities it presents to increase my network by meeting new people and reconnecting with those I already know. I renewed acquaintances

with many of my American colleagues in Arlington, and with my European and Indian colleagues duringACHEMA, in Frankfurt.

Every conference has networking receptions that provide further opportunities to expand your professional circle. Even short coffee or lunch breaks can be opportunities: Sit beside someone you don't know during these breaks and introduce yourself.

Here are some other networking tips:

- Break away from friends or colleagues that you already know. Sit at a table where you don't know anyone—it's a great way to start up conversation. If you always only sit with those you know you might miss out on meeting someone new.
- Not sure what to say? Ask someone what they do and how they became involved in ISPE or another organization.
- Keep up the connections you make. Within a day or two of the conference, make sure you reach out via LinkedIn or email and try to maintain your new connection. You can comment or like something they post, or just send them a note every now and then to say hello.
- If you know that someone from the International YP Committee will be at a conference, contact them in advance and plan a face-to-face meetup. This is a great way to use your YP network.

Join the conversation on the YP Community page: <http://cop.ispe.org/yp>. To join the YP Community, select it during registration or update your account on ispe.org.

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ISPE FOUNDATION LAUNCH

New Ways to Address Key Industry Needs

On 19 June, ISPE officially launched the ISPE Foundation. The philanthropic arm of ISPE “will enhance ISPE’s ability to support its members and the pharmaceutical industry as they prepare to address new and evolving industry demands,” according to Michael A. Arnold, ISPE Foundation Board Chair, and John E. Bournas, ISPE CEO and President.

The foundation will initially focus on three key needs of the pharmaceutical industry.

BUILDING THE WORKFORCE OF THE FUTURE

GOALS: Attract, support, educate, and train talented young people entering the industry. Through the ISPE Travel Grant Program, students and young professionals can receive financial support to further their professional development and contribute to building the industry’s future workforce.

PURPOSE: Establishing an appropriately skilled and plentiful workforce for the future is one of the biggest challenges facing the pharmaceutical industry today. Workforce composition and required skills are changing due to technological innovations in drug manufacturing, such as biotechnology, automation, and multifunctional manufacturing sites. There is a critical need for a robust global pharmaceutical workforce to ensure safe, effective, efficient, and continuous supply of quality medicine for patients.

EMPOWERING WOMEN AND INCREASING DIVERSITY

GOALS: From providing professional training and education to fostering mentorship and networking for women and ethnically diverse people, these initiatives will drive the successful career progression of underrepresented groups in the pharmaceutical industry.

PURPOSE: The pharmaceutical industry is behind the trend in addressing imbalances in the representation of women and diversity in the workforce, as a recent McKinsey & Company study illustrated. To create greater equality, opportunity, and corporate success, there is an imperative to increase the numbers of people from underrepresented groups. The financial benefits of building this workforce can be great as well: The McKinsey study found that companies in the top quartile for gender diversity are 15% more likely to have above-average returns; those in the top quartile for racial/ethnic diversity are 30% more likely to have above-average returns.¹

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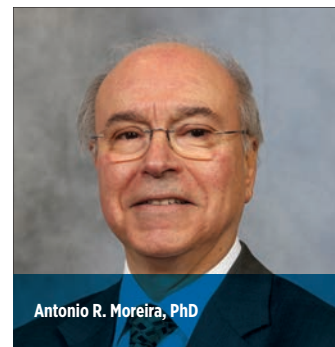
GOALS: Make ISPE’s highly regarded industry Guides available to emerging markets through the Emerging Markets Knowledge Exchange, and train and harmonize global regulators in industry best practices through the Global Training and Harmonization Fund.

PURPOSE: Aging populations and strong emerging economies are fueling a growing demand for medicines. Drug production is moving into new markets and companies are adapting current facilities to keep pace with technological advances. To meet this growth and the new challenges it presents, companies moving into new markets must plan and deliver manufacturing processes. Harmonization of regulations, scientific standards, and production quality is needed to maintain established industry standards.

ISPE EMBRACES THE CHALLENGES

ISPE determined that a foundation to fund a range of initiatives tackling the pharmaceutical industry’s central and pressing issues will help to support its growth and success.

Now is the right time to establish a foundation to address issues that affect the industry’s future because “a primary objective of ISPE is to support our members and provide opportunities to enhance their career skills, to assist them in preparing for future demands of the industry,” explained Arnold. The



ISPE Foundation “will provide us with a means by which we can support the young professional, workforce of the future, and industry-wide efforts that are consistent with our strategic initiatives.”

The launch of the foundation fulfills ISPE’s mission, added Dr. Antonio R. Moreira, an ISPE Foundation Board Director. “Through its focus on facilities of the future, manufacturing and technical operations, quality matters, and strategic collaborations with regulators, ISPE provides important support to its members on the manufacture of the quality medicines so much needed by the patient population throughout the world.” The Foundation’s establishment is a natural next step, he noted. “Establishing the ISPE Foundation now provides ISPE the opportunity to expand its support to the pharmaceutical industry. The ISPE Foundation will carry out key initiatives that are central to the needs of the current industry globalization and development of advanced medicinal therapeutic products.”

And the work that the ISPE Foundation will support is familiar territory, said Chris Reid, Secretary of the ISPE Foundation Board. “ISPE has always been passionate about supporting innovation and advancement in our industry, including supporting new professionals, diverse groups, and research into problems faced by our industry and approaches to addressing such problems. Such initiatives include our academic outreach, young professional communities, Women in Pharma®, research into the causes of drug shortages, and research into quality metrics. The ISPE Foundation provides an effective vehicle to support these initiatives and beyond to ensure that ISPE is focused on the priorities of our members and the needs of the industry.”

FOCUS: DEVELOPING PEOPLE

The three initial initiatives of the ISPE Foundation were chosen with care by the foundation board. “ISPE membership is comprised of many of the most talented and driven pharmaceutical scientists in the world. They contribute their time and skills in solving worldwide industry challenges, training and process development in critical areas such as biopharmaceuticals, regulatory, and process design and development,” Arnold noted. “We need to supplement these expert skills with additional and more diverse skills that will be necessary for future professionals to be successful. For these reasons, the foundation has initially identified these three areas of focus.”

Multiple initiatives were considered as potential focus areas that would support the foundation’s mission and vision, Moreira said. “Through a process of vetting and prioritizing these initiatives, the foundation board agreed unanimously that the workforce of the future, women/diversity, and global knowledge exchange represented the most impactful areas that the foundation would address from the start.”

One component that will be supported in the Empowering Women and Increasing Diversity goal is ISPE’s Women in Pharma®, which provides a forum through which women in the pharmaceutical industry can connect and collaborate on technical and career advancement. It also provides opportunities for women to speak on pharma issues, including delivering technical presentations and contributing to panel discussions. A community of Women in Pharma® mentors, resources across all levels, and educational sessions will be an enabler for career success and work–life balance.

Developing people is the focus of these three initiatives, noted Reid. “ISPE is passionate about patient welfare and supporting the advancement of health care solutions. To do this, our industry must engage the brightest

Industry Challenges Determined ISPE Foundation Initiatives

Three key challenges facing the pharmaceutical industry form the backdrop for the Foundation’s first initiatives:

- **Workforce shortage:** In the United States alone, 60% of the country’s 3.4 million pharmaceutical industry jobs could be vacant by 2025 due to a scarcity of people entering the industry.
- **Globalization:** Pharma revenues are shifting from west to east: In 1995–2005, less than 20% of big pharma revenues came from emerging markets. In 2005–2015, up to 35% of corporate revenue was derived from the Asia-Pacific region and emerging markets.¹
- **Lack of diversity:** Only 28% of engineers in research and development are women, and women hold board seats on just 17% of the top 50 pharma companies. Ethnically diverse directors hold just 8% of those seats. This dearth of diversity “negatively impacts companies’ performance across the board,” according to a 2015 McKinsey & Company report. “More diverse companies are better able to win top talent and improve their customer orientation, employee satisfaction, and decision-making, leading to a virtuous cycle of increasing returns.”²

The future of the industry is affected by potential challenges to efficiency and effectiveness because of the growing needs to create a pipeline to feed the workforce of the future, close gaps in workforce gender and diversity, and meet the pressing educational demands of the global workforce. Failure to meet these needs could hinder patients’ access to quality medicines.

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About the ISPE Foundation

Mission Statement

The ISPE Foundation supports education, training, and research for the advancement of innovative technologies and provides solutions to global challenges in the development, manufacture, and supply of quality pharmaceutical products for the benefit of patients around the world.

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talent. The ISPE Foundation offers a tremendous opportunity to support the development of our brightest assets and to encourage a diverse workforce to ensure our industry draws from the deepest possible talent pool.”

NEXT STEPS

Now that the ISPE Foundation has officially launched, the next step is to build funding from contributions. Planning for the foundation’s future initiatives is on the horizon.

“The foundation board of directors and ISPE staff are excited about the opportunities we can provide through your donations to the foundation,” Arnold said. “As we firmly establish our goals and objectives for the near term we will be working as well on the longer-range initiatives and opportunities for our members. We are in the process of establishing a fund-raising committee to assist us in promoting our message and speaking directly with prospective donors. We encourage you to consider donating to the foundation and sharing this opportunity with others who may wish to do the same.”

The ISPE Foundation will support cooperation among industry, academia, and regulatory agencies, Moreira noted. “Such cooperation will continue to be essential to the solution of current and future challenges. The ISPE

Foundation is focused on initiatives that will contribute to such solutions by expanding on the unique strengths of ISPE as the premier professional society for the pharmaceutical industry.”

Reid predicted that the contributions of the ISPE Foundation will be felt in the industry for years to come. “The ISPE Foundation is just starting out and focusing on some key areas that impact our industry and society today. Its ambitions reach beyond our current objectives, with future potential to support research into new strategies, approaches, and technologies that will further advance our industry and ultimately, patient care.”

YOU CAN HELP

The ISPE Foundation needs your donations to fund its initiatives. Donors can contribute to a general foundation fund or to any of the three current initiatives. To learn more about the ISPE Foundation or to make a donation, visit www.ISPE.org/Initiatives/Foundation.

—Susan Sandler, Editorial Director

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RAPID MICROBIAL MONITORING

Adoption, Applications, and Regulatory Guidance

Nissan Cohen

Rapid microbial monitoring (RMM) is the real-time or near-real-time determination of microbial presence in a sample without the need for incubation, laboratory services, or intervention. RMM is a definition, not a single methodology.

Regulatory guidelines accept many methods of bioburden detection and measurement. The detection method is less important than its ability to determine microbial presence, especially in continuous manufacturing processes. Evaluative guidelines are prescribed to show equivalency between different methods and devices but not the number duplication in the colony forming unit (CFU) format. This paper describes applications for RMM in pharmaceutical waters; it also delves into the regulatory guidelines that support its adoption and use, with a focus on biopharmaceutical production and critical utilities.

USP38-NF33, CHAPTER <1223> Validation of alternative microbial methods

This revised chapter stresses that analyses

conducted with alternative methods may differ significantly from traditional growth-based incubation, but that does not necessarily indicate a greater risk to the patient or a greater chance of pathogenic species.

The chapter also repudiates a common comparison, stating: “The statistical comparison of results expressed as CFU obtained by signals analysis made by biochemical, genetic, or physiological methods is of little value.” The monograph then identifies possible protocols for validating any RMM instrument regardless of its method of detection:

... It is critical to consider that in microbiology, the finding of “no microorganisms present” does not mean in absolute term that zero cells are actually present. A result of “no growth” in a current compendial method is properly interpreted as “no growth was detected under the specified conditions” ... Studies on the recovery of microorganisms from potable and environmental waters have demonstrated that traditional plate count methods reporting cell count estimates as colony

forming units (CFUs) may recover 0.1%–1% of the actual microbial cells present in a sample.

Understanding the strengths and weaknesses of the CFU as a signal is vital in the validation of an alternative method that uses an alternative signal. The CFU cannot be considered the only unit of microbiological enumeration, because it is only an estimate of cells present rather than an absolute measure.

The enumerative values, given as CFU results in association with reference methods, typically cannot be used as acceptance criteria for the assessment of articles via candidate alternative methods. Instead, it is the users’ responsibility to propose values that they consider acceptable and unacceptable for the method that they have chosen; this will be done independently of existing standards expressed in terms of CFU.

Absolute CFU-to-CFU comparisons between RMM and traditional growth-based methods are impossible. Bacteria culturable in R2A

TABLE A

Option	Demonstration	Comparison to official compendial method	Based on numerical results or conclusions	Number of characteristics
1. Acceptable procedures	Acceptable	No	Results	Multiple
2. Performance equivalence	Equivalent or better	Yes	Results	Multiple
3. Results equivalence	Equivalent	Yes	Results	Single
4. Decision equivalence	Equivalent	Yes	Conclusions	Single

media (agar) may represent < 1% of the total bacteria count in the sample. Fricker notes that “[t]he pharmaceutical industry routinely uses Tryptic Soy Agar (TSA) as a culture medium with incubation at 37°C, but this tends to detect fewer bacteria than using either the Reasoner’s 2A agar (R2A) medium and incubation at 22°C, or yeast extract agar at either temperature. Waterborne bacteria generally prefer lower temperatures and lower levels of nutrients. Choosing the right conditions for the culture are essential. An RMM that can measure all bacteria will have a large discrepancy in comparison to growth-based CFUs. Methods outlined in USP <1223> describe how to validate an RMM without growth-based-media CFUs.

USP <1223> explains the formulation of equivalence, not exactitude. You do not have to read the same number for validation to ensure your method of detection is sound. Performance is demonstrated by the consistency of readings when tested against known bacteria concentrations, as shown in Table A.

1. Acceptable procedures
 - a. Does not require a direct comparison with a compendial method.
 - b. Does require a reference material as a standardized inoculum of a specific microorganism.
2. Performance equivalence
 - a. Demonstrate that the alternative method is equivalent or better than the compendial.
 - b. Validation criteria include accuracy, precision, specificity, limit of detection, limit of quantification, robustness, and reproducibility.
 - c. RMM may have worse results for one or more of the seven validation criteria but still be considered acceptable because of the advantages it offers, especially if it is relevant to assessing the quality of the material in question (scan time in the case of cytototherapy, regenerative medicine, or radiopharmaceuticals, for example).
3. Results equivalence
 - a. Demonstrate that the alternative and compendial methods give the same result.
 - b. Microbiological analysis must be established for a tolerance interval with the alternative method, which must be numerically super-

rior or inferior. Using statistics and relative standard deviation in fairly high percentages can help with acceptance.

- c. Because alternative methods, not based on growth, provide significantly higher cell-count values, the two methods can be compared using calibration curves and R² calculations.
4. Decision equivalence
 - a. Generates a pass/fail indication, not a numeric result. With this approach, the frequency of positive and negative results should not be pejorative to the compendial.
 - b. To qualify the RMM unit, laboratory tests that use spiking techniques with varying levels of microorganisms are preferred.

If the RMM instrument reads X and the culturable bacteria reads Y, it does not mean that either or both are right or wrong. It only means that the detection methods are different and consistent readings are needed to show equivalency of the RMM method to gain confidence in the data.

instrument displays the validation protocol and results during validation, providing a needed touchstone for the uninitiated:

Primary validation in order to characterise a specific microbiological method, the principle of detection must be clearly described by the supplier... The method must be fully detailed with respect to the conditions required for application, the materials and equipment needed, and the expected signal. The application principle should be described in a peer-reviewed journal. The principle of detection must be characterised in a model system and/or with a panel of test microorganisms, by at least:

- Prerequisite treatment of sample or microorganisms
- Type of response
- Specificity of the response
- Limit of detection
- Range
- Linearity of the response
- Accuracy and precision of the response

EU PHARMA-COPOEIA, CHAPTER 5.1.6 (50106) Alternative methods for control of microbiological quality

This has aspects and mandates similar to USP <1223>, with two additional validation criteria: range and specificity of the response. The chapter includes an example of alternative microbial detection validation, titled, “Example validation of an alternative method: detailed protocol followed by a laboratory for the implementation of bioluminescence.” The European Pharmacopoeia example for a specific type of RMM

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Once the method has been characterised in this way by the supplier, the principle of detection need not be verified by each user.

EP 5.1.6 was written in 2008, with little or no revision since then. The monograph cites different types of RMM detection methods and lists three major areas of concern for each: “principles of measurement,” “critical aspects,” and “potential uses.” It also cites risk-benefit analysis and validation methods to enhance acceptance of RMM technology.

PDA TR33

Parenteral Drug Association Technical Report 33 is the most up-to-date document for those who need a guide on choosing and validating RMMs. The first part of the document contains a series of considerations on alternative methods, more rapid than traditional ones, and covers the following points:

1. Limits and weaknesses of classic methods:
 - a. Long response times.
 - b. Potential inability to highlight microorganisms (stressed or viable nonculturable).
 - c. Inability to bind to principles of quality by design and quality risk management.
2. The positions of leading authorities (US Food and Drug Administration, European Medicines Agency, Australia’s Therapeutic Goods Association, Japan’s Pharmaceutical and Medical Devices Agency), with particular attention to validation requirements and assessment of the need to submit a formal request. Considerations of regulatory agencies in other countries are also included.
3. Economic considerations and return on investment.
4. Potential quality risks arising from the use of quick or alternative methods and tools for identifying and assessing risks.
5. Automation of classical methods and simplified validation requirements.
 - a. Reviews of methodologies and alternatives (available or under development) and their

scientific bases, citing over 60 methods for bacteria detection under six classifications: growth-based, viability-based, cellular-component-based, optical spectroscopy, nucleic acid amplification, and micro-electro-mechanical systems. There is no advantage to any detection method when the guidelines are applied as long as the instrument or technology provides the option to follow the guidelines for application in a pharmaceutical environment.

ASSUMPTIONS AND REALITIES

All RMM methods, regardless of detection method, will most likely have false positives or false negatives. There will be virtually no equivalence between any two detection methods.

It’s important to establish confidence in the RMM by having continuous data, and to evaluate trending levels. Both manual and online or rapid sampling can be used to compare different detection methods. The data can trend very similarly, even though there may be a significant difference in actual values.

APPLICATION EXAMPLES

RMM will be the main online tool for monitoring microbials in the near future. Grab sampling with growth-based incubation will continue to be used for product release. RMM will monitor the microbials in real time, and if there should be a value or consistent values above the standard deviation of 1 σ , then a grab sample is performed to confirm the microbial values deemed trending.

Installing an RMM unit in the 24/7 purified water system to record the health and operation of the water system can complement the 24/7 online instrumentation, analysis, and readings for all mandated and performance measurements, while adhering to process analytical technology (PAT) guidance.⁴ This provides complete knowledge and interaction with the water system. Product liability, unplanned shutdowns due to bad microbial tests, loss of production, and investigations can be severely curtailed, increasing uptime, productivity, quality, throughput, and compliance.

“Cycle time” is the period between the beginning of a production cycle and the beginning of the next product or batch initiation using the same vessels. This includes the use of a clean-in-place (CIP) regimen for 3–5 hours, after which production vessels are idle until the CIP residual

microbial data is confirmed by sampling and incubation, which can take from 2–7 days, depending on the protocol. Using RMM technology, the vessels could have been released for the next cycle immediately after the completion of the CIP regimen. This can dramatically decrease cycle time, allow for dozens more cycles per year, and increase revenue without additional investment in infrastructure, utilities, or vessels.

CONCLUSION

Online RMM with other online instrumentation can determine the health, operation, and status of a water system in real time, preventing unplanned specification excursions and downtime, while maintaining 24/7 compliance.

Upfront evaluation of RMM using the regulatory guidelines in USP <1223>, EP 5.1.6, and PDA Technical Report 33 will help increase acceptance of RMM with internal and external regulatory entities. Online RMM, after proper validation and installation of the instrument, can increase cycles, increase revenue, shorten idle time, minimize downtime, and provide compliance with PAT guidance. <>

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Nissan Cohen, an ISPE member since 1994, is a worldwide expert in total organic carbon, high purity, ultrapure, reclaim-and-recycle water systems, with profound expertise in instrumentation, automation, and organic contamination oxidation systems using ozone, UV, ion exchange, and catalysts.



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NEW AND IMPROVED: MEET THE ANNEX 1 REVISIONS

Jean-François Dulière, Marick Paris-Cadet, and Alexandra Yath

Disclaimer: This is a brief and informal synopsis of responses from UK MHRA, US FDA, and Russian State Institute of Drugs and Good Practices (SID & GP) regulators during a panel dialogue at the ISPE Europe Annual Conference in March 2018. It has not been vetted by any agency and does not represent official guidance or policy of the MHRA, FDA, or SID & GP.

On 20 December 2017, the European Commission (EC) published its long-awaited revision draft of Annex 1: “Manufacture of Sterile Medicinal Products.”¹ The Annex, part of the European Union good manufacturing practice (GMP) guidelines, has undergone several targeted updates since it was originally published in 1989; the last was in 2008. This is the first complete revision.²⁻³

In drafting the revision, the EC worked closely with the World Health Organization and PIC/S to maintain existing global standards; each organization will review the revised annex in a parallel public consultation.

Revisions and additions were significant, increasing the document from 16 to 50 pages. One of the most notable changes is the inclusion of quality risk management (QRM) principles, which are used to reduce the risk of contamination and maintain the quality of a medicinal product throughout the product life cycle. QRM, described in ICH Q9 and used in GMP since 2013, evaluates the manufacturing process and equipment to identify patient risk as well as document mitigation and management processes commensurate with that level of risk. While QRM is not specific to sterile products, its application is at the heart of the new Annex 1.

Additional changes include:

- New sections: scope, utilities, environmental monitoring, process monitoring, and glossary
- Reorganized and restructured content for a more logical flow
- Introduction of QRM principles
- Existing sections enhanced and expanded for better clarity

After the revised draft was released, targeted stakeholders from industry and national competent authorities were invited to consult and comment on the revision from 20 December 2017 to 20 March 2018.³

ISPE COMMENTS

ISPE members submitted more than 700 comments on all of the document’s

11 chapters. After consolidation by SMEs and a final review by the Regulatory Steering Committee, 290 ISPE comments were submitted to the EMA.⁵ These were also presented at during the 2018 Europe Annual Conference in Rome.

ISPE’s Annex 1 comments and responses were also presented during the 2018 Europe Annual Conference in Rome, followed by a panel discussion with three regulators—Andrew Hopkins from MHRA, Rick Friedman from FDA, and Vladislav Shestakov from SID & GP. This Q&A session provided a lot of information and gave participants a chance to raise many additional questions and comments. While the discussion covered the entire annex, QRM was a frequent topic of discussion, as expected.

SCOPE

The following statement was the focus of much attention:

However some of the principles and guidance, such as contamination control strategy, room qualification, classification, monitoring and gowning, may be used to support the manufacture of other products that are not intended to be sterile (such as certain liquids, creams, ointments and low bioburden biological intermediates) but where the control of microbial, particulate and pyrogen contamination, to reduce it as far as possible, is considered important.

This raises industry concerns that all points of Annex 1 would become compulsory for nonsterile products.

Regulators stated that this reference to nonsterile products was included because there were no other references in other chapters or annexes about room classification (Grades A to D), gowning requirements, or contamination control strategy, even though those principles are not specific to sterile products. Though the inspectors understood the possible confusion and will try to clarify this point, it deals with products that require thorough controls and have low contamination limits.

Regulators also restressed the use of QRM principles to determine which points of Annex 1 should be applicable to nonsterile products.

PERSONNEL

This chapter deals with personnel, and although it is a small section, it generated questions as well.

Annex 1 states that microbial monitoring of personnel in Grade A and B

rooms should be done “upon each exit from the cleanroom.” While this was not stated in the previous version of the annex, it was clearly desirable even before the revision, because manufacturers should know the contamination risk for and from operators in their environments. Monitoring provides valuable data, so it is recommended as much as possible.

The draft also introduced a new concept: “personal disqualification.” While personal qualification is fully integrated into GMP and is mandatory before entering a cleanroom, the new term “disqualification” was unclear to many participants. When is someone disqualified, and when is requalification necessary? Is a person who was sick for 2 to 3 days disqualified in the same way as someone who had a serious illness and was absent for 3 months?

Regulators explained that this statement was intended to cover trained operators who demonstrate unacceptably high contamination levels that harm product integrity. In cases like this, disqualification and requalification are mandatory. Operators with a cold, flu, or other mild illnesses are temporarily barred from entering airlocks and cleanrooms, but do not need requalification once they recover. Those returning from long illnesses require requalification, if only because after a protracted absence they will not be familiar with the process or able to work in alignment with GMP.

PREMISES

Another change with potentially profound effects is the stated preference for separate cleanroom entry and exit airlocks. Many participants felt that the new text was unclear, and asked if the revision required separate airlocks for both new and existing facilities. Regulators explained, however, that this requirement currently applies only to new facilities.

A single airlock combined with a contamination control strategy (cross-contamination control) is acceptable for existing facilities. Nevertheless, regulators indicated that upgrading facilities by implementing barrier technologies such as isolators, RABS, or separate entrances and exits can reduce possible cross-contamination and provide better control.

While upgrading facilities to adapt to new guidelines can be troublesome, it’s an important component of patient safety and product quality. As such, it is industry’s responsibility to adapt to new regulations. Old facilities cannot ensure the quality required from new guidelines as they were not built to these standards.

With regard to the cost of upgrading, regulators acknowledge that implementing barrier systems can be a financial challenge, but they pointed out that supporting facilities built before 1990 is as costly as upgrading them. Regulators indicated they would study contamination risks for both old and new facilities.

While expensive, installing isolators can often reduce the grade of cleanroom needed; the background required is at least a Grade D. Nevertheless, background grade must be determined by each individual case and risk assessment. Loading and unloading a lyophilizer where the stopper is not fully inserted, for example, makes contamination more likely to occur, and only grade A would be acceptable. A negative pressure isolator would also need a Grade A background.

Grade A or B is required for all operations prior to containment without a subsequent sterilization process, since vaporized hydrogen peroxide (VHP) is no longer considered a sterilizing agent, although regulators allow it to be used as a disinfectant. Liquid peroxide solution removes bacterial contaminants more reliably with enough contact time on every surface (i.e., dipping).

Exceptions can be proved if they use QRM and demonstrate a 6-log reduction.

Cleanroom classification also underwent a significant change in this draft: While 0.5 micrometer (μm) particle size is still used for room qualification, 5 μm particles, while not relevant for qualification, are now used for monitoring, as they tend to be the first indicators of a problem.

Additional discussions covered HVAC filters, environment background, and air flow visualization.⁴

UTILITIES

The Annex 1 revision includes the EMA Q&A document on production of water for injection (WFI),⁶ although WFI requirements are still not well developed. While the draft now states that WFI must be produced from purified water (previous versions required only drinking water), GMPs must be harmonized with the European Pharmacopoeia monograph 169. The EU Pharmacopoeia also recommends the use of reverse osmosis to produce WFI, but regulators prefer distillation. For the time being, the Q&A document is still the reference for producing WFI using reverse osmosis.

PRODUCTION

Chapter 8, “Production and Specific Technologies,” is the most substantial chapter in the draft: Not surprisingly, it received the most comments and questions.

To decide whether the correlation between stopper height and microbial ingress is acceptable in experimental data, for example, scientific experiments must use QRM to prove their ability to limit ingress and containment. Another example is using risk analysis in filter integrity tests.

During this part of the panel discussion, regulators provided some clarification on the pre-use post sterilization integrity test, or PUPSIT. EMA regulators appear to strongly favor its use. Hence, to justify rejecting PUPSIT in Europe, manufacturers will have to prove their case using QRM principles. Some manufacturers say that PUPSIT is difficult to implement, but regulators strongly disagree. A. Hopkins stated that he managed to implement PUPSIT 30 years ago when he was working in industry. It should be much less challenging now, he said, since technologies have progressed and better systems have been developed.

Other comments in this section centered on definition and wording clarifications, sterilization operations, autoclaves, and freeze dryers.⁴

LANGUAGE

Another issue discussed during the session was the prescriptive language (“shall,” “should,” “must”) used throughout the document. Participants found it difficult to determine whether such statements were requirements or advice. In a regulatory document like Annex 1, clarity in terminology is important, especially for non-native-English speakers. In addition, the document should not be overly prescriptive, since QRM is not mandatory for the entire manufacturing process, although it is highly recommended for some stages. Other language-based comments included requests to improve the glossary, clarify definitions, and distinguish laminar from unidirectional flow.⁴

SINGLE-USE INTEGRITY TESTING

The panel dialogue ended with a question on single-use integrity testing. Because single-use systems appear more reliable, their integrity can be



Q & A with Jean-François Dulière

Pharmaceutical Engineering magazine caught up with Annex 1 Comment Team Lead Jean-François Dulière to discuss the Annex 1 revision ISPE member comments.

What is Annex 1 and why is it important?

Annex 1 is a GMP document published by the European Commission and dedicated to the manufacturing of sterile products. All pharmaceutical companies that produce sterile products must comply with these regulations. The document is a joint initiative between the EMA and PIC/S.

What are the major changes?

The last revision to Annex 1 in 2008 contained 123 items. This revision has produced a completely new document, reorganized in alignment with GMP in Europe. With 269 major points, it addresses significantly more details. This revision is not as stringent as the pharmaceutical industry had expected and is based on quality risk management. This is critically important for the pharmaceutical industry.

Who will be most affected by this revision if or when it is put into force?

All companies that manufacture sterile products. Some parts also apply to products that require clean air or a clean manufacturing environment.

Does the revised annex differ from other agency guidances?

In some instances, yes. The goal was to create a consensus document with all PIC/S parties, and input from greater than 70 different countries was received. Not all differences were resolved, however.

How serious are these differences?

The most significant was on the requirement for PUPSIT—pre-use, post-sterilization integrity testing—of filters. European regulators believe that this should be a requirement, while those in the United States do not. Many companies think that PUPSIT increases risk to the product because it may damage the filters.

What were some common concerns expressed by ISPE members?

Common concerns included questions surrounding PUPSIT and clarification of facilities design, as well as the use and operation of isolators and restricted access barrier systems.

What were the most significant?

Questions and concerns surrounding PUPSIT were the most significant. Extensive use of QRM was also a concern for industry, particularly how their QRM practices will be received by regulators.

What did you find most surprising or interesting about the comments?

Industry stakeholders asked for clarification of quality risk management guidelines. This was surprising because these have been in use for many years. However, clarification is important because without clarification, regulators may assume greater flexibility to accept or reject industry QRM practices.

Did you see any regional differences in the members' concerns?

There was not much regional difference in the comments regarding the key points. This is likely due to the globalized nature of the pharmaceutical industry.

Is there evidence that science- and risk-management principles were applied during development of the annex?

Yes. One example is the approach to particle-size monitoring. In this version of Annex 1, regulators require sterile product manufacturers to monitor the size of particles present in cleanrooms. Standard classification practices and qualification will be done with 0.5 μm particles. If larger particles are detected, this is considered an early indicator of potential problems. The presence of these particles alone would not call for a batch to be rejected but should initiate a risk assessment process to prevent other problems in the system.

How did the Comment Lead Team reconcile so many comments in the allotted time?

The commenting period lasted from 20 December 2017 to 8 February 2018. The comments were then reviewed by a team of 18 people divided into seven groups based on subject-matter expertise. From 12 February to 9 March each group reviewed the comments for a specific chapter. I met several times with each subject matter expert team. At the conclusion of this period, all of the accepted comments were combined and reviewed by the entire Comment Lead Team. We then sent the document to the Regulatory Steering Committee, which did the final review.

Has there been any early response from regulators to industry's reaction?

Early responses came during the panel discussion at the EU Annual Conference in Rome. There was some surprise regarding industry's request for clarification on quality risk management; as mentioned earlier, these guidelines have been in place for many years. There has also been some discussion around PUPSIT, with European regulators explaining why they want to maintain it, and US regulators saying that the decision should be based on quality risk management. There was also some discussion surrounding best practices for sterilization and decontamination. Despite industry support for vaporized hydrogen peroxide, regulators may require other methods.

THE GOAL WAS TO CREATE A CONSENSUS DOCUMENT WITH ALL PIC/S PARTIES, AND INPUT FROM GREATER THAN 70 DIFFERENT COUNTRIES WAS RECEIVED

Has EMA indicated whether the next version of Annex 1 will be final, or is it likely that another draft will be issued for comment?

Normally, a new draft would be issued by September or October, but the resources to do that may not be available. The EMA's goal is to have a final document issued by the end of 2018.

Was the US FDA requested to comment on Annex 1? Is it possible that the FDA could adopt the final version of Annex 1?

The FDA has issued comments on Annex 1. It is not likely to become law in the United States but may become a guidance for industry.

Once Annex 1 is finalized, will there be a transition period for its adoption by industry in Europe?

Normally, the adoption period would be six months. In this case, however, it is likely to be longer because of the significant number of details in the document. We could potentially see industry allowed one to two years for implementation for topics that require a long period for implementation in existing facilities

In the previous revision of Annex 1, which was finalized in March 2008, certain points were not required to be implemented until March of 2010 because they required facilities modifications and industry needed time to do this.

Any further thoughts about Annex 1?

In addition to the major points already discussed—PUPSIT, particle size, quality risk management, facility design, sterilization, and decontamination procedures—there were also some comments around how to qualify facility personnel. Overall, this latest version of Annex 1 is a significant improvement, as it provides significantly more detail, is better organized, and is based on quality risk management.

—Emily Burke, PhD

overestimated. Regulators cautioned that the ability to detect integrity failure does not guarantee a leak-free, contamination-free system. Single-use systems, therefore, still need integrity testing and do not necessarily remove operators from the process.

CLOSING

As the session concluded, Hopkins explained that with the comment period over, EMA will now review and assess all comments received to determine which should be included in the final version.⁴ The final release of Annex 1 is expected in December 2018. <

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Alexandra Yath, Process Engineer at TechnipFMC, works closely with Jean-François Dulière and Marick Paris-Cadet. She also is part of the ISPE YP group in France. She has been an ISPE member since 2017.

About the regulators

Andrew Hopkins has been a GMP Inspector at MHRA since March 2005, with responsibility for inspecting sterile and nonsterile pharmaceutical manufacturing facilities as well as biotechnology facilities and for ensuring that the companies inspected are compliant with EU GMP. He is currently Chair of the joint EMA and PIC/S Working Group regarding the Annex 1 update. He holds a BSc Honours in microbiology with genetics, a post-graduate diploma in industrial pharmaceutical science, and is a member of the Institute of Biology. He has been an ISPE member since 2011.

Rick Friedman, Deputy Director, Science and Regulatory Policy, Office of Manufacturing and Product Quality, has worked for the US FDA since 1990. In this position, he oversees case reviews relating to drug manufacturing quality, reviews regulatory action recommendations, and promotes sound regulatory policy development. Mr. Friedman has been an adjunct faculty member of Temple University School of Pharmacy in their QA/RA graduate program since 2003. He holds a BS in biology with honors from Montclair State University, and an MS in Microbiology from Georgetown University School of Medicine. He has been an ISPE member since 1997.

Vladislav Shestakov is Director of the Russian State Institute of Drugs and Good Practices, and Deputy Head of the State GMP Inspectorate and Head of Good Practices Committee for professional qualification of the National Pharmaceutical Chamber. In 2005 he graduated from the State University of Management majoring in state and municipal management, and from the Academy of Labor and Social Relations in 2008, majoring in business management. In 2016 he received a diploma of advanced professional training at the Moscow Institute of Physics and Technology, where he majored in current good manufacturing practices of pharmaceutical production and quality control, theory and practice of GMP inspections, and audit. He has been an ISPE member since 2017.

ISPE Proposes an Advancing Pharmaceutical Quality Program



The ISPE Quality Metrics team has proposed an industry-led approach to advance pharmaceutical quality beyond the submission of data for three harmonized, reportable metrics: the Advancing Pharmaceutical Quality (APQ) program. The basic framework of the program is to “assess and aspire” quality maturity. Evolving concepts, assessment tools, and key performance indicators of the APQ framework are:

- Quality culture maturity and improvement
- Preliminary quality appraisal (PQA)
- Corrective and preventive action (CAPA) maturity

ISPE has continued to have a team at readiness for responding to further advances in the FDA Quality Metrics program and this team has highlighted some best practices from across the industry regarding collection, management, and use of data for metrics.

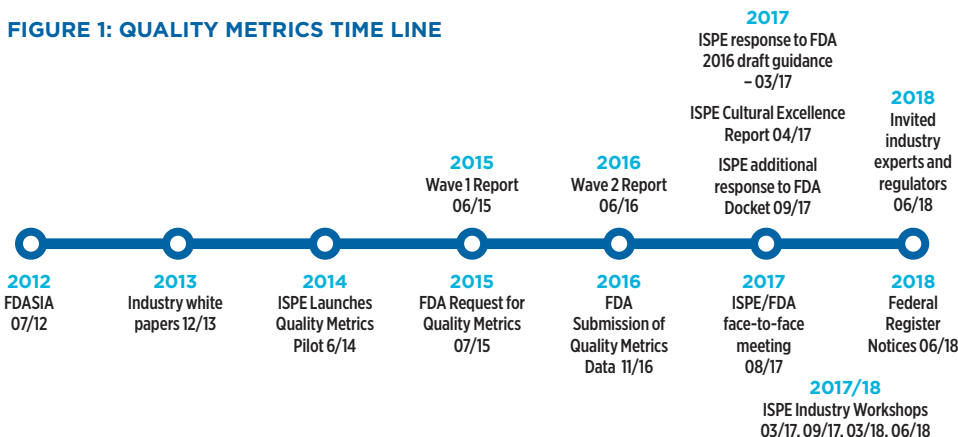
BACKGROUND

ISPE’s Quality Metrics program has been active since 2013 (Figure 1).

In March 2017, ISPE submitted an extensive and detailed response¹ to the 2016 FDA draft guidance² “Submission of Quality Metrics Data,” the associated *Federal Register Notice*,³ and webinar.⁴ These data-driven comments were informed by:

- Four years’ work with industry leaders and experts by the Quality Metrics core team
- Two pilot programs (Waves 1 and 2) involving 83 sites and 28 companies
- A workshop with 22 companies

FIGURE 1: QUALITY METRICS TIME LINE



After concluding that:

- Requirements are complex and preclude standardization due to challenges with unclear definitions
- Lack of clear and standardized quality metrics data elements will confound attempts at data analysis
- Burden is significant

ISPE recommended that the agency issue a final guidance for a carefully structured FDA pilot program before a program commences.

As an alternative, ISPE suggested that FDA review the stated goals of its quality metrics program and consider other approaches to its 2016 guidance, which is based on industry submission of harmonized data elements.

ISPE representatives had a further series of interactions with FDA to seek clarity about its comments. Following these interactions, FDA requested further explanation of ISPE’s recommendations for definitions of lot acceptance rate, product quality complaint rate, and invalidated out-of-specification rate as they related to the FDA 2016 draft guidance, as well as alternative approaches. These recommendations and some preliminary thoughts on alternative approaches were provided in October 2017.⁵

APQ PROGRAM

Goals, benefits, and concepts

At a September 2017 workshop for Wave 1 and 2 participants, preliminary proposals were developed on potential processes for achieving FDA goals.

Emergent themes included:

- Voluntary
- Phased
- Well-defined assessment criteria
- Incentives/recognition inclusion

A voluntary program, it was considered, would self-propagate through engagement of early adopters/change ambassadors and would show industry leadership and commitment. To encourage participation, benefits should be demonstrable.

Processes for developing an alternative program could be based

on existing programs such as OSHA's Voluntary Protection Program (VPP) and the FDA's Case for Quality Program, which is administered by the agency's Center for Devices and Radiological Health. It could also take elements from the UK Medical and Healthcare Products Regulatory Agency (MHRA) pre-inspection information request process.

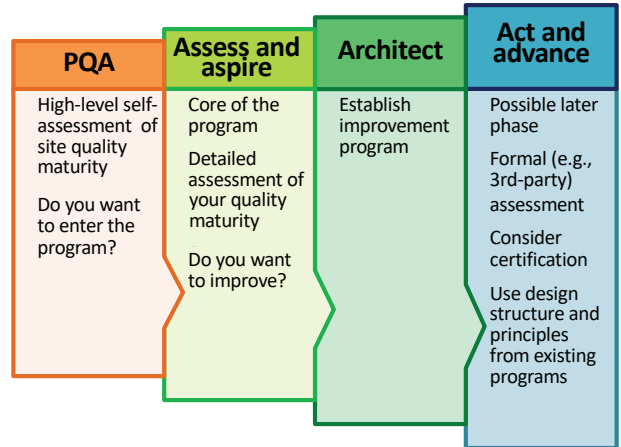
To move these early proposals forward, the industry-led "Advancing Pharmaceutical Quality" program is being developed. The vision for this developing program continues to be that elucidated by FDA as:

*A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight.*⁶

The proposed program would:

- Evolve the primary focus of the ISPE Quality Metrics team from the FDA quality metrics program to establishing a platform for advancing the state of pharmaceutical quality that could be leveraged by industry and FDA to achieve quality metrics program objectives
- Integrate tools and experiences in culture, quality, and operational excellence disciplines that demonstrate value to industry, regulators, and patients
- Assign deliverables that include assessment and continual improvement tools, education (conference, articles), industry engagement workshops, benchmarking forums, and interactions with regulators, especially FDA

FIGURE 2: ISPE APQ FRAMEWORK



Proposed program goals are:

- Enable and foster industry ownership of quality beyond compliance
- Integrate quality, cultural, and operational excellence principles and learnings
- Support and incentivize continual improvement
- Promote efficient use of resources by improving execution
- Increase reliability of supply for quality product

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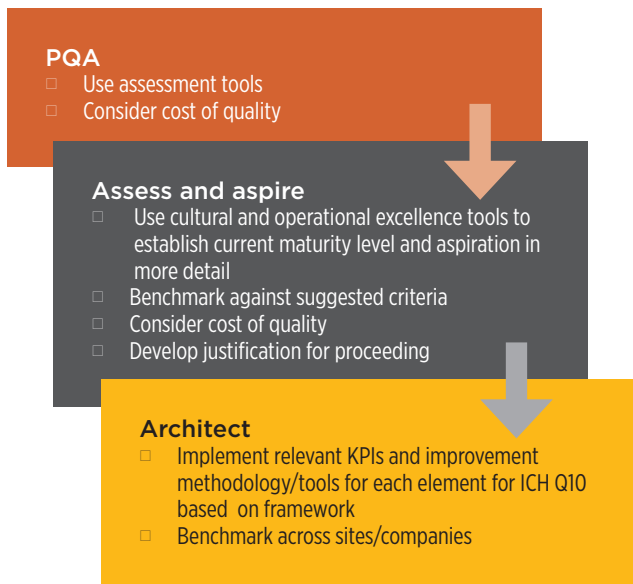
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FIGURE 3: APQ FRAMEWORK DETAIL



- Fuel benchmarking, sharing, and learning among companies
- Provide a program that has value to industry whether it is adopted by regulators or not
- Encourage self-improvement and supplier improvement
- Have potential competitive advantage
- Program could be adopted by regulators, providing additional benefits to industry through regulatory interaction and regulatory relief

Guiding principles are:

- “By industry, for industry,” at least at the outset
- Must have value and benefits to industry
- Be seen as attractive to and beneficial for regulatory agencies
- Be applicable across all sectors of the pharmaceutical industry
- Use “as-is” company data and site procedures as much as possible
- Minimize additional work
- Leverage existing methodologies and principles where relevant (e.g., ISO, VPP, MHRA, ICH Q10)
- Engage FDA and others in design
- Complement existing FDA initiatives (e.g., quality metrics, New Inspection Protocol project, data analytics)
- Simplicity

These principles were tested at a workshop of industry representatives in March 2018, and supported for further development and testing at a June 2018 workshop with wider industry participation.

Proposed framework

An overview of the proposed program framework is given in Figure 2. The core of the program is shown in the middle two columns, where there are two components. The first component would be to “assess” your own quality

maturity and decide, based on this assessment, how much you “aspire” to improve. Should you decide that you wish to improve, the program would point to tools and key performance indicators (KPIs) that would be the “architect” of your improvement (see page 32).

As a first step, in the left-hand column we are considering a PQA in which the goal would be to use a low-resource step to evaluate if you were justified in spending more resources to conduct a fuller quality maturity assessment.

In the right-hand column, there is the possibility of introducing a more formal assessment of quality maturity, potentially at a later stage, using a third party. This could be recognition of performance using some sort of certification system. More detail of the middle two columns is given in Figure 3.

In summary, tools and KPIs to conduct a PQA, along with those to assess, benchmark and improve quality maturity would be identified from those that are already available. Where tools and KPIs do not exist, ISPE teams would propose new or alternative options.

A key element of both the PQA and the fuller assessment would be an exercise to calculate the cost of quality—essentially the cost of poor quality. An ISPE team has been considering how to conduct these assessments and will provide suggestions and possibly even case studies.

A major vision of this program is that regulators may become involved in the design of its framework and ultimately adopt and/or evolve relevant parts of the program to help achieve their goals.

ICH Q10

A fundamental basis of the developing program is ICH Q10 Pharmaceutical Quality System Model,⁷ as shown in Figure 4. To deliver quality product to customers on time and in full, a site in a supply chain delivering that product should have a quality system that is underpinned by and fits with the site’s operational excellence practices. As recommended in the *ISPE Good Practice Guide: Operations Management*,⁸ a company’s manufacturing operations strategy is likely to be applied differently across a series of sites due to differences in technology, geography, regulations, or location in the supply chain. Given this, sites may have slightly different KPIs to balance operational efficiency and service within an acceptable cost structure.

As demonstrated in ISPE Quality Metrics Pilot programs, Waves 1 and 2,⁹⁻¹⁰ excellence in quality culture is required to deliver robust and sustained quality metrics performance. It is well understood from other studies, such as the University of St. Gallen work with FDA,¹¹ that cultural excellence is positively associated with good business performance. Hence in Figure 4, culture underpins all other elements. Tools for assessing and improving cultural excellence are given in the *ISPE Cultural Excellence Report*.¹²

The Parenteral Drug Association (PDA) has also developed and implemented a quality culture assessment tool.¹³ ISPE and the PDA are engaged in preliminary discussions regarding future potential collaboration in quality culture assessment and improvement (see page 30).

CONTINUED FDA ENGAGEMENT

In October 2017, following its submission of detailed further recommendations regarding definitions for FDA’s harmonized quality metrics program, ISPE established a cross-functional subteam (working title: “Metrics Reporting and Analytics”) to evaluate, summarize, and provide feedback on the FDA quality metrics portal experience, sharing those learnings with ISPE members

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FIGURE 4: OVERVIEW OF RELATIONSHIP TO ICH Q10

Program could have 9 elements

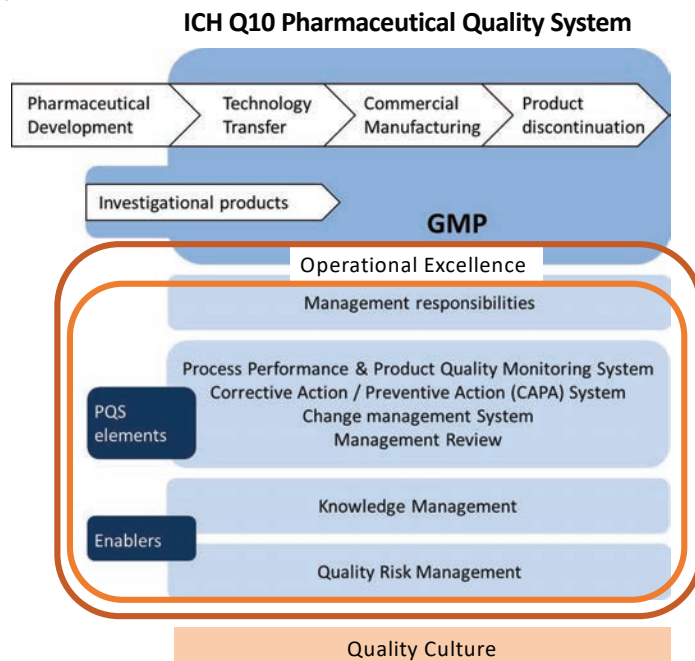
Elements 1–7

- Based on ICH Q10 and assess:
 - Management responsibilities
 - Knowledge management
 - Quality risk management
 - Process performance & product quality monitoring system
 - CAPA system
 - Change management system
 - Management Review

Element 8 would assess quality culture

Element 9 would assess operational excellence

Proof of concept for beta testing (e.g., CAPA)



and companies. The ISPE team has also discussed and shared approaches and best practices from across the industry regarding the local collection, management, and use of data for metrics. These experiences, learnings, challenges, and opportunities will be considered for input to the APQ program.

2018 FEDERAL REGISTER NOTICES

In June 2018, the FDA published two *Federal Register* notices (FRNs) announcing new voluntary efforts to gather stakeholder feedback on the use of quality metrics.

The first notice described a quality metrics feedback program with efforts that include formal and pre-ANDA meeting requests, as well as a pilot study to gain feedback from establishments.¹⁴ The second announced a 2018 CDER and CBER staff experiential learning site visit program to provide learning opportunities for FDA staff involved in the agency’s Quality Metrics program and to give stakeholders an opportunity to explain the advantages and challenges associated with a robust quality metrics program.¹⁵ Stakeholders are encouraged to participate in these efforts.

In conclusion, it is very pleasing that FDA recognized that “it should perform further studies of the FDA Quality Metrics program through a pilot program and additional discussions with stakeholders.” As requested in the first FRN, ISPE will continue to engage with FDA to gather feedback from industry subsectors and to provide industry options to advance pharmaceutical quality to achieve the stated vision. ♦

—Christopher Potter, PhD, Technical Advisor

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ISPE Advances Its Focus on Cultural Excellence

Nuala Calnan, PhD, and Tami Frederick

Since the publication of ISPE's groundbreaking *Cultural Excellence Report* in April 2017 the team behind its development remain committed to driving their message forward: Focus on culture and behaviors to deliver sustainable quality excellence.

It has been a busy year. In addition to new publications and pioneering collaborations underway, ISPE Quality Culture Team members have been invited to participate in a range of international conferences to share the key

concepts represented in the Six Dimensions of Cultural Excellence framework. The reception from industry and regulators alike has been a resounding endorsement of the work.

CULTURAL EXCELLENCE FRAMEWORK

The six-dimensions framework, which lies at the core of the *Cultural Excellence Report*, provides powerful, practical approaches and improvement tools for the elements required to foster, develop, monitor, measure, learn, and ultimately improve an organization's quality culture. Maurice Parlane, a member of the ISPE Australasian Affiliate and Co-Chair of the Regulatory Quality Harmonisation Committee's Asia-Pacific Regional Focus Group, defined its essence at the May 2018 ISPE Indonesia Annual Conference, noting that cultural excellence offers an opportunity to "redefine the 'c' in cGMP by realizing a culture which focuses on organization-wide ownership of quality for medicines and patients."¹

One point highlighted by the team is that high-performing companies think and act differently about culture; they treat quality not as a hindrance for success, but as a necessity that allows them to make decisions that best benefit patients.² For many, however, culture remains a nebulous concept. The key insight from the team is to emphasize and demonstrate desired behaviors and results.

The *Cultural Excellence Report*, therefore, provides 24 practical tools and case studies, many of which focus on techniques to address behavior gaps

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FIGURE 1: THE SIX DIMENSIONS OF CULTURAL EXCELLENCE FRAMEWORK



Source: *Cultural Excellence Report*

that may exist. The report also includes the easy-to-score Cultural Excellence Assessment Tool, which helps evaluate the maturity level of 21 key behaviors.

IMPACT OF BEHAVIORS ON DATA INTEGRITY

Speaking at the June 2018 ISPE Quality Manufacturing Conference in Arlington, Virginia, Dr. Aidan Harrington, Principal Consultant, CQV & Regulatory Science, DPS Engineering, stated that it is hard to recall any industry issue other than data integrity that has generated as much international guidance. The guidance, which has stemmed from all quarters, outlines a broad range of technical, governance, and human factor expectations and recommendations. In an exciting development, the ISPE Quality Culture Team have been delighted to join forces with their colleagues on the GAMP® Data Integrity Team to collaborate on the *GAMP Good Practice Guide: Practical Approaches to Data Integrity, Part 1: Key Concepts*, currently scheduled for publication in Q3 of 2018.

Our cultural excellence work aligns and complements the concepts introduced in the earlier *GAMP Guide: Records and Data Integrity* (March 2017), particularly those presented in the Management Appendix M3. This partnership confirms the critical importance of culture on overall business performance and the data integrity program specifically. The new GPG will include contributions from the ISPE Quality Culture Team on:

- How leader behaviors can set the tone and direction for an organization's data integrity practices and expectations
- Strategies for shaping data integrity mindsets and attitudes
- Influencing the key behavioral criteria of accountability, ownership, action orientation, and speak-up
- How to design leading quality indicators to drive desired behaviors related to data integrity

- Assuring appropriate mentorship and training by building an improvement road map
- A practical guide on performing a data integrity Gemba walk, including an insightful laboratory-based case study

COLLABORATION WITH PDA

This year has also seen another collaboration between the industry's two largest associations. In May, ISPE and PDA announced that they have signed a memorandum of understanding to exchange information regarding their respective efforts on quality metrics and quality culture.³ This has opened communication between the two associations' quality culture teams to explore potential collaboration in this area. The core quality culture work of the two teams is complementary. PDA's very thorough Quality Culture Assessment Model and associated training can be used to identify gaps in quality systems maturity and behaviors, while the *Cultural Excellence Report* provides an improvement framework with practical tools to help organizations on their journey toward excellence.

After meeting at the recent Quality Manufacturing Conference, the two teams agreed to explore collaboration on improvement practices and tools. This joint effort is intended to help guide industry in evolving and identifying best practices, tools, and appropriate references for effective root cause analysis. Stay tuned for updates and outputs from this exciting engagement.

THINK BEHAVIORS

It is important to remember that cultural excellence is not a project, but an ongoing commitment by leaders and individuals to model desired behaviors and hold others accountable to standards. The ISPE Quality Culture Team are committed to improving value for both patients and the business by unleashing the potential energy of the human capital involved in the development, manufacture, and supply of life-changing treatments.

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About the authors

Nuala Calnan, PhD, has over 20 years' experience in the pharmaceutical industry and is currently an Adjunct Research Fellow with the Pharmaceutical Regulatory Science Team at the Dublin Institute of Technology. She has led a research study examining product recall and quality defect data at the Irish medicines regulator, HPR, and is currently a member of the University of St. Gallen team awarded an FDA research grant to examine the role of quality metrics in determining risk-based inspection planning. Nuala co-leads the ISPE Quality Culture Team and the ISPE/PQLI Task Team on Knowledge Management. She has been an ISPE member since 1997.

Tami Frederick is a Global Quality Leader with 25 years' experience in the pharmaceutical industry. She is a chemical engineer by education, joining Perrigo in 2000. Tami has held positions in quality assurance and control, research and development, operations management, and technical engineering. Tami has led multicultural quality teams in the implementation of global quality systems such as global change control, EDMS, SQM, quality investigation and CAPA, corporate quality metrics, global quality programs, global technology council, and auditing to support compliance. She has been an ISPE member since 2015.

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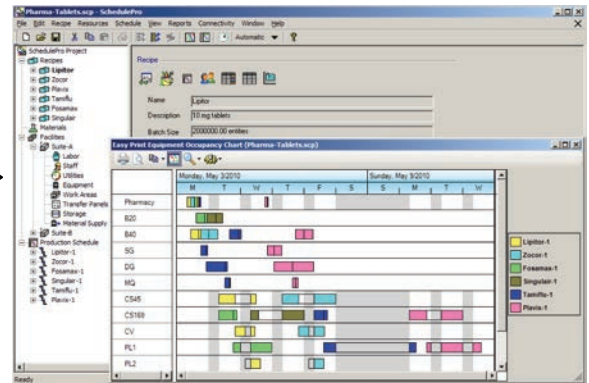
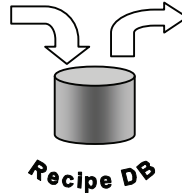
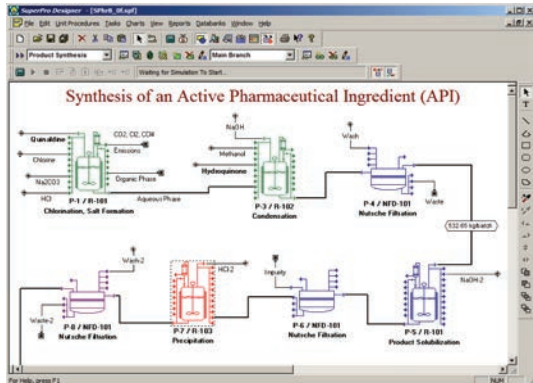
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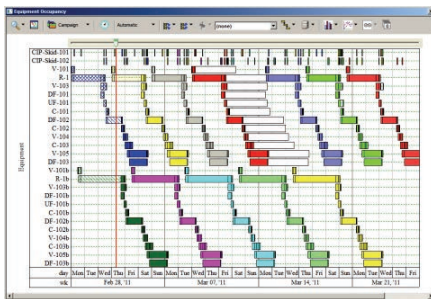
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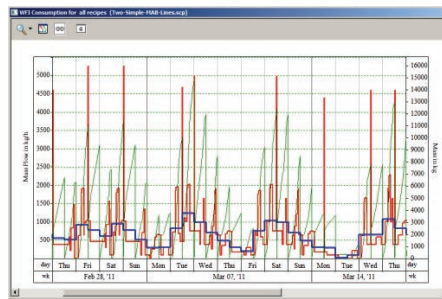


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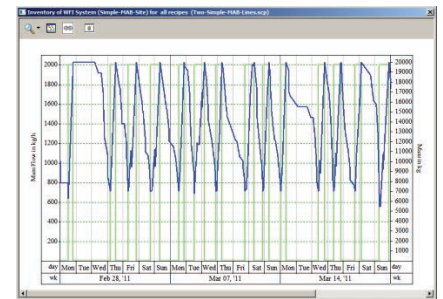
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Corrective and preventive actions (CAPAs) are indicators of company health. They demonstrate whether issues are acknowledged, tracked and, ultimately, remedied in an effective and permanent manner.

The timeliness and robustness of these records also indicate whether a company demonstrates effective planning and/or has sufficient resources to manage and resolve past and potential issues. In this way, the effectiveness of a company's CAPA program also has a relationship with other key indicators of company health including, but not limited to, management responsibilities.

The ISPE Advancing Pharmaceutical Quality (APQ) team is developing a framework by which a company can assess its maturity in relation to quality culture, operational excellence, and ICH Q10 elements, using the CAPA system as the focus of the pilot. As a primary tool leveraged for tracking and resolving issues, a robust CAPA program is designed to identify signals and improvement opportunities from multiple inputs (Figure 1). Additionally, a robust CAPA system can strengthen the performance and efficiency of other areas of the business as demonstrated through studies such as the University of St. Gallen work with FDA.¹

The program being developed will:

- Collect signals from your CAPA system to identify issues that indicate a need for improvement.
- Identify the root causes of issues to enable an appropriate remediation.
- Implement corrective actions to eliminate those root causes and prevent recurrence.
- Implement preventive actions to eliminate potential root causes to prevent future occurrence.

This program will consist of three parts:

- Identify current maturity levels against a number of CAPA elements (e.g. root cause analysis, CAPA effectiveness, governance, and management oversight).
- Suggest tools to help improve each area.
- Track KPI measurements in each area as needed.

Assessment results will be presented in a table format similar to a “heat map” that indicates a company’s place on the maturity continuum (Figure 2). It will help users assess and prioritize which areas of the CAPA program will yield the best return for their improvement efforts.

Once a company determines where they fall on the maturity continuum, they may leverage suggested improvement tools to increase performance, then track it by using the metrics integral to each element.

For example, if a company were to measure effectiveness of the CAPA element “root cause analysis” and identify deficiencies in that area, they may choose to utilize the “5 Why” fishbone diagrams or other tools to improve performance. They may then choose to measure their success using a metric that tracks the effectiveness of their CAPA remediation efforts and/or repeat CAPAs.

As each focus area improves, companies may choose to reprioritize CAPA

FIGURE 1: INPUTS TO A ROBUST CAPA PROGRAM

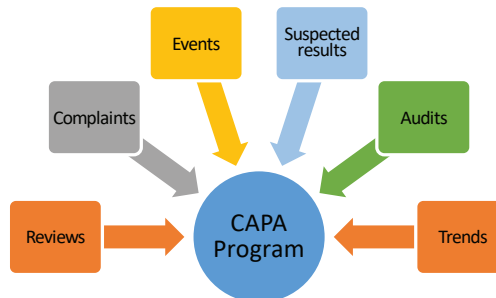
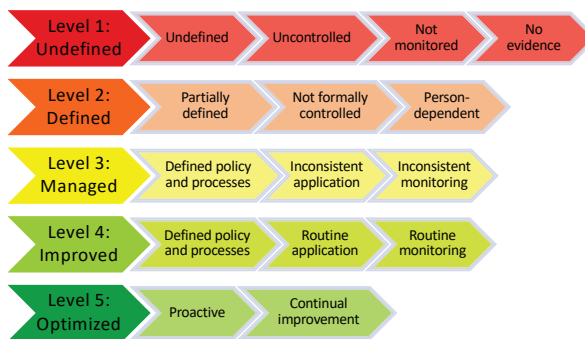


FIGURE 2: MATURITY ASSESSMENT RESULTS HEAT MAP



elements and/or modify each performance target related to existing metrics until they have reached their target level of CAPA maturity.

As the APQ Team continues to develop the assessment program, learnings from the CAPA pilot will be built into the overall assessment suite for quality culture, operational excellence, and ICH Q10 elements to assist companies in their assessment and improvement journey. <>

About the authors

Lori Chelemedos is the Associate Director of GxP Inspection Management at BioMarin. Prior to this position, she worked in the Global Inspection Management team at Roche/Genentech supporting the Americas, Asia-Pacific, and Europe, with subsequent roles in information technology, production, and quality either leading or participating in business process and technology improvements. Prior to entering the biotechnology field, she performed business process and technology work in the semiconductor, telecommunications, energy, shipping, and apparel industries with a focus on manufacturing, supply chain, and quality operations. Lori holds a master of business administration degree from Golden Gate University, and a certificate in quality and compliance from UC Berkeley. An ISPE member since 2014, she is a member of the Operations Management Steering Committee and Quality Metrics team.

Kira L. Ford is currently Director, Global Quality, responsible for the quality standards, practices, business processes, and implementation tools for both the Lilly quality system supporting the company's pharmaceutical enterprise and the global quality system supporting manufacturing and product supply. Ms. Ford received her BSc in biochemistry from Virginia Tech and has over 29 years' experience with Eli Lilly and Company. Over this time she has developed extensive manufacturing site experience through a variety of roles within technical services/manufacturing science, operations, quality control, and quality assurance. An ISPE member since 2014, she is currently a member of the ISPE Quality Metrics and Cultural Excellence Teams.

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- Applying Bio Manufacturing Principles, 13-14 December
- Overview Bio Manufacturing Processes, 13-14 December
- Quality Assurance for Facilities Management, 13-14 December

Metrics Reporting and Analysis

Jason Schneider

In mid-2017, ISPE established a cross-functional subteam (working title: “Metrics Reporting and Analysis”) under the Advancing Pharmaceutical Quality (APQ) core team to evaluate, summarize, and provide feedback on the FDA quality metrics portal. The results of that exercise are expected to be shared with ISPE members and companies. While this is still the primary charge of the subteam, delays in opening the portal gave the team an opportunity to take on a slightly broader and more thoughtful approach to the evaluation process.

In addition to simply “testing” the portal for the submission of the FDA-requested data, the team also shared approaches and best practices from across the industry regarding local collection, management, and use of data for metrics. These experiences, learnings, challenges, and opportunities were summarized and shared with industry and agency thought leaders during ISPE’s Quality Week, 4–8 June 2018, and are now being considered for inclusion in the broader APQ program.

TEAM CHARTER

Choosing a well-structured approach to test the portal, the cross-functional subteam was chartered to ensure clarity among team members and alignment with the APQ program. Under this charter, the group went on to establish themselves as a data-reporting, solution-focused subteam tasked to:

- Discuss various approaches adopted by industry in preparation for the opening of the portal
- Agree upon best practices for consideration and inclusion in ISPE portal testing plans
- Evaluate the FDA quality metrics portal, once it is open for testing, through execution of representative case studies and scenarios
- Summarize and share testing results, experiences, and learnings with ISPE members

The results of testing and associated lessons learned would then serve as potential input to the broader APQ program. With the team chartered ahead of portal opening, they capitalized on the opportunity to validate expectations by sharing approaches taken by organizations further along the planning and preparation spectrum.

INFORMATION SHARING

Since several organizations represented within the subteam had already taken significant steps toward preparation to participate in the voluntary

phase of the FDA metrics reporting program, the group was able to conduct a number of demonstrations and presentations. These not only showed the overall direction taken by the presenting organizations, they also highlighted key focus areas, including where significant spend was incurred, time was required, and resource commitment and burden was at its highest.

Although these early results reinforced several initial concerns around burden, they also confirmed a number of the benefits provided by a robust internal metrics program for organizations that chose the path of early preparation. With the pending FDA program as the driver, several organizations capitalized on the opportunity to improve their internal metrics, reporting, and analytics initiatives though:

- **Harmonization:** Implementing process improvements in other functions and departments by establishing standard definitions, formulae, and processes
- **Organization:** Normalizing and “mapping” data elements to account for all applicable values across multiple standalone and disparate systems
- **Consolidation:** Create new data repositories, reports/exports, and scorecards for shared data use within the organization
- **Innovation:** Leverage validated data sources as inputs to the data submission to produce a leaner verification/validation process

GUIDING PRINCIPLES

Having gained insights regarding preparation for testing, the team began to establish basic guiding principles by which all testing would be executed. This aligned ISPE team members participating in the early testing phase of the metrics submission program. Because new or updated guidance could be released ahead of the portal opening, it was important to clarify the boundaries for testing governance:

- Testing will be bound by the parameters set forth in the FDA “Quality Metrics Technical Conformance Guide”¹ and “Submission of Quality Metrics Data”² guidance as currently written, until/unless feedback from the 2017 review cycle leads to additional changes and requires a process modification.
- Sufficient instructions and/or training on the use of the FDA portal will be provided prior to test initiation.
- To protect any company-specific data used in testing, no data used in testing would be utilized for any official analysis.

RECOMMENDATIONS

With basic ground rules and operating parameters established, the team identified several items for FDA consideration with respect to how testing would be conducted. Beyond simply posting or uploading a file of three predefined metrics and associated data elements, the team wanted to explore the possibility of including additional and/or alternative value-added metrics and more extensive testing by being permitted to:

- Use “test” or otherwise “blinded” (yet known and traceable by the submitter) data where possible.
- Execute both “positive” and “negative” (challenge) testing, including the submission of partial data sets and stress testing the portal
- Incorporate alternate testing approaches and additional context (e.g., additional metrics, data, charts, visualizations) in the development of testing plans, scenarios, and execution tasks

- Leverage various IT solutions in data submissions (automation where possible), presuming the output aligns with the current TCG and/or portal training received
- View the data once submitted (on the FDA side), in order to ensure successful transmission and aligned understanding of the data and what it represents (i.e., trends, patterns, relationships)
- View summary results, lessons learned, and/or FDA takeaways that result from execution of the broader program (not only results of ISPE participation)
- Receive details on the confirmation/rejection of data submission, the portal support model, and system release notes and/or change control details to ensure ongoing alignment with site systems and supporting processes

These recommendations not only support a more extensive testing opportunity, but allow for the inclusion of metrics and data elements that are more representative and indicative of what is currently in place across the industry. It was further agreed that a broader testing program scope (with a reduced burden by being allowed to leverage existing data “as is”) would be seen as a very positive step and increase the likelihood of success through increased participation by industry.

LESSONS LEARNED

With the portal not yet open as of the publishing of this article, lessons learned have been focused on and limited to content provided by those organizations that were early adopters and took significant steps toward preparing for the opening of the portal. Key and consistent themes seen throughout the knowledge sharing exercise included:

- The concept of “quality beyond compliance” is at the very foundation of a strong metrics program, whether industry or agency
 - While the voluntary FDA program may have been the driver for many, there are numerous internal benefits to be realized by implementing a robust and evolving analytics, reporting, and metrics program
- The quality data landscape is critical and not to be underestimated
 - Understand your data sources (including data availability, reliability, and accuracy)
 - Establish standard terminology, definitions, scope, and expectations within your organization to help minimize inconsistencies and discrepancies
 - Harmonize and consolidate data where possible (i.e., data repository, lake, warehouse, etc.)
 - Ensure reporting continuity and accuracy through lean and robust business processes
- Start small, with a well-thought-out proof of concept and pilot
 - Establish and maintain a strong relationship with your data providers, stewards and process owners
 - Confirm requirements, functionality and usability across a small number of products and locations
 - Ensure agility, flexibility and scalability to keep pace with both internal and external (agency) process and requirement changes



THE TEAM SHARED BEST PRACTICES FROM ACROSS THE INDUSTRY REGARDING LOCAL COLLECTION, MANAGEMENT, AND USE OF DATA FOR METRICS

- Governance is critical to the success of any metrics program
 - Develop and sustain a clear (enterprise) understanding of the quality data and business process landscape to ensure the ongoing reliability, stability, and sustainability of the program
- Clarity and final requirements can only improve the program
 - Removing uncertainty and ambiguity around the benefits of the program will help increase industry participation
 - Alignment and (testing) standardization will ensure a more successful pilot execution

Expanding on these lessons learned could help industry prepare for a site visit under the new FDA proposals or provide a road map for building a robust metrics reporting and analytics program within individual functions and organizations. <>

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About the author

Jason Schneider is a Senior Manager in the Corporate Quality Strategic Program Office for Baxter Healthcare, with 20 years’ experience in the pharmaceutical industry. In this capacity, he is responsible for driving the analysis, optimization, and delivery of various business process and technical solutions that support the quality system. He successfully established and implemented a global data excellence program based upon the principles of robust processes, transparency, data integrity, and sustainable governance. An ISPE member since 2017, Jason is a member of the Advancing Pharmaceutical Quality core team and leads the Metrics Reporting & Analytics subcommittee. He graduated from the University of Wisconsin-Whitewater with a degree in biology.



2018 ISPE ANNUAL MEETING & EXPO

Welcome to Philadelphia

This year's Annual Meeting will be held from 4 to 7 November in Philadelphia, Pennsylvania. The theme is "Vision to Reality: Delivering Next-Generation Therapies." The first keynote presentation, by Lars Fruergaard Jørgensen, President and CEO, Novo Nordisk A/S and Honorary Conference Chair, will address leadership in diabetes management and groundbreaking manufacturing innovation.

Jørgensen's presentation is titled "From Vision to Reality: Delivering Next-Generation Diabetes Treatment." As Novo Nordisk moves toward a regulatory submission of its new oral diabetes drug semaglutide, Jørgensen will talk about how to strive for leadership in diabetes management and simultaneously provide groundbreaking innovation in manufacturing.

In a conversation with *Pharmaceutical Engineering*, Jørgensen discussed the Annual Meeting and the meaning of this year's theme to pharmaceutical engineers.

Why is this theme of such great importance right now? What knowledge will attendees take away related to this theme that will help them in their day-to-day work?

Diabetes continues to rise at an alarming rate around the world and too few people receive good treatment that allows them to reach a level of control where they can live lives without risk of disease-related complications. Global prevalence of diabetes has almost doubled in the past 16 years—from 4.6% in 2000 to over 9% in 2017; it's forecast to rise to 11.7% in 2045.

In Novo Nordisk, we are strongly committed to breaking the curve and will do so by continuing to aim high, and discover and develop next-generation biological medicines for the benefit of patients throughout the world.

At the ISPE Annual Meeting I will speak to how we work with *lifting* the innovation bar in Novo Nordisk, and strive to obtain the *almost* impossible for the benefit of patients.

What can you share about your keynote presentation?

Two years ago, we announced our investment of \$2 billion in our first US-based active pharmaceutical ingredient production facility in Clayton, North Carolina, which will expand our footprint in the US significantly.

At the ISPE Annual Meeting I will speak to how this will enable us to deliver next-generation therapies, and how our new production facility will play an important role for Novo Nordisk in serving people with diabetes for many years to come.



I SEE THE 2018 ISPE ANNUAL MEETING & EXPO AS AN EXCELLENT OPPORTUNITY FOR PHARMA PROFESSIONALS TO ENGAGE IN INDUSTRY-CRITICAL CONVERSATIONS, LEARN FROM PEERS, AND EXPAND THEIR PROFESSIONAL NETWORK

The ISPE Annual Meeting brings together both new members and more seasoned industry experts. How can new and expert industry members make the most of the opportunity to interact at the Annual Meeting?

I see the 2018 ISPE Annual Meeting & Expo as an excellent opportunity for pharma professionals to engage in industry-critical conversations, learn from peers, and expand their professional network. Hence, I encourage all to be active and seek dialogue.

What are you looking forward to hearing about at the Annual Meeting?

Meeting industry colleagues and learning how they plan to deliver next-generation therapies is something that I am excited about. Furthermore, I am also looking forward to getting a glimpse of the latest technologies and services for the pharmaceutical industry at the ISPE Expo. <>

Jørgensen's keynote presentation will be part of the opening plenary session on Sunday, 4 November from 15.30 to 17.30.



2018 ANNUAL MEETING & EXPO

VISION TO REALITY: DELIVERING NEXT GENERATION THERAPIES

4-7 NOVEMBER | PHILADELPHIA, PA | PHILADELPHIA CONVENTION CENTER

Vital Statistics

What Vision to Reality: Delivering Next Generation Therapies

- **51** technical education sessions
- **8** networking/social events
- **3** plenary sessions
- **205** exhibitors in the convention center
- **And much more**

When 4-7 November 2018

Where Pennsylvania Convention Center, Philadelphia, Pennsylvania, USA

Why

- Raise your level of technical knowledge through education from recognized experts in the field.
- Network with fellow ISPE members.
- Enhance individual and company recognition among industry colleagues.

How Register here: ISPE.org/AM18

Networking and Social Events: Something for Everyone

SUNDAY, 4 NOVEMBER

17.30-19.00

Welcome Reception in Expo Hall

Mix and mingle with attendees, speakers, and exhibitors.

Includes: complimentary hors d'oeuvres and two drink vouchers.

MONDAY, 5 NOVEMBER

06.30-08.00

5K Charity Run/Walk

Start the day with a run/walk along the Schuylkill River.

Separate registration required

US\$40

07.00-08.15

New Member/First-Time Attendee Orientation

Learn about the benefits of membership and how to make the most of your Annual Meeting experience.

19.00-22.00

Young Professionals networking event at Yards Brewery and Taproom

Includes: food, one drink voucher, nonalcoholic beverages, brewery tour with tasting, and cash bar *Separate registration required*

US\$55

► **For updated information please visit ISPE.org/AM18**

19.00-20.30

Women in Pharma® networking dinners

Complimentary dinners will feature a variety of topics, each hosted by a leading pharma executive.

Separate registration required

TUESDAY, 6 NOVEMBER

08.00-10.00

ISPE Membership and Awards Breakfast

Celebrate as the 2018 Overall FOYA winner and ISPE International Honor Awards are presented.

Included with full education registration

US\$50

19.00-22.00

Tuesday Night Party at Reading Terminal Market

Includes: dinner, beverages, and entertainment

Included with full education registration

US\$225

WEDNESDAY, 7 NOVEMBER

Facility Tour: Adaptimmune

Includes: transportation, lunch, and tour. Register early—tour sizes are limited.

Separate registration required

US\$55



FOYA | 2018

Facility of the Year Awards

FOYA Emphasis on Excellence

Highlights from the stories of the five Category Winners and two Honorable Mentions of this year's Facilities of the Year Awards (FOYA) showcase pharmaceutical industry achievements.

SPE's annual Facility of the Year Awards (FOYA) competition brings out the best in the pharmaceutical industry and offers the opportunity to share advances and achievements. These mini-profiles highlight the seven organizations and projects recognized this year: winning

entries in five categories and two entrants that received Honorable Mentions. The complete profiles are here: *FOYA 2018 Facility of the Year Awards 2018 Category Winners: Spotlight on Excellence* (ispe.org/facility-year-awards).

FOYA recognizes organizations large and small in the pharmaceutical, life sciences, and medical device industries. This year's Category Winners were announced at the 2018 ISPE Europe Annual Conference in Rome, Italy. The Overall Winner will be revealed on 6 November during the ISPE Annual Meeting & Expo in Philadelphia, Pennsylvania.

FOYA Events

FACILITY OF THE YEAR AWARDS

Category Winners present their award-winning projects on Sunday, 4 November. The Overall Winner will be announced during the Membership and Awards Breakfast on Tuesday, 6 November.

Facility Integration

Shire

Facility of the Future

Vetter Pharma-Fertigung GmbH & Co. KG

Project Execution

BioMarin Pharmaceutical Inc.

Operational Excellence

Shire

Sustainability

Wyeth Pharmaceuticals Co., a Pfizer Company

Honorable Mention

Emergent BioSolutions, Inc.

Honorable Mention

Government Pharmaceutical Organization (GPO)

SUNDAY, 4 NOVEMBER

13.00-15.15

FOYA Category Winner Presentations

Get an in-depth look at excellence delivered via innovative thinking.

19.00-22.00

Facility of the Year Awards Banquet

Join us as we formally recognize and celebrate the winning companies during an award presentation ceremony and dinner. *Separate registration required*

TUESDAY, 6 NOVEMBER

08.00-10.00

Membership and Awards Breakfast

Be among the first to recognize the Overall Winner of the 2018 Facility of the Year Award.



FOYA | 2019

Facility of the Year Awards

It's an exciting time in our industry. Thanks to your innovative designs, we're changing the way we work and deliver quality medicines to the people who need them.

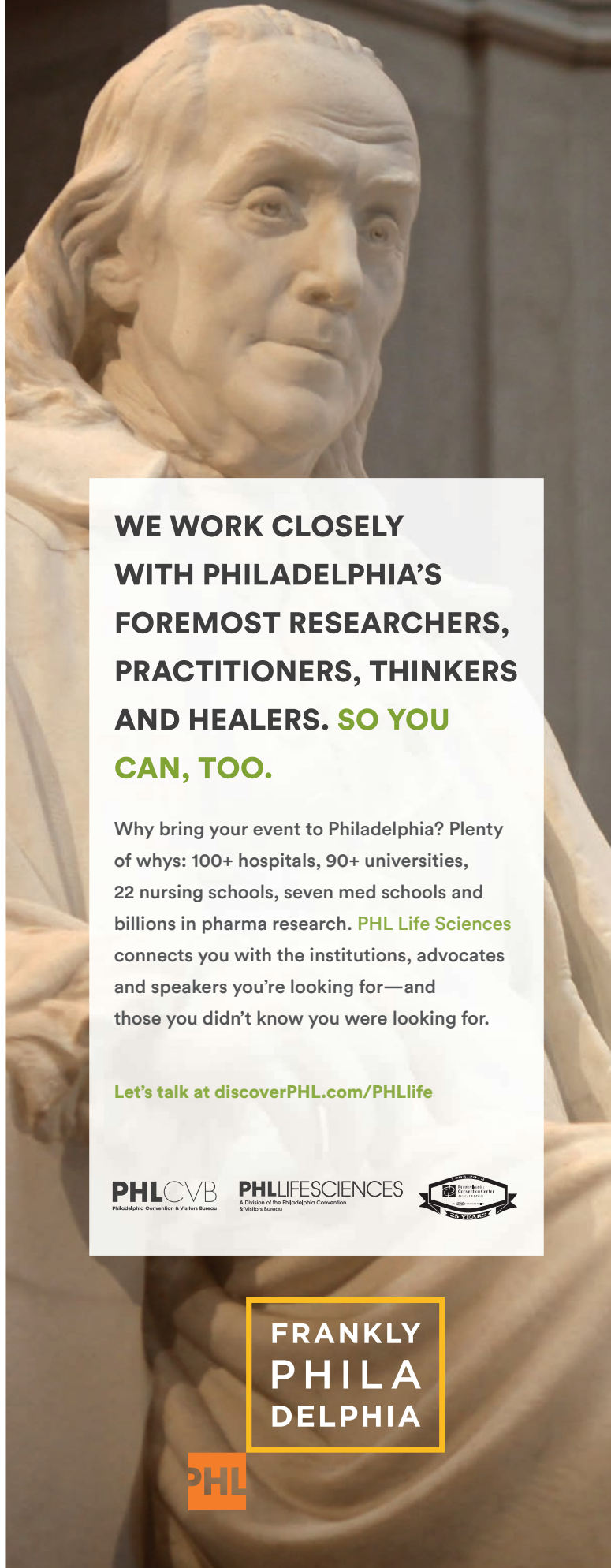
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For more information, visit: www.ISPE.org/FOYA

SUBMIT YOUR PROPOSAL TODAY

2019 Deadline
28 November 2018



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Facility Integration: Shire



NEW PLASMA FRACTIONATION FACILITY FITS RIGHT IN

Building a new facility to relocate existing processes is a major undertaking. Now consider the challenge of building that facility a) within a confined space, b) without disrupting existing operations, c) while staying under budget, and d) adding new capabilities. Shire, a global biotech company focused on developing treatments for underserved patient communities, especially those living with rare diseases, did just that at its campus in Los Angeles, California. The facility is one of the largest plasma fractionation sites in the world.

Tight Quarters

The campus is situated on 11.6 acres in a light industrial zone on the edge of Los Angeles. Before the new construction was commissioned in 2010, the complex was home to seven buildings and a parking garage. Building 8, a 120,000-square-foot facility, was added to house the purification process for two commercial products. The project was also designed to improve material and personnel flows.

Prior to the construction of Building 8, the purification steps for these products were performed in Building 1, a structure that predates acquisition of the property in 1952. “Building 1 was constructed in the 1930s and was originally a warehouse,” says Brian Danahy, Engineering Director at Shire. “You can imagine that over the years, with process changes and equipment changes, along with expansion, it got to the point where the facility wasn’t the most optimal and efficient. So that is really what drove us to create Building 8, the purification building.”

Additional challenges were space constraints in every direction (north, south, east, west, elevation, and excavation), as well as occupancy limitations, which compressed the building layout to two above-ground floors. Ongoing manufacturing operations had to continue during construction, as well, which provided multiple opportunities for creativity and innovation.

The land on which Building 8 would sit was full of underground utilities such as electrical power distribution lines, a main sewer line, and a main site fire-protection distribution water line. “In the footprint of where Building 8 is now, there used to be a 100,000-gallon underground fire water storage tank. There were also temporary trailers on-site and utilities running under the driveway. All of those needed to be rearranged, and some of them had to be resized,” explains Danahy. Shire used the annual plant shutdowns to relocate and reroute underground utilities.

Advanced Technologies

Project execution success factors included lean construction concepts such as working in a colocated space and utilizing advanced technologies. Offices for the entire Building 8 team, including the owner, designers, construction manager, key subcontractors, and the automation contractor, were co-located to

accelerate decision-making and to promote the use of the latest in design and construction technologies. This saved time, saved money, and improved quality.

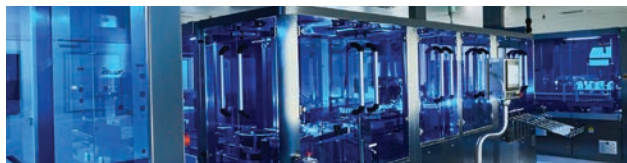
The project team used building information modeling (BIM) to model systems including conduit, hanger rods, and seismic bracing. Since designers and detailers worked side-by-side in the project’s “BIM cave,” the team was able to resolve over 10,000 “clashes” per week during the design phase. Users were able to review the 3D process design weekly and could even “fly through” the model to adjust equipment access and optimize process flow. As a result, complex system field installations were completed without any costly rework.

New Capabilities

In addition to purification processes, Building 8 includes a full GMP pilot plant that was built using modular construction to provide an extremely flexible operating environment. The HVAC, for example, allows any room to be operated at ambient to cold processing (< 0°C) temperatures. Critical utilities—WFI, compressed air, nitrogen, alcohol, and clean steam—are available via utility panels on the walls of the main production rooms. The ceiling was constructed in a grid to allow for easy relocation of lights and HEPA filters.

This pilot plant has already been used to create a bulk batch of an orphan drug. Only one bulk batch of this product is created every five years, so the flexible design of the Building 8 GMP pilot plant was an ideal location to produce this product. “We plan to use that area for future products and future clinical material as well,” says Danahy. “So I think that is a really nice flexible space that the campus will be able to use to create new products and to manufacture small batch products.”

Facility of the Future: Vetter Pharma-Fertigung GmbH & Co. KG



VETTER FACILITY SETS NEW STANDARDS

When organizations make capital investments to ensure the future, many choose to do what’s necessary. Others decide to go above and beyond. Vetter Pharma-Fertigung GmbH & Co. KG chose the latter for its Center for Visual Inspection and Logistics, a state-of-the-art storage, inspection, and material testing facility that has set new standards for the pharmaceutical industry. Vetter is a leading contract development and manufacturing organization in aseptic filling and packaging. The company supports customers from around the world from the early stages of clinical development to market launch and beyond. With industry projections pointing toward both increased demand for prefilled injection systems and increased global regulatory requirements, Vetter decided to build its RVW (Ravensburg Vetter West) facility.

Beyond State of the Art

Construction planning started in 2009. "We ran out of space at one of our existing sites and we needed additional capacity for growth, so the company decided to erect a completely new facility," says Thomas Ruebekeil, Vice President, Project Management. "We also wanted to improve all processes which were implemented there. We took the opportunity to build a new facility that is more than state of the art, where we would run extremely efficient processes and be flexible enough for further growth."

The plan was to erect an autonomous site in Vetter's headquarters city of Ravensburg, Germany, that could act as a central hub for the company's logistical processes. The first construction stage was commissioned in 2012, followed by the second in 2016.

The concept for RVW is a supply chain with optimized product flows that incorporates perfectly harmonized processes. The site provides warehousing for cold-storage and room temperature products, capacity for freezers, constant-climate chambers, and state-of-the-art incubation chambers. Visual inspections can be performed manually or automatically.

Unlike many facilities, optimization starts from the moment materials arrive.

"We ensure the security of our customer's products, which arrive refrigerated between 2 and 8 degrees Celsius, as we have a seamless temperature door that is also refrigerated to between 2 and 8 degrees. This is quite unique for a warehouse," explains Michael Schmitz, PhD, Vice President Planning and Logistics.

RVW also features a lab for packaging-materials testing, storage space for auxiliary materials, a central archive, and 200 office work stations. Departments and staff from an existing Vetter building were moved into the new location in 2017.

Securing the Supply Chain

Guaranteeing cold-chain integrity for cold-storage products is crucial. Vetter achieves this through a variety of systems that are deployed and linked intelligently, guaranteeing predefined temperature areas that are matched with the stringent requirements for pharmaceutical products.

The facility's high-bay storage area is divided into two temperature zones with automatic temperature and humidity control. There are 26,500 pallet spaces for room temperature products and 7,100 for cold-storage products. This allows substances, primary packaging materials, and filled-and-finished injection systems to be stored under current good manufacturing practice (cGMP) and consistent climate conditions. "That

means we have a cold zone (2–8°C) and we have a room temperature zone. And you will never find pallets mixed in any temperature zone," explains Schmitz.

"For the logistical flow, we have short routes—direct connections between areas and automatization with conveyor belts in place," Schmitz continues. "For example, we have a direct connection from the warehouse to the visual inspection area, which consists of manual visual inspection plus automatic visual inspections (AVI) machines. We have implemented a just-in-time process to supply the visual inspection so that we have a very limited number of pallets sitting in front of the rooms or machines; we just have one-hour stock, and when the visual inspection

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is finished the pallets are put back into the warehouse immediately.”

RVW also has freezer capacity used for active pharmaceutical ingredients (API). There are seven chambers for storing raw materials, enough space for a total of 317 chest freezers. Each chest has a volume of 556 liters and storage temperatures that range from -20 to -80°C. The highly sensitive and very valuable pharmaceutical substances are stored in these chests under strict safety standards. To make sure the freezers are always in operation, RVW offers multiple emergency power supplies and backup chests.

To ensure the round-the-clock integrity of all products and processes within the facility, the Vetter team implemented an energy-supply system with an incredible six levels of backup. The facility’s basic power comes from two separate connections to the public grid. In the event of a failure, autonomous standby units can power the entire facility. Should these also fail, additional standby units, including a mobile 400-volt power unit, are available to supply all temperature-critical areas.

Future Expansion

RVW was built with modular components, and has space available for future expansion, if required. “When we constructed and planned the facility, we looked at future trends, such as digitalization or smaller batch sizes, as well as trends from the regulatory side,” says Ruebekeil. “What we have here at RVW is for the next 30 years, and I would say we can fulfill the upcoming requirements. But we don’t want to stop now; we are looking to see where we can further improve our processes.”

Operational Excellence: Shire



STATE-OF-THE-ART QC LAB

Determined to deliver faster and more economical results and to instill a lasting culture of continuous improvement, global biotechnology company Shire is reinventing its world-class plasma manufacturing campus in Los Angeles. As part of that initiative, the company relocated its quality control (QC) lab to another building to thoroughly examine and refine its QC processes and design a next-generation lab that may set a benchmark for the pharmaceutical industry.

Founded in 1986, Shire focuses on developing treatments for underserved patient communities, especially those with rare diseases. The Los Angeles campus, which manufactures treatments for primary immunodeficiency, hemophilia A, fluid imbalance, emphysema, and infant botulism, is one of the largest plasma-fractionation sites in the world. The complex and sensitive nature of these processes means that the company is highly dependent on its internal quality control capabilities.

With the existing QC lab located in a building slated for demolition, the company selected a 16,000-square-foot area within an office building as its new home. The new location will permit future expansion. In addition

to supporting the Los Angeles manufacturing operations, this QC lab will support other Shire facilities.

To enable this capability, Shire has fully decoupled the QC lab from Los Angeles manufacturing operations and infrastructure.

Deconstructing All Processes

From the project’s inception in April 2015, the goal of the Shire QC team was clear: Redesign their QC operation to deliver faster and more economical results while instilling a culture of continuous improvement.

Under the mentorship of their Lean Six Sigma Master Black Belt, the team went through a series of kaizen* events to map out current operational flows, identify improvement areas, and eliminate wasteful practices. Together, the team developed the guiding principle that all processes had to be simple and clear, with direct customer-supplier connections.

“There are three main areas of our QC lab—a biochemistry lab, a microbiology lab, and lab support, which supports the incoming samples materials and how they flow,” says Bert Chai, Associate Director of Engineering at Shire. “We looked at how many samples we needed to test. We looked at how samples arrive, in what format, and by what transportation method, and then recorded how many samples are coming in at a time, how much space we needed, and so on. We painstakingly analyzed every step of the process.”

Construction began in January 2017 and was completed in seven months. The design was developed with exceptionally clear lines of sight, offering increased safety, quality, and efficiency. Management stations at a central hub in the transparent facility enable management to identify and respond to issues rapidly.

While the traditional isolated, low-visibility laboratory concept required the use of a two-person “buddy system” to ensure safe operations, the new design allows team members to pursue individual tasks while being visually connected to the entire group.

Not only do these connections promote a shared sense of pride in team accomplishments, but the natural light and breathtaking views of the city and hillsides elevate the work environment.

“We are very pleased with the end result of how the physical lab came together,” says Chai. “We are pleased with the aesthetics of the lab—it is very bright, open, and cheerful—as well as its efficiency. We use a just-in-time process, so anything that we don’t need in this lab can be stored in the warehouse or at our supplier’s warehouse. So we really don’t have a lot of waste.”

Optimizing Space

The QC team also evaluated the space required for each analyst. “Rather than each person having their own dedicated lab space, we decided to give everybody a laptop and have them share workspaces. Since this is a 24/7 operation, once analysts’ shifts are done, they take their belongings and laptops home with them.” This reduced capital investment and reinforced teamwork while conserving space and maintaining the showcase appearance of the new lab.

The results have been well received by all involved in the lab’s day-to-day functioning.

A benefit not initially envisioned by the project team is increased capacity. “When we first started discussing this move,” says Sam Kitchell,

* Kaizen (Japanese: “change for better”)—the practice of continuous improvement; industrial or business techniques for implementing continuous improvement; “kaizen events” are short-duration projects with a specific aim for improvement.



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Vice President of Engineering at Shire, “in the context of the lab, we were concerned about whether or not we could handle the capacity for just that location. By changing the way we work, we not only met existing capacity needs but created additional capacity through efficiency. For me, that’s one of the tangible outcomes that makes me most proud.”

Project Execution: BioMarin Pharmaceutical, Inc.



KEEPING THE FAITH: GENE-THERAPY FACILITY COMPLETED IN 11 MONTHS

Based in Novato, California, biotechnology company BioMarin Pharmaceutical is a leader in the development and commercialization of biopharmaceuticals for rare diseases with genetic causes. Its pipeline is robust, with several therapies at various stages of development and trials.

In the summer of 2016, as development of their investigational gene therapy for hemophilia moved forward, the company embarked on a project to construct a new manufacturing facility within a seemingly impossible time frame. The resulting facility, built and commissioned in only 11 months, demonstrates that the impossible can be achieved with dedicated people, a solid plan, and the right amount of faith.

On a Fast Track

The company launched Project FAITH on 2 August 2016. One year later, BioMarin announced that valoctocogene roxaparvovec, its AAV-factor VIII vector investigational gene therapy for hemophilia A, was ready for Phase III trials. The building project was fast-tracked for both business and therapeutic reasons, with the new facility targeted to support clinical trials before the end of 2017. To meet this goal, BioMarin elected to repurpose their existing office/warehouse building in Novato.

Because therapies such as valoctocogene roxaparvovec have life-changing potential, the Project FAITH team understood the need to work quickly while keeping their eyes on longer-term objectives. “Although it has a specific purpose right now, the intent is that this facility will be flexible and able to expand to meet not only our current manufacturing needs but also our future needs for other gene therapies,” said Carl Albertson, Director of Capital Projects at BioMarin.

While many gene-therapy firms farm out virus production, the fierce demand for these specialized services often results in delays. To avoid these problems, BioMarin plans to use the facility to manufacture viruses for its products, said Dr. Robert Baffi, BioMarin’s Executive Vice President of Technical Operations, in a 2017 *New York Times* article. “The new facility also will give the company complete control over manufacturing,” he added.

An Impossible Time Frame

BioMarin’s project team was tasked with developing a plan to repurpose

the existing office/warehouse building within the desired time frame. The new facility would include allocations for manufacturing and quality control testing, as well as filling and packaging suites. It also included new utilities, material staging, a loading dock and site-access modifications. To accomplish this, several parallel critical paths were swiftly set into motion.

“We held a kickoff meeting and then the next day we started demolition drawings, which were completed in two weeks,” explained Logan Kelley, Senior Project Manager at BioMarin. “By the third week we had started demolition, and at that point, we’d already started our structural drawings and our underground drawings to complete the core and shell. We had those done in approximately six weeks and submitted them to the city so we could start the work.”

Much of the existing facility was gutted, with only about one-third of the office space maintained. The roof was reinforced to support new HVAC requirements and the building shell was strengthened to surpass seismic codes for the area, which is prone to earthquakes.

While the exterior work and site access were still under construction, the building’s interior was outfitted and connected to the good manufacturing (GMP) utility systems. This enabled the process development team to commence their critical test runs in May 2017; these included two process development runs, an engineering run, and three successful media fills, followed by GMP release for production in August 2017.

“A key piece of our success was that we had an overarching vision; we knew we needed to separate the packages to stagger design and construction activities, so they could overlap each other and we could achieve our aggressive schedule,” said Kelley.

Defining a New Process

“We dedicated all our key resources and co-located them in the same area with the contractors and consultants, so that everybody just focused on talking to each other as opposed to emailing or calling or trying to set up a meeting. We could make decisions and communicate on the fly and have morning huddles to make sure everybody knew what everyone else was doing,” said Albertson.

“And while we were constructing the building, we were concurrently doing manufacturing for process development and testing in the same facility. So we had to coordinate the activities and keep everyone safe while we were doing multiple tasks in this building.”

Bringing BioMarin’s first-ever sterile filling and packaging suite online in the prescribed time frame presented its own unique technical challenges. The operational readiness team met this challenge head-on, hiring and training new staff in parallel while construction took place. Operators were trained on the filling equipment as it was being installed, and were given a full-scale wooden model of the isolator to help them refine their procedures while preparing for the finished equipment train.

In keeping with industry trends, the validation team quickly set to work as design documents were developed, allowing factory and site acceptance testing to be leveraged. BioMarin also quickly formed strong relationships with their raw materials suppliers, which helped them understand and overcome challenges in setting up critical supplies for start-up testing as well as GMP runs. In total, BioMarin developed and approved 1,546 GMP documents to support the fully operational facility in under eight months!

Final cost for the project came in at an amazing 1% above the approved

budget. According to Kelley, the key to the project's notable success was about getting everyone involved and moving in the same direction.

Sustainability: Wyeth Pharmaceuticals Co., a Pfizer Company



OSD FACILITY: WORLDWIDE MODEL FOR SUSTAINABILITY

Pfizer Consumer Health has manufactured oral solid dosage (OSD) pharmaceutical and health supplement products at its facility in Suzhou, China since 1995. In recent years demand for the Caltrate and Centrum health supplements manufactured there has increased rapidly. To meet the demand and to plan for future growth, the company decided to build a second manufacturing facility in Suzhou. The new facility has become a model for sustainable design, not just for China and not just for Pfizer, but the pharmaceutical industry as a whole.

Committed to Sustainability

From the beginning of the project, the project team highlighted environmental sustainability as a key driver, in alignment with Pfizer's corporate objectives.

In its 2017 Annual Review, Pfizer Inc. reiterated its commitment to protecting the environment through its Environmental Sustainability Council, which focuses on three core areas: "mitigating climate change and its impact through reductions in our greenhouse gas emissions; reducing waste through the lifecycle of our products; and reducing water use."

Paul Chiu, Global Engineering, explained that "at Pfizer, Senior Management in the United States pushes all sites to think about sustainability, and they want to see it reflected in facility design. Very early in the project, we set an initial objective to achieve LEED (Leadership in Energy and Environmental Design) Gold for the site, for both the manufacturing building and for the office building."

Project leaders also recognized the potential to set a new benchmark for the industry in a region with serious sustainability and environmental challenges. "On one side we are responding to Pfizer's objectives, but in parallel we are also responding to the Chinese government's expectations of how Western companies in China should be performing," says Chiu. "It is not unusual for the government to expect Western companies like Pfizer to set a higher standard in the hopes that we will influence the local companies to follow."

Beyond GEP

"I commend our team in China for their thoughtful approach to this project, incorporating energy conservation and environmental protection technologies, including highly efficient equipment, solar power generation, a water recycling system, a heat recovery system, and a smart rainwater harvesting

system," said Kirsten Lund-Jurgensen, President, Pfizer Global Supply.

Led by Yuyi Meng (Engineering Leader) and Jianlong Xie (Utilities Leader), the local team worked closely with Pfizer's subject matter experts in the United States and Europe. Corporate practices advocate that all Pfizer engineering projects include good engineering practices (GEP) for environmental sustainability.

For the Suzhou facility, these included but were not limited to:

- Energy-efficient mechanical equipment, such as chillers, cooling towers, air compressors, and air handlers
- Efficient water-conservation equipment, such as cooling towers, laundry washers, toilets, and shower fixtures
- Air, water, and steam discharge systems to maximize energy recovery, such as steam condensate heat recovery to preheat hot water for processes and domestic use
- LED lamps throughout the facility
- Parameters that challenge the air-conditioning systems to allow for the widest possible temperature and humidity ranges without compromising GMP or product requirements

As the plant becomes operational, energy and water utilization will be reviewed for additional opportunities in design and operational practices.

To push the boundaries of sustainable design, Meng and his team consulted with employees from the first Suzhou facility. "The idea was to get the entire plant staff to be engaged in support of an energy-saving design,"

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explains Chiu. “The team received many submissions from employees making suggestions on how we could make contributions. However, the goal was not just to solicit ideas but also to make them feel that they are part of a very noble effort.” Many employees’ ideas were adopted in the new facility design.

LEED Platinum

As the team finished their design, they realized that in surpassing GEP, they were also able to move beyond their initial target of LEED Gold certification. Chiu said, “We received LEED Platinum certification in the fourth quarter of last year as the project came close to completion.”

Both the manufacturing and the office and laboratory building were certified, making the Pfizer Suzhou facility the world’s first LEED Platinum certified pharmaceutical manufacturing campus. It also received the China Two Star Energy certification for a manufacturing site, with requirements very similar to LEED Platinum.

While the new site is destined to produce health supplements, Chinese regulations classify it as a pharmaceutical plant, no different than if it were producing prescription drugs.

“Our sustainable design has enabled us to reduce carbon emissions by 4,000 tons per year, which is equivalent to planting 235,000 trees,” says Meng. “In addition, our water consumption is reduced by 40,850 tons per year.”

Chiu believes that it was the passion of senior management and the local team that allowed the project to go the extra mile to achieve LEED Platinum certification. And it was well worth the effort: “Some people think that you have to spend a lot of extra money to achieve that Platinum standard, but I don’t think we spent more than 0.5% of the project budget to achieve this certification.”

The new Pfizer Suzhou facility has been producing performance lots since October 2017; it expects to receive certification from the Chinese authorities to enter full production in the second quarter of 2018.

“What was unique about this project,” says Chiu, “is that it was 100% built by the local team. I am not sure if I know of any other greenfield facilities in China built by Western companies that are 100% entirely built by the local team.”

Honorable Mention: Emergent BioSolutions, Inc.



NEW FACILITY PROTECTS AGAINST PUBLIC HEALTH THREATS

Since 2000, the United States has endured biological attacks with anthrax-laden letters; natural outbreaks of diseases like severe acute respiratory syndrome, Ebola, and Zika; as well as influenza pandemics. In response to such national emergencies, the Biomedical Advanced Research and Development Authority (BARDA) in the Office of the Assistant Secretary of Preparedness and Response within the US Department of Health and Human Services, set out to enhance

the government’s ability to develop and manufacture medical countermeasures to address these and other threats using the public-private partnership model.

In 2012, BARDA entered into a 25-year partnership with Emergent BioSolutions, a global life sciences company that provides specialty products to address accidental, intentional, and naturally occurring public health threats. Emergent was designated one of three national Centers for Innovation in Advanced Development and Manufacturing (CIADM), a network of sites designed to provide development and manufacturing capabilities for rapid deployment in response to public health emergencies.

“Our FOYA project was centered around being able to make 50 million doses of pandemic flu vaccine within four months of pandemic declaration [by the World Health Organization],” says Scott Battist, VP, General Manager and Site Head for Emergent’s Bayview site. “We knew we needed a facility with significant capacity that could run a wide range of processes, but we didn’t know on which specific expression platform (microbial, mammalian or insect cell culture, viral vector, etc.) the pandemic flu vaccine would best be developed.” This upstream uncertainty demanded flexibility to handle a wide range of downstream processing requirements.

Designing for the Unknown

In mid-2013, the Emergent team began conceptual design for a 56,000-square-foot CIADM facility to be built adjacent to its existing Bayview facility in Baltimore, Maryland. Design and site work began in 2014, followed by construction in the summer of 2015. As of early 2018, the facility is in the final stages of commissioning and qualification. In engineering this building, Emergent defined a new type of biotech facility: one that is operationally agile enough to change product campaigns quickly, with minimal limitations. The iterative design process was instrumental in delivering the flexible, responsive, process-agnostic platform that BARDA demanded while still giving Emergent a facility that could meet internal needs.

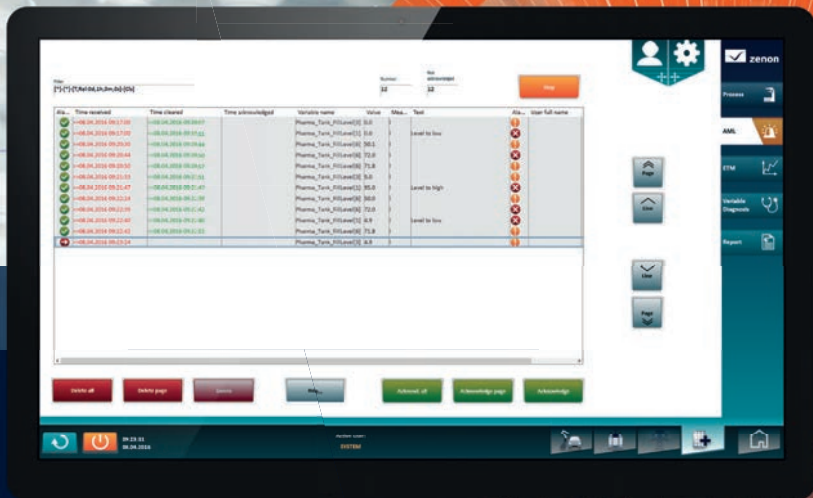
Flexibility is a key design feature. Unlike most pharmaceutical production facilities, Emergent did not design for a specific process, but instead considered a variety of processes that it could potentially run in the future. “It could be anything covering microbial, cell culture, or viral expression systems to produce the bulk vaccine,” says Battist.

As a result, the facility’s scalable space, coupled with a singular focus on single-use technologies, can accommodate varied process platforms and is ready for the plug and play of current standard cGMP equipment trains. If demand and supply timelines require higher downstream throughput, for example, the operations team has the capacity to run parallel units to meet the required productivity. The utilities and space are available, and in most cases, existing equipment can be moved to accommodate any necessary new equipment.

Flexible Production

BARDA’s partnership with Emergent requires the company to react quickly to declared emergencies. “If a flu pandemic were declared, we would receive notification from BARDA to start vaccine manufacture and would be expected to produce 50 million filled, final doses of vaccine within four months, with first doses being delivered within 12 weeks of the notification from BARDA,” says Battist.

Once a platform is validated, the pandemic production schedule includes:



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BARDA's partnership also requires that the government keep the CIADM facility busy for six months of each year. This includes work on influenza viruses as well as other clinical trial material. "In addition to pandemic flu vaccines, the facility is also capable of manufacturing other medical countermeasures for the US government under the same CIADM contract with BARDA. To date these have included production of anti-Ebola therapeutic monoclonal antibodies from a CHO (Chinese hamster ovary) cell line. This facility-flexible approach also allows the site to accept contract manufacturing work as well as produce its own products, and has been building a strong business around all three sources of work. The facility is capable of manufacturing products from a variety of platforms including microbial, cell culture, and viral/cell culture for their customers and stakeholders," explains Battist.

The company recently adapted the facility in response to its acquisition from GSK of raxibacumab, the only monoclonal antibody therapeutic licensed by the US Food and Drug Administration to treat and prevent inhalational anthrax. This product, which will serve as the site's anchor commercial product, will be produced using Emergent's first-in-kind 4,000-liter single-use bioreactors, an equipment capability that was neither considered nor discussed during facility design. It was easily accommodated, however, by the flexible nature of the facility, which allows these systems to be installed with minimal utility distribution systems modifications and no necessary changes to building architecture, structure, or infrastructure.

Honorable Mention: Government Pharmaceutical Organization (GPO)



GMP FACILITY SECURES A SUSTAINABLE SUPPLY OF HIV MEDICINES

Despite much progress, HIV/AIDS continues to be a global health issue. The problem is particularly severe in Thailand, which accounts for approximately 9% of cases in the Asia-Pacific region. Out of a national population of 66 million in 2016, an estimated 450,000 people were living with HIV and 6,400 died of AIDS-related illnesses. The situation is compounded by the high cost of importing HIV drugs as well as the difficulty of producing enough medicine domestically.

The Government Pharmaceutical Organization (GPO) has responded to the challenge by building a new facility that follows international best practices to greatly increase its ability to produce cost-effective, high-quality, much-needed HIV drugs.

Adopting Best Practices

GPO is the largest pharmaceutical producer and distributor in Thailand. GPO purchases API from countries such as India, China, and the EU to produce and package drug products, then distributes them to hospitals, clinics, and its own retail outlets.

The company's desire to boost capacity at its 50-year-old production site in Bangkok led to a major construction project: a new medicine manufacturing facility north of the capital in Rangsit. The plant, which follows Association of Southeast Asian Nations (ASEAN) alignment to PIC/s international good manufacturing practices (GMP), has become a key part of the Thai government's efforts to control and treat HIV infections. The plant produces antiretroviral (ARV) medicines, in addition to other drug products.

While the existing Bangkok facility still uses paper-based processes, the Rangsit facility has integrated IT systems that allow an entirely paperless and compliant operation. "When we created the new facility, we looked at how we could reduce the paperwork and how to easily track every batch of every medicine we produce," explains Dr. Mukdavan Prakobvaitayakit, Deputy Managing Director of GPO. "We integrated key systems, including MES (manufacturing execution system) for managing the process, eQMS (electronic quality management system) for managing documents and training, and LIMS (laboratory information management system) for managing the laboratory, in addition to the legacy ERP (enterprise planning system)."

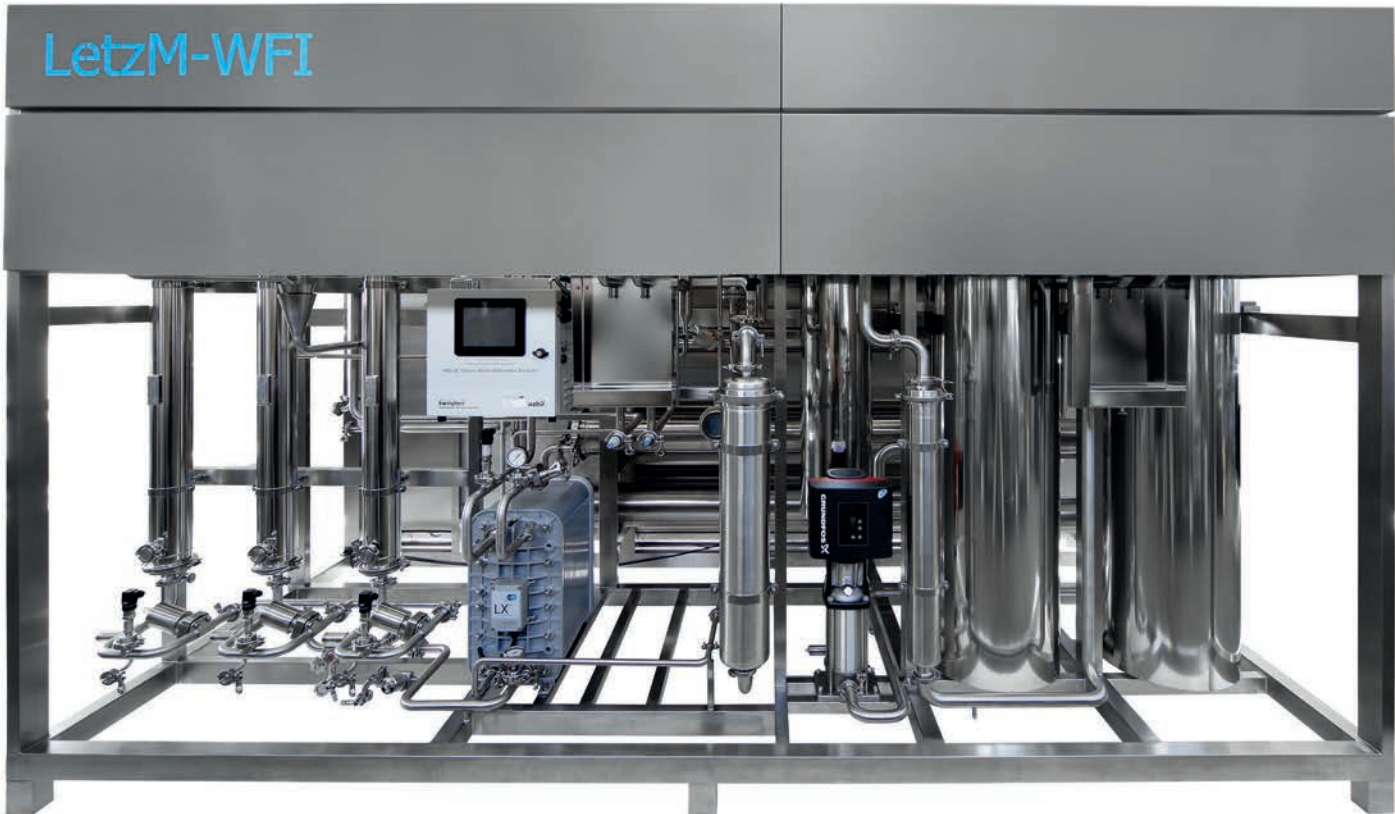
"GPO produces more than 5,000 batches per year, and we wanted to gain more efficiency out of the system," says Mr. Teerapong Cheepchol, Deputy Managing Director of Factorytalk Co., Ltd., the IT solutions supplier on the Rangsit project. "We looked into systems like MES batch recording and LIMS systems to make sure that all information is highly integrated and we are able to transfer back to the originator. No one else in the region has this high integration of their systems; this is a case study for the industry here in Thailand to see the benefit using IT systems."

Its alignment with PIC/s GMP, coupled with GAMP® best practices, has made the Rangsit facility able to supply local HIV medicines at a price 20 times lower than imported medicines, while still achieving global quality standards. In 2017, the facility's production capability was 1.5 billion tablets/capsules. According to Dr. Prakobvaitayakit, expansion of the facility is imminent, which will increase annual production capacity to 4.5 billion tablets/capsules by 2020.

"The technology is very important because it helps us to reduce our costs," she says. "We serve many patients at the public hospitals, and this means that we can serve more people in Thailand for this price. It makes us proud because this project is for the patients who gain access to specialty medicines. We worked so hard to have this factory and now our hard work has been fruitful."

The Rangsit facility has been inspected by the World Health Organization (WHO) and found satisfactory, since GPO submitted the HIV dossier for HIV drugs to the WHO Prequalification Program—the first plant in Thailand to achieve such status. "We love that we can supply medicines to our Thai patients, and now elsewhere in the region, like Myanmar and Cambodia," says Dr. Prakobvaitayakit. "The government pharmaceutical factory in Myanmar also want us to do a technology transfer, so we are happy that our project can be shared with the other nearby countries; that makes us very proud." ◆

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ISPE QUALITY MANUFACTURING CONFERENCE

Patient-focused harmonization efforts in the spotlight

Disclaimer: This article contains brief, abridged, and informal synopses of remarks from UK MHRA and US FDA regulators during the ISPE Quality Manufacturing Conference proceedings in June 2018. This content has not been vetted by any agency and does not represent official guidance or policy of the MHRA or FDA.

We serve patients.” This statement from the opening plenary address by Ronan Farrell, Global Head of Quality and Compliance, F. Hoffmann–La Roche AG, Basel, Switzerland, set the tone and the focus for the ISPE Quality Manufacturing Conference, held 4–6 June in Arlington, Virginia. As other speakers during the first conference sessions also noted, regulatory harmonization to enhance quality and get needed drugs to market is how the industry is trending to provide that service to patients.

“Patients are waiting.” This was Farrell’s second point to the approximately 250 attendees, emphasizing the critical nature of the pharmaceutical industry’s mission. Patients are waiting for supplies of both existing drugs as well as the delivery of new innovations, he said. Fulfilling the mission to deliver these presents both challenges and opportunities to the industry.

The Quality Manufacturing Conference was part of ISPE’s Quality Week, which included the ISPE Continuous Manufacturing Workshop on 6–7 June. About 25 regulators attended the Quality Manufacturing Conference from US FDA, UK MHRA, and Japan PMDA. Regulatory and quality topics were featured with the patient-centric focus as the theme.

OPENING PLENARY: DEVELOPING AREAS

In his plenary presentation, Farrell highlighted several developing areas.

New modalities and technologies

Cancer care is becoming more personalized and is moving toward a one-patient, one-tumor profile, with an individual treatment plan for each patient. Farrell spoke about what his company is doing and about the challenges this revolution in treatment brings with it.

F. Hoffmann–La Roche has a personalized cancer vaccine program in clinical development to produce treatments via on-demand production. The therapy, which is potentially suitable for most tumor types, is custom made and individualized for each patient to induce a tumor-specific immune response. Phase 1 trials began last December.

Personalized treatment leads to manufacturing and quality challenges, he said. “We will need very adaptive quality systems, maybe new interpretations of cGMP, new approaches to change control, and process validation.” Will all regulators agree with cGMP, or will it vary around the world, he asked? Challenges from artificial intelligence and machine learning as data is processed to develop an individual solution for each patient and each tumor also need to be addressed.

Accelerated timelines

Speed to market is getting faster, Farrell noted, pointing out that FDA approvals now range anywhere from about 2.4 to 6.7 years; the average used to be 9 years, he said. Rapid clinical development is needed for faster time frames; expedited technical development is also necessary. Data analytics can replace clinical trials in some cases if they are well designed, Farrell said; this can be a development time saver. Post-approval changes will be needed to continuously improve processes, although securing these for products marketed in multiple countries is challenging to manage.

New skills and capabilities

Life cycle management and regulatory convergence for accelerated filings and inspections are other components of accelerated development, but Farrell noted that a mindset shift is needed to be able to move forward with these initiatives.

A workforce that can serve these changing needs is also crucial. Internal development, collaboration with academia, partnerships, and mergers and acquisitions are some ways to build the needed skills and capabilities to serve the changing marketplace, he said.

“We all have a lot to learn on how to manage quality questions that come up from these modalities,” Farrell noted. When the industry turns to a one-batch, one-patient quality culture, the direct focus on the patient becomes very real. “It gives new meaning to ‘getting it right the first time.’”

REGULATORY FOCUS

Other presentations during the first day’s plenary sessions focused on regulatory agencies and the work that is underway to expand harmonization around the world.

ORA update

An opening plenary presentation on US FDA Office of Regulatory Affairs (ORA) inspections by Alonza Cruse, Director, Office of Pharmaceutical Quality Operations, ORA/FDA, gave an overview of the work that ORA is doing in several inspection areas.

Overall ORA inspections through 31 May 2018 (not including bioresearch monitoring) have totaled 1,070. Of those, slightly more have been domestic (635) than foreign (436). Total inspections in recent years totaled 2,174 in FY 2017, 2,420 in FY 2016, and 2,161 in FY 2015.

The “Never-Inspected Firms” initiative, started in 2017, ties in with FDA’s aim to increase global oversight of all foreign drug firms, since never-inspected firms present a significant risk. The initiative’s three-year goal of inspecting all firms that have not yet received FDA inspections will likely be met during FY 2018. Between June 2016 and January 2018, these inspections have produced

38 warning letters and added 68 firms to the import alert list due to either GMP issues or refusal to allow the inspection. Cruse explained that this data can help feed the ORA's risk model.

Top warning letter charges for OTC and other finished dosage form manufacturers from the never-inspected list include testing and approval or rejection of components, drug product containers and closures, and written procedures and deviations.

Cruse also provided a short update on the mutual recognition agreement (MRA) between the United States and the European Union, which came into effect in 2017 after nearly three years of FDA and EU cooperation as part of the Mutual Reliance Initiative. The MRA allows US and EU regulators to utilize each other's GMP inspections of pharmaceutical manufacturing facilities. FDA and the EMA can now rely on information from drug inspections conducted within each other's borders; this will avoid duplication of inspections, lower inspection costs, and allow regulators to devote more resources to other parts of the world where there may be greater risk. As of November 2017, the FDA had completed capability assessments of eight EU countries' regulatory authorities. The goal is to complete all capability assessments by July 2019.

As of the Quality Manufacturing Conference, Cruse said that the FDA and EU have begun to exchange GMP documents; CDER reviews the site selection inspection list for facilities that require MRA review and works with partners to translate GMP documents; ORA and the Office of Pharmaceutical Quality Operations review and classify reports. FDA has now recognized 14 EU countries as capable of conducting human GMP surveillance inspections per US law: Austria, Croatia, Czech Republic, France, Greece, Hungary, Ireland, Italy, Lithuania, Malta, Romania, Spain, Sweden, and United Kingdom.

Finally, Cruse gave an overview of CDER's Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations (ConOps), which was introduced last year to improve oversight of increasingly complex global drug manufacturing. ConOps outlines workflow, roles, and responsibilities for ORA and CDER staff involved in pre- and post-approval, surveillance, and for-cause inspections at domestic and international drug facilities. It does not cover compounding, bioresearch monitoring, and pre-approval inspections for biotech products. The model establishes accountability for both ORA and CDER, creating clearer roles and responsibilities and better-defined timelines. It will inform additional operational plans scheduled to roll out in FY 2018.

MHRA and EMA

Mark Birse, Deputy Director, Inspection, Enforcement and Standards and Head of Inspectorate at MHRA, gave an overview of various regulatory harmonization initiatives from the MHRA and EMA points of view in "Global Regulatory Harmonisation."

He briefly described the Joint Audit Programme and Joint Reassessment Programme, in which different agencies audit each other's work on a five-year cycle. The initiative harmonizes with PIC/S and supports MRAs, including the United States and Canada. The goal is for participating nations to be able to rely on each other's inspections performed in a third country.

Birse provided an overview and update of PIC/S, which leads international development, implementation, and maintenance of harmonized GMP standards and quality systems of inspectorates in medicinal products. There are only subtle differences between PIC/S and the US FDA, he noted.



Left to right: Giuseppe Randazzo, Tom Cosgrove, Mark Birse, and John Groskopf

Birse discussed the recently launched PIC/S Inspectorates Academy, a web-based educational center to harmonize and standardize international GMP training, and the Joint Visit Programme, which brings inspectors from different countries to watch inspections in other countries and then share what they have learned back home.

Birse also gave an overview and update on the International Coalition of Medicines Regulatory Authorities (ICMRA), a voluntary group of 23 member agencies and five associate members that works to leverage changes. The group does not itself implement any changes—the goal is to move regulation forward on a global basis. Projects undertaken since 2012 include a GMP project led by MHRA, supply chain track and trace, pharmacovigilance (big data, increasing adverse drug reaction reporting, vaccines post-immunization), innovation (global best practice for horizon scanning, leverage from outcomes—expertise and skills, novel licensing/early access scheme), and crisis management. An upcoming GMP project will address future assessment of risk.

FDA OPQ

Giuseppe Randazzo, Acting Director, Office of New Drug Products, CDER, FDA, updated attendees on Office of Pharmaceutical Quality (OPQ) initiatives and strategic priorities in "Global Quality—Promoting Better Medicines." OPQ includes five elements: policy, assessment, inspection, surveillance, and research. These cross multiple programs, including new drugs, biologics, generics, biosimilars, OTC, and compounded drugs. OPQ's work goes from development through post-market.

Quality metrics are important for reasons that go beyond FDA requirements that manufacturers have an ongoing program to maintain and evaluate product and process data related to product quality, Randazzo said. Quality metrics facilitate continual improvement and are mandated by ICH Q10. In addition, he cited research from St. Gallen University in Switzerland that indicates quality metrics programs are a good business practice.¹ Quality metrics also provide the FDA with quantitative and objective insight into the state of quality for both product and facility, enhance risk-based surveillance inspection scheduling models, and improve the effectiveness of inspections.

Randazzo shared OPQ's strategic priorities through 2022:

- Strengthen OPQ's organization: Leverage a collaborative culture, an engaged and empowered workforce, streamlined processes, and effective teaming to ensure an efficient, high-performing, innovative, and results-oriented organization.
- Promote availability of better medicines: Minimize barriers to encourage innovation within FDA and in the manufacturing sector through sensible oversight, research, risk-based decision-making, and continuous process improvement.
- Elevate awareness of and commitment to the importance of pharmaceutical quality: Effectively communicate the importance of quality and that the American public can trust their drugs.

- Strengthen partnerships and engage stakeholders: Build productive relationships with business partners within and outside FDA and jointly foster effective stakeholder engagement to meet the needs of the American public.

He outlined OPQ quality initiatives that are now underway.

- The Emerging Technology Program supports development and implementation of innovative approaches in pharma design and manufacturing, identifies and resolves potential scientific and policy issues related to new approaches (for instance, the program enabled the approval of the first switch from batch to continuous manufacturing process for an approved drug). A web page² and Guidance for Industry document³ were produced in 2017.
- OPQ Science and Research includes manufacturing science and innovation, immunology, tumor biology, pharmaceutical analysis and characterization, and infectious disease and inflammation.
- White paper published in January 2018⁴ describes key considerations when creating a QOS:
 - Explain product and process development in a patient-focused context
 - Effectively summarize the overall control strategy
 - Guide the regulator through the submission
- Many generic applicants have effectively used a QOS based on a question-based review and may continue to do so in the future.

Randazzo also described the integrated quality assessment (IQA), in which subject-matter experts conduct a quality assessment on an application, integrating assessments and inspections.

IQAs are designed to benefit patients by creating better interactions between industry and the FDA. This is accomplished through a deep understanding of the products and processes, proactive communication, QOS, and other methods. The goal is a clear submission with a rationale for the proposed control strategy, timely responses to FDA inquiries, and securing the supply chain.

Randazzo also reported on enhancements to modernize quality assessment and knowledge management throughout the drug product lifecycle:

- A dashboard interface centered around quality risks for critical quality attributes, plus corresponding mitigation and control strategies for drug substance and drug product
- A computer-aided interface for lifecycle knowledge management and standardization of ANDA quality assessment
- A benefit-risk assessment framework that balances clinical context with potential product quality issues

Shared challenges for both regulators and industry include:

- Facility quality issues that affect approvals of all application types; enhanced communications by both regulators and industry will help
- Managing complex supply chain and manufacturing arrangements: multiple facilities and back-up facilities create the need for better quality agreements and enhanced communication for both contract manufacturers and API suppliers
- Data reliability issues/concerns have significant impact on applications and FDA resources

HARMONIZATION AND QUALITY

The final speaker in the first day's plenary sessions, John Groskoph, Executive Director, Global CMC, Pfizer, Inc. focused on the importance of harmonizing approaches to quality around the globe with a discussion about the challenges to harmonization and how they affect the industry's mission to serve patients.

The first challenge is the difficulty of defining quality for a specific product, Groskoph noted. This presents many negatives for the industry, including increased manufacturing costs, barriers to continuous improvement, stifled innovation, overcomplicated supply chains, increased quality risks, and reduced quality assurance. The consequences for patients include delayed therapies, drug shortages, increased costs, and reduced trust in supply chains.

Additional challenges include multiple stakeholders with different objectives, multiple local/regional pharmacopeias, and increasing requirements for detailed cGMP information in regulatory applications. In addition, he said, post-approval implementation is complicated by extensive and uncertain regulatory review timelines. When under pressure to demonstrate that quality is assured for local populations, for example, regulatory authorities may deviate from global standards. Economic and political tension can result from the difference in quality expectations between local companies and multinational corporations. In some countries, ICH guidelines are only a minimum (i.e., some demand more stability data than ICH expects).

Groskoph cited the international initiatives working toward harmonization, many of which were discussed in greater detail by other speakers, including

- ICH's regulatory expectations/guidelines for harmonization
- Mutual recognition agreements such as the recent MRA between the EU and the US (to be fully implemented in July 2019)
- ASEAN 11-nation work-sharing program to develop a collective approach to assessing regulatory applications
- PIC/S's work to harmonize inspection criteria
- Establishment of technical standards

Common themes among these initiatives and organizations:

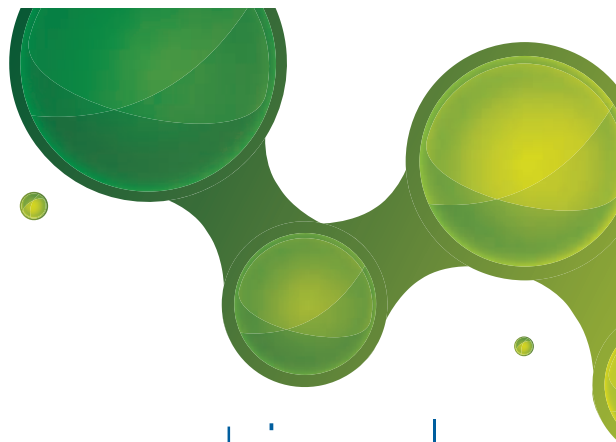
- Improve inspection criteria/focus to harmonize inspection reports and deficiencies descriptions and justifications
- Improve convergence of pharmacopoeial monographs and procedures
- Align harmonized application content, assessment timelines, and format
- Align strategic interactions between industry and regulatory authorities—possibly joint interactions
- Improve transparency and alignment for interactions among regulatory authorities

He concluded the morning's presentations by noting that "We have come a long way, but we still have far to go." ◀

—Susan Sandler, Editorial Director

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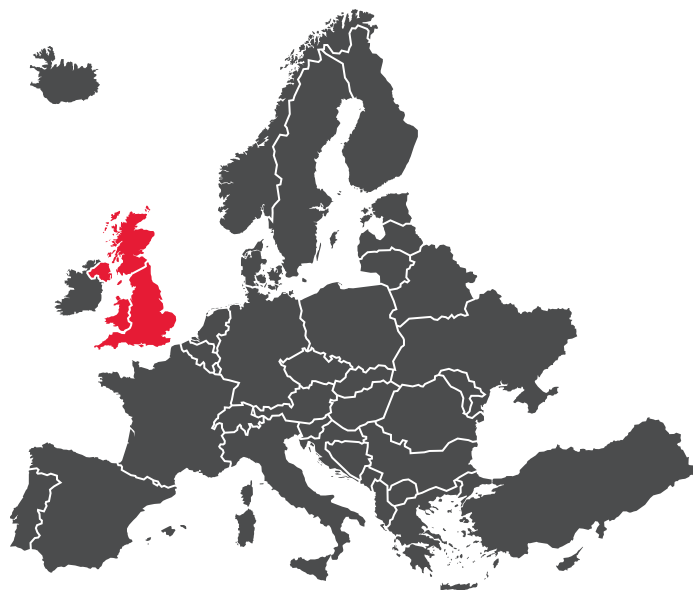


ISPE.org/Biopharma18

REGULATORY UPDATE

ISPE Presents Industry Initiatives at EMA Interested Parties Meeting

Nuala Calnan, PhD



Nuala Calnan

SPE, along with 11 other industry associations, were pleased to participate in the most recent interested parties meeting of the European GMP/GDP Inspectors Working Group (IWG) held at the European Medicines Agency (EMA) on 6 December 2017. The meeting was chaired by Brendan Cuddy, Head of Manufacturing and Quality Compliance at EMA; preparations and contributions were expertly coordinated by Esther Martínez on behalf of the GMP/GDP IWG secretariat.

appropriate to review them once the proposed new veterinary legislation is finalized. Nevertheless, industry input toward a future revision of both Annex 4 and 5 is welcome either through EMA or via the national competent authorities.

Importation: The European Commission's current view is that fiscal transactions should be considered as importation, even if the goods remain in the EU. The IWG acknowledged that harmonization is needed on this matter; therefore, the draft Annex 21 (new guidance for importers of medicinal products) will be developed accordingly. Presentation to the IWG is expected in the first half of 2018. The European Federation of Pharmaceutical Industries and Associations (EFPIA) questioned the need for recertification, retesting upon importation, and compliance with the delegated regulation on safety features for products that are fiscally imported (i.e., not physically leaving the EU). The IWG noted those concerns, indicating that they would apply as much flexibility as possible to address these challenges, within the framework of the EU Commission's guidance.

IWG UPDATE

The EMA provided an overview of work undertaken by the IWG in 2017 as well as key topics in the 2018 work plan. The presentation also covered the status of each mutual recognition agreement (MRA), with particular emphasis on the US, as its provisions for recognition of inspections had just entered into force on 1 November 2017.

Following EMA's update, the IWG provided their feedback on the questions raised by the interested parties:

MRAs: It was clarified that veterinary immunologicals are not regulated by FDA and therefore, currently out of the scope of the EU-US MRA.

Non-harmonized GMP inspection procedures: The IWG indicated that this concern is not unique to the veterinary sector and that various working groups are scheduled to review harmonization.

EU GMP Guide Annex 4: The IWG noted that both Annexes 4 and 5 would benefit from updates, given their age, but noted that it would be more appro-

BREXIT

The next major item for discussion was the impact of Brexit, including an update on the risk minimization measures and actions being undertaken by industry to assure continuity of supply to the EU market. EMA provided an overview of the steps taken by the agency in preparation for UK withdrawal from the European Union, which included a number of stakeholder interactions as well as the publication of updated Q&As and procedural guidance.

EFPIA, on behalf of the interested parties, delivered a presentation outlining measures being taken by industry to address the supply chain changes that will ensue when the UK leaves the EU. This illustrates the extent and complexity of the work required, which will most likely continue beyond the end of March 2019. The interested parties requested that the IWG facilitate the implementation/transition period wherever possible.

The European Industrial Pharmacists Group supported EFPIA and raised questions about additional challenges posed by the timelines for implementing the delegated regulation on safety features, which would come

into application on 9 February 2019, the same quarter as the UK withdrawal from the EU, which is scheduled for 29 March 2019.

EMA indicated that a sub-working group made up of inspectors (including representatives from UK) and EMA colleagues had been formed to gather Brexit-related questions from industry to try to address them. They also indicated that results from the January 2018 EMA survey requesting information from industry on planned variations affecting batch release and batch control testing sites would be posted on the EMA's "News and Events" website page ("EMA Identifies Gaps in Industry Preparedness for Brexit"). In direct response to a question from the IWG if industry had developed different Brexit-related scenarios, it was confirmed that industry is currently preparing for a "hard Brexit" coming into effect on 29 March 2019.

ASSOCIATION PRESENTATIONS

The first industry association presentation was delivered by Karoline Bechtold-Peters on behalf of European Trade Association representing Biopharmaceutical Companies—the European Biopharmaceutical Enterprises—a new member to the Interested Parties meeting. The presentation, "A Risk-Based Approach to ID Sampling of Biologic products," reviewed the challenges of performing 100% inspection of biological drug substances. This necessitates a thaw and integrity breach of the bulk drug substance container to take a sample. The presentation outlined links with Annex 8 to the EU GMP guide, PIC/S guide to GMP, and the WHO Annex 4 in presenting a potential risk-based approach. The IWG indicated that risks are case-specific, however, and should be handled on a case-by-case basis with the local competent authority. At this point in time, they concluded, a revision of Annex 8 does not seem warranted.

ISPE made two presentations. The first on Pharma 4.0, presented by John Berridge, outlined some novel technologies under the umbrella of Pharma 4.0 manufacturing strategies that were receiving industry consideration. It was delivered to brief inspectors on what they may encounter on the shop floor in the coming years. One question raised by the IWG was the likely need for revision of GMPs to accommodate 4.0 technologies. The interested parties answered that it was not an expectation at this time, as the technologies will likely make it easier to comply with current regulatory requirements rather than require any specific changes to GMPs or existing guidance.

ISPE's second presentation covered the subject cultural excellence. Nuala Calnan, PhD, outlined the ISPE *Cultural Excellence Report* (April 2017) and the practical resources it provides to help industry organizations develop and foster healthy quality cultures. The PDA Quality Culture team's complimentary work on assessment and training related to quality culture was highlighted, as was recent University of St. Gallen/FDA research results confirming the impact of cultural excellence on overall pharmaceutical quality system effectiveness. Acknowledging that the GMPs do not currently contain specific requirements on organizational culture, Dr. Calnan noted that a planned update to the Eudralex Volume 4, Chapter 1 introduction offered an opportunity to include some positive reinforcement for companies to consider. She also encouraged the IWG to promote a focus on culture and behavior to enhance patient protection. Finally, as inspectors play an influential role in encouraging adoption within industry, she asked the IWG to commend organizations that are making efforts in this area.

The meeting closed with valuable discussion between industry associations across the range of topics highlighted during the meeting. <>

We're Moving! A New Online Platform for CoPs

Communities of Practice (CoPs) are the lifeblood of our association. It is within our CoPs that ideas are born for technical documents, articles, conference sessions, and so much more. We encourage all members to join one or more of our 16 CoPs to communicate, learn, and contribute.

For several years ISPE used Socius as a platform for discussion boards, group email, shared libraries, and a searchable member directory. The system made it easy for any member to join a group and immediately participate in the discussions. Members were able to use the discussion boards to ask questions, seek advice, and share opportunities with their peers. Our communities blossomed over the years and our platform supported over 8,000 CoP members.

In 2017 Socius was bought by Higher Logic, an industry leader in cloud-based community platforms that powers over 250,000 online communities like ours. The acquisition presented us with an opportunity to make some changes. Over the past year we have been hard at work listening to feedback about the current platform experience and planning big changes with our new partner.

In 2019 we will begin the conversion to the Higher Logic platform. Members will immediately notice the cleaner look and improved site navigation. Committee members will appreciate the updated folder structure in the file library and the refined search feature for easier content access. The system will allow members to post in-line pictures and videos in the discussion threads, recommend and like discussion posts, and send messages to other members through the community email system. Members will be able to track their activities and receive recognition for their contributions. These changes will help us to build a dynamic environment where members can continue to network, solve problems, and explore new ideas. The conversion will take several months to complete but it will be well worth the effort.

But this is only the first part of the change. Higher Logic is part of a larger strategy that combines design, education, and technology to create more opportunities for our members to have meaningful discussion through new and traditional media channels. Community resources will be enriched with on-demand video series, live webinars, and presentations from past conferences and meetings.

We want to thank you for your continued support and valuable feedback that helped guide us toward these exciting changes. <>

—Konyika Nealy, Senior Director, Guidance Documents and Knowledge Networks

We look forward to bringing you more news about our new platform launch in the coming months. Already a CoP member? Excellent! If not, join today! ispe.org/communities-practice

IN-LINE, REAL-TIME POWDER FLOW AND PROCESS MONITORING

Drag Force Flow Measurement as a PAT

Tim Freeman

Innovative technology for in-line real-time powder flow monitoring based on drag force flow measurement offers great potential for efficient monitoring of powder-processing operations.

Most pharmaceuticals are handled in powder form at some point during production, notably those delivered in oral solid dosage form. This makes efficient powder handling and processing essential for competitive drug manufacture. While the process analytical technology (PAT) available for powder processes has advanced considerably over the last decade, there are still areas where the current analytical solution is suboptimal, particularly as the industry embraces continuous manufacture.

DRAG FORCE FLOW MEASUREMENT

The defining features of a sensor for in-line measurement of the instantaneous local forces associated with the movement of powders, granules, or a wet mass, shown in Figure 1, are a hollow cylinder with two optical strain gauges (fiber Bragg gratings, or FBGs), mounted on the inner surface. Material flowing past the sensor causes a deflection, the magnitude of which is quantified by the FBGs to characterize the in-process material real-time.

An FBG is a periodic structure of varying refractive index embedded in

THE BEST PAT ANSWERS TO AN INCREASINGLY WELL-UNDERSTOOD LIST OF REQUIREMENTS, INCLUDING ISSUES RELATED TO THE PROCESS INTERFACE

the core of an optical fiber. It reflects light traveling through the fiber at a wavelength that depends on its grating constant and refractive index. These two parameters are influenced by ultra-low levels of strain in the FBG region and by temperature (between -20°F and 200°F).

Using two FBGs opposite one another differentiates wavelength changes associated with deflection of the probe from changes associated with temperature to determine localized flow forces. The resulting raw-flow-force data are usefully converted into force pulse magnitude (FPM) measurements, where FPM is the difference between the maximum and minimum forces in a defined period. As a differential measurement, FPM is always positive and unaffected by baseline drift, making it a robust parameter for process monitoring.

The best PAT answers to an increasingly well-understood list of requirements that include issues relating to the process interface—ease of installation plus cleaning, reliability, and safety. It also assesses the value of the data: Is the measurement frequency sufficiently high? Are the data relevant? Such criteria are helpful in assessing the potential of new PAT.

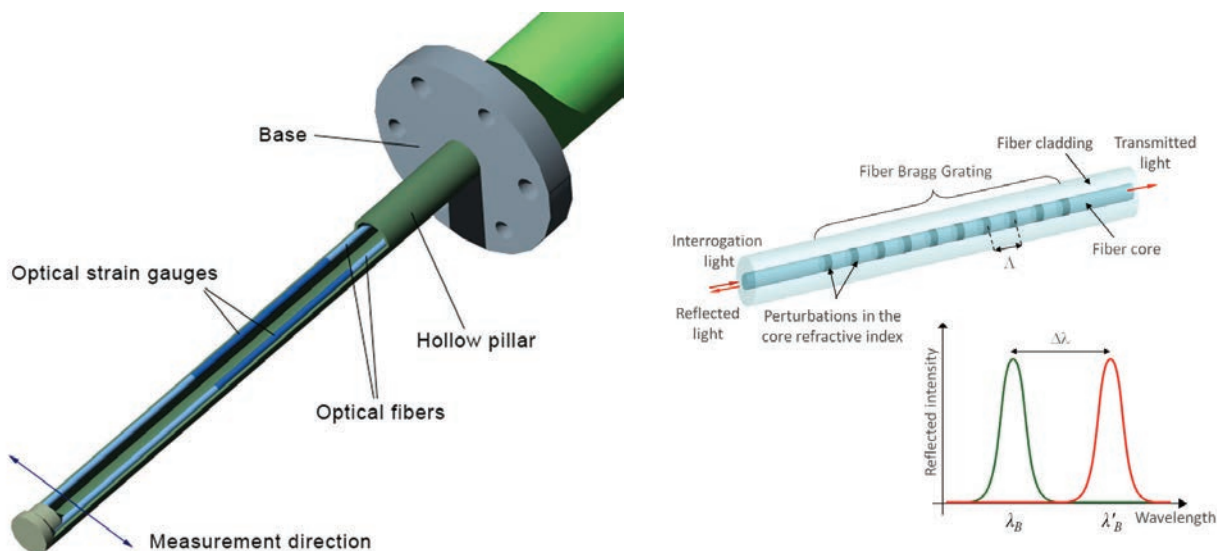
Practicalities of measurement

Drag force flow sensors are typically around 3 millimeters in diameter, a small footprint that creates minimal flow disruption and a low risk of fouling. The instrumentation has a chemically resistant, easy-to-sterilize stainless steel construction, presents no ignition hazard, and is not subject to electromagnetic interference.

The dual-FBG design makes the technique self-calibrating with respect to temperature, enhancing data robustness. Since measurements can be recorded at a frequency up to 500 hertz, drag force flow sensors offer precise temporal resolution. The technique is highly sensitive; deflections in the region of just one micron are reproducibly detectable (forces of ~ 0.5 milliNewtons), which translates into the ability to characterize particles with a density as low as 0.15 grams per cubic centimeter, for example.

In summary, the technique can provide direct and precise measurements at frequencies that match the dynamics of even rapidly changing processes, and is inherently well suited to in-line implementation. But what are the measurements' relevance and value in terms of improving process performance?

FIGURE 1: DRAG FORCE FLOW SENSORS (LEFT) USE FBGs (RIGHT) TO MEASURE, WITH HIGH SENSITIVITY, THE LOCAL FORCES ASSOCIATED WITH MOVING POWDERS



Source: Lenterra, Inc. Reprinted with permission.

DATA RELEVANCE

The terms “powder” and “particles” are often used interchangeably. Powders, however, are bulk assemblies of particles, liquid (usually water), and gas (typically air). Measuring particle properties is not the same as measuring bulk powder properties. PAT is well-established for particle-size measurement, and there are often direct links between the particle size of an active ingredient and, for example, its rate of dissolution/bioavailability. This may encourage the use of such technology.

Particle size, however, is just one of many variables that influence powder flowability. This in turn can affect aspects of process performance such as blend time, fill uniformity, and tableting speed. If PAT is being considered to control these aspects of performance, then measuring particle size, or indeed any other particle property, is an inherently limited approach.

Considering the measurement of bulk powder properties, the issue often becomes one of interpretation and secure correlation with critical quality attributes (CQAs) of the product. This can compromise the application of potential PATs for high-shear wet granulation (HSWG) monitoring, such as acoustic, microwave, stress, and vibration measurements and power drawn by the agitator.¹ These techniques enable continuous measurement, but it can be difficult in some instances to interpret the resulting data to exert effective control, because that data is affected by a number of variables.

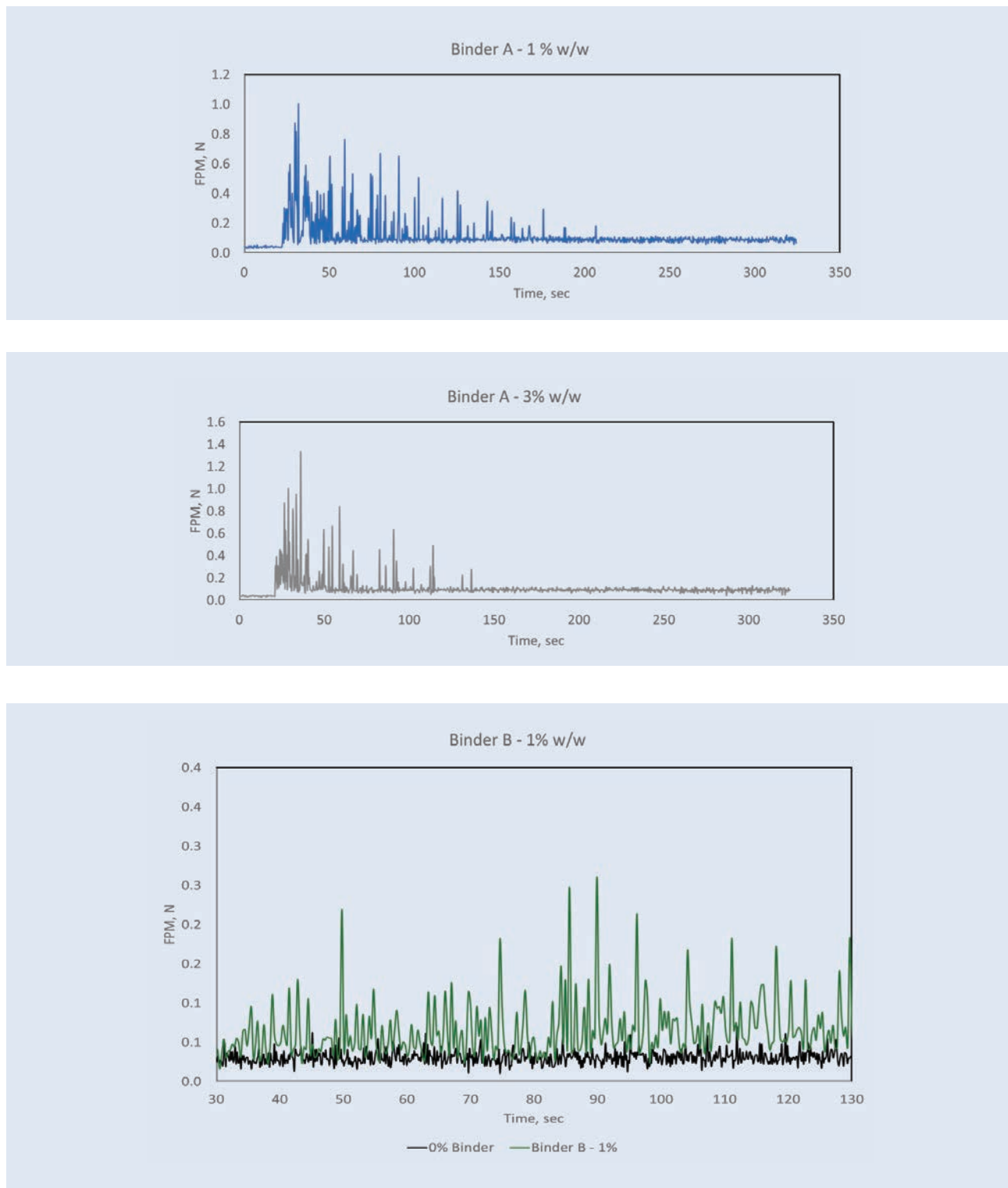
A notable success in developing robust relationships between powder properties and CQAs has been the demonstration of direct correlations between

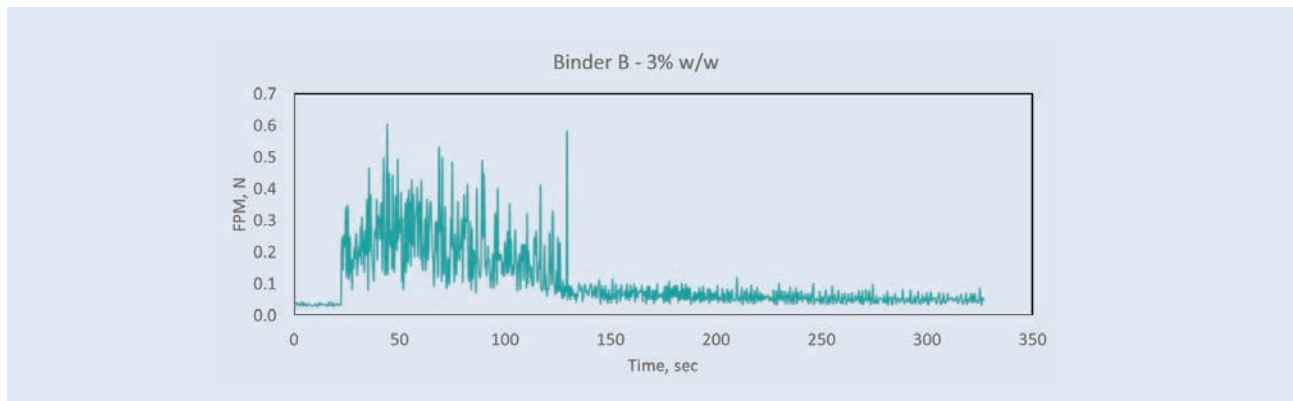
the dynamic flow properties of granules and the hardness of tablets produced from them.² Dynamic flow properties are determined using a powder rheometer to measure the force and torque acting on a helical blade as it rotates through a sample of the powder. Though this at-line technique is significantly different from drag force flow measurement, the fundamental approach of measuring the forces associated with a bulk powder in motion has certain similarities. The two techniques have been shown to produce comparable data in HSWG trials carried out by a major pharmaceutical company.³

In these trials, the water-addition step was shown to trigger a significant rise in the basic flow energy (a dynamic flow property) or FPM associated with movement of the granulating mass, with both parameters providing a secure basis for end point detection. Both techniques, furthermore, clearly differentiated granules produced with different levels of binder: 1%, 3%, and 5% hydroxypropyl cellulose. Higher levels of binder are associated with stronger granule formation and high flow energy/FPM values.

These early correlations with dynamic powder properties, which have proven process relevance across a range of unit operations, indicate that though drag force flow measurement is still in its infancy, it may prove to be a PAT that is more tractable to correlation with process performance than others. As such, it could prove a valuable monitoring solution for blending, mixing, agglomeration, and many other powder-handling applications. A case study further illustrates the capability and potential of the technique.

FIGURE 2: FPM MEASUREMENTS DIFFERENTIATE THE PERFORMANCE OF BINDER A AND BINDER B, SHOWING THE BLENDING TIMES REQUIRED TO ACHIEVE A UNIFORM DISPERSION, WHERE FEASIBLE





CASE STUDY

Investigating binder distribution using drag force flow measurements

The effect of binder viscosity on blending performance was investigated using Binder A, viscosity 0.001 pascal second (Pa.s) and Binder B, viscosity 100 Pa.s. Following 20 seconds of dry mixing, 1% or 3% by weight of binder solution was added to an excipient bulk, and blending was carried out for a further period of 300 seconds. Excipient mass and shear rate were kept constant throughout.

Comparing the two sets of data gathered for Binder A (top two traces, Figure 2) increasing binder concentration reduces the time required to reach content uniformity, the point at which FPM becomes effectively constant. Comparing the results for Binder A with those for Binder B indicates that a lower concentration of the less viscous binder (A) is required to achieve a uniform blend. In fact, at low concentration (1%), Binder B does not appear to reach a state of uniform dispersion, forming instead relatively stable agglomerates that cause spikes in the FPM trace. This poor dispersion can be attributed to high viscosity. Another notable conclusion that can be drawn from the 1% Binder B trace is that the sensor can clearly differentiate a formulation containing modest levels of binder from the excipient alone (black trace).

CONCLUSION

Identifying optimal PAT for powder processing remains an ongoing task, with the drive toward continuous manufacture intensifying requirements for smarter solutions. New in-line technology for real-time powder-flow characterization offers considerable potential within this context and opportunities to boost the efficiency of process development, scale-up, monitoring, and control. <>

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Tim Freeman is Managing Director of Freeman Technology, a powder characterization company for whom he has worked since the late 1990s. Through his work with various professional bodies and involvement in industry initiatives, Tim is an established contributor to wider developments in powder processing.



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PASS-THROUGH BOXES IN LIFE SCIENCES CLEANROOMS

Design and Application

Norman Goldschmidt and Andrew Ricker, PE

This article provides an overview of pass-through boxes as they relate to the life sciences industry, defining their purpose, applications, and available options.

Pass-through boxes reduce contamination in life science environments by providing a safe transfer method between a cleanroom and an adjoining room (Figure 1). Because they are never occupied by personnel, they greatly reduce risk for both spaces.

These chambers are actually small airlocks with unique features that make them perform differently (and often better) than their larger cousins. Various sizes are available to meet requirements for different applications. Some allow only small pieces of equipment to be transferred; others are large enough to contain a cartload of material. While pass-through boxes have received quite a bit of attention in regulatory and industry guidance, these chambers and their unique characteristics are poorly understood and rarely addressed.

ATTRIBUTES AND OPTIONS

In this article, “life sciences pass-through box” refers to a box or tunnel that passes through the wall of a cleanroom (or contained enclosure) into an adjacent room (Figure 2). The box is fitted with doors at both ends, allowing material to be placed into it on one side and removed on the other.

To keep the atmospheres of both rooms separate, pass-through boxes have interlocked doors that cannot be opened simultaneously. They should be easily cleanable, especially for cGMP applications, with construction and hardware that are resistant to cleaning chemicals. Windows or see-through panels are usually added to provide visibility. Optional features include, but are not limited to:

Timed interlocks that prevent a door from being opened until a timer has expired, assuring compliance with the SOP(s) for sanitizing agent exposure or providing sufficient time for a ventilated pass-through to dilute airborne contaminants.

Notification lights and sounders to indicate that materials in the box are ready for withdrawal.

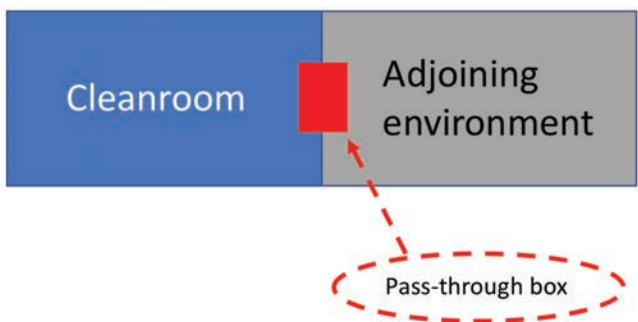
Automatic doors to enforce interlocking or coordinate with automated material transfer.

Conveyors to provide automated material movement. They are typically confined to the pass-through so that the conveyor belt or table doesn't traverse multiple zones.

FIGURE 1: BASIC PASS-THROUGH BOX



FIGURE 2: PASS-THROUGH BOX LOCATION



Automatic sanitizing uses chemical sprays, vapors, gases, or ionizing radiation (e.g., ultraviolet light) to sanitize items in the pass-through. This can produce a validated log reduction in surface contaminants and may elevate the pass-through to the level of an autoclave or sanitizing chamber (which is beyond the scope of this paper).

TABLE A: TRANSFERS BETWEEN GRADE CLASSIFICATIONS

Particle Concentration Change		Cleaner Room			
Less Clean	Grade	A	B	C	D
	A				
	B	2 log**			
	C	3 log	1 log		
	D	4 log*	2 log*	1 log*	
	U/C	5 log*	3 log*	2 log*	1 log*

* Assumes a classification change of one full step “in-operation” for illustrative purposes.

** Transitions from Grade B to Grade A space are commonly small controlled openings, with no pass-thru or airlock (i.e., a “mouse hole”).

TO UNDERSTAND PARTICLE TRANSFER FROM THE LESS CLEAN SPACE INTO THE PASS-THROUGH, AND FROM THE PASS-THROUGH INTO THE CLEANROOM, IT’S IMPORTANT TO CONSIDER THE FACTORS THAT CAN CAUSE PARTICLES TO FLOW INTO AND OUT OF A BOX WITH FIVE CLOSED SIDES

Gaskets minimize air transfer between spaces:

- *Near-airtight* gaskets minimize air exchange between spaces, but do not have uniform clamping force that assures zero leakage. These are used in most pass-through boxes to minimize passive ventilation.
- *Airtight* gaskets can be mechanical or pneumatic; these are employed in only the most hazardous applications (e.g., biosafety level 4) where sanitizing is required.

Ventilation can take several forms:

- *Defined leak paths* in unventilated pass-through boxes allow room-pressure differences to ventilate the box with sufficient volume to dilute internal contaminants. Defined leak paths may be unrestricted or filtered openings.

- *Passive ventilation* uses the pressure differential between rooms, the airflow within rooms, and door opening as a motive force to transfer particles into or out of the box. This is the most typical type of ventilation used in pass-through boxes.
- *Active ventilation* uses mechanically introduced air to preserve a pressure regime between rooms, create a “bubble” or “sink” to the communicating rooms, dilute contaminants drawn into the box during door opening, or maintain an area classification.

Active ventilation, more than any other feature, distinguishes these boxes from the passively ventilated or near-airtight boxes that are more prevalent in the industry. The application of these two types of boxes motivated this investigation.

IMPACT ON SURROUNDING ENVIRONMENT

The functions and cleanliness classifications of adjoining spaces that communicate via a pass-through are quite diverse. In small-scale clinical biotechnology operations (including cell and gene therapies) pass-throughs may be used to transfer raw materials into an EU Grade B from an adjacent Grade C, or transfer trash from a Grade B to an adjacent Grade D. In small-scale aseptic filling, the product may pass from Grade B to Grade D via a pass-through box in lieu of the “mouse hole” (Figure 4) used in larger-scale continuous manufacturing. Therapeutic protein manufacturers may use pass-throughs to transfer small equipment from Grade D or an unclassified space to Grade C. These challenges are summarized in Table A.

The direction of travel through a pass-through box is a key concern. Since materials leaving a clean area present less contamination risk to the room they enter (with the exception of biosafety and potent compound containment), the risk of compromising space classification varies with the direction in which materials travel of through the box. Table B offers a qualitative assessment of risk depending on travel direction.

NUMERICAL ASSESSMENT

To assess the veracity of the qualitative approach, let’s consider the following situation:

TABLE B: QUALITATIVE ASSESSMENT OF RISK DEPENDING ON TRAVEL DIRECTION

Particle Concentration Change		Entering				
Exiting	Grade	A	B	C	D	Unclassified
	A		Very Low	Low	Moderate	Moderately high
	B	Low		Very low	Low	Moderate
	C	Moderate	Low		Very low	Low
	D	Moderately high	Moderate	Low		Very low
	Unclassified	High	Moderately high	Moderate	Low	

TABLE C: IMPACT CALCULATIONS

Impact	Run 1* Small difference in classification	Run 2 Larger difference in classification	Run 3 Largest difference in classification
Assumed classification			
Cleanroom	ISO 7: 352,000 particles/m ³	ISO 7: 352,000 particles/m ³	ISO 7: 352,000 particles/m ³
Adjoining area	ISO 8: 3,520,000 particles/m ³	ISO 9: 35,200,000 particles/m ³	Unclassified: 100,000,000 particles/m ³ †
Particle emission rate			
	3,520,000/m ³ × 1 m ³ /1 min = 3,520,000/min	35,200,000/m ³ × 1 m ³ /1 min = 35,200,000/min	100,000,000/m ³ × 1 m ³ /1 min = 100,000,000/min
Total particle count			
Cleanroom	352,000 /m ³ × 300 m ³ = 105,600,000	352,000/m ³ × 300 m ³ = 105,600,000	352,000/m ³ × 300 m ³ = 105,600,000
Adjoining area	109,120,000	140,800,000	205,600,000
Average particle concentration			
<i>Without considering ventilation</i>	109,120,000 ÷ 301 m ³ = 362,525/m ³	140,800,000 ÷ 301 m ³ = 467,774/m ³	205,600,000 ÷ 301m ³ = 683,056/m ³
<i>Percent change</i>	± 3%	± 33%	± 94%

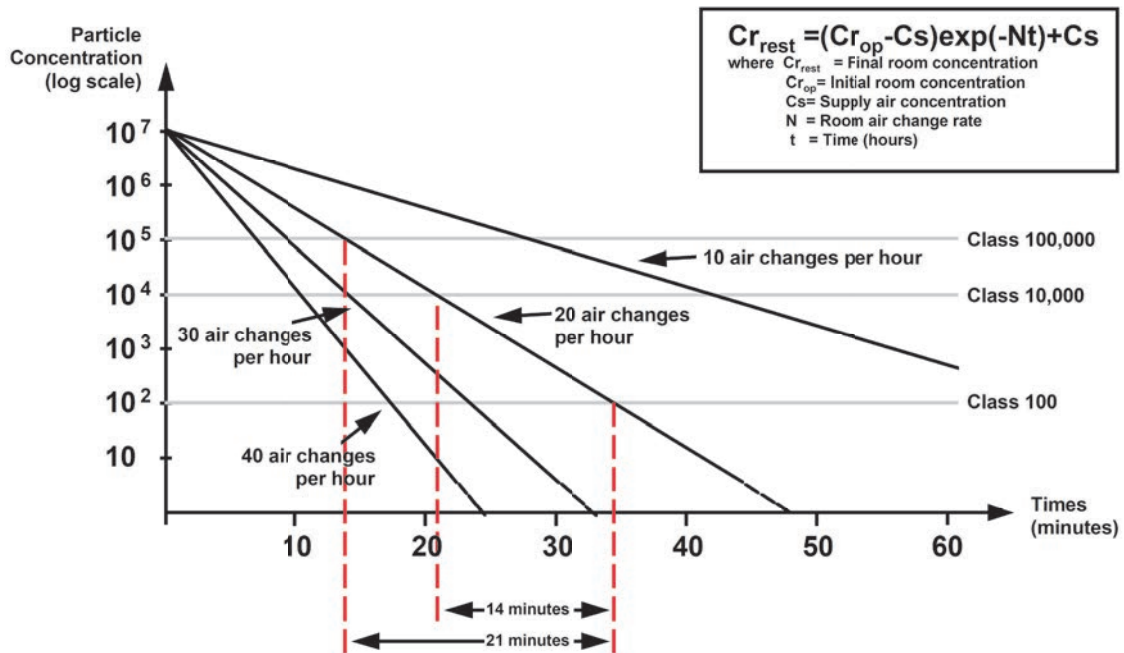
* Results will vary with different box sizes and room volumes. A larger unventilated pass-through box entering a smaller ISO 7 room will yield different recovery times.

† Per American Association for Aerosol Research, *Aerosol Science and Technology* 32 (2000): 527–544

- Cleanroom volume: 300 cubic meters (m³)
- Pass-through box volume: 1 m³
- Air change rate per hour: 20 ACH
- Particle size: 0.5 micrometers (µm)
- Temperature: 20° C, 293 K
- Box type: Near airtight, passive ventilation

To understand particle transfer from the less clean space into the pass-through, and from the pass-through into the cleanroom, it's important to consider the factors that can cause particles to flow into and out of a box with five closed sides. We suggest evaluating the particle diffusion that will cause particles to flow from an area of higher concentration to an area of lower concentration.

FIGURE 3: RECOVERY FROM UPSET



Source: *ISPE Sterile Baseline Guide*, Vol. 3, Second Edition. Copyright ISPE. Reprinted with permission.

Particle diffusion

We can use the Stokes-Einstein equation to approximate the diffusion rate for 0.5 µm particles in still air; this is likely not the best model, however. Since the average room velocity is orders of magnitude higher than mass flux rates (diffusion velocity across a plane), the mechanism of diffusion is of less interest than the mechanical distribution of the particles from the pass-through box.

Personnel intervention

While there is no formula to describe all possible interventions that cause particles to enter a space from a box with five closed sides, for the purposes of this evaluation we suggest the aggressive assumption that the pass-through box reaches equilibrium with the cleanroom in just one minute.

Recovery from upset

For these calculations, we will make the conservative assumption that the box was open to the lower classification area for sufficient time to reach equilibrium. At 20 ACH, the time to recover from an upset is approximately 7 minutes per log reduction. Recovery from a 3% upset requires approximately 1.3 seconds (Figure 3). In a real-world 30 or 40 ACH the time to recover from an upset is even shorter.

In Table C, Run 1, we see that opening a box containing air from an area of 1 log higher contamination to one of lower contamination will have less effect than might be expected and is quickly abated. Run 2 is a more significant upset; as seen in the preceding run, however, recovery from a 33% upset requires approximately 14 seconds. The calculations in Run 3 show a

VENTILATING THE PASS-THROUGH BOX INTERIOR REDUCES THE PARTICLE COUNT WITHIN THE BOX AS WELL AS THE PROBABILITY THAT PARTICLES WILL ESCAPE OR ENTER THE BOX

significant upset that is not to be taken lightly. Recovery from this 94% upset requires approximately 40 seconds.

The transient nature of these upsets explains why a high particle count within a pass-through box does not produce a prolonged effect on the surrounding cleanroom. There is often a significant time delay between cycles of door openings, and the door does not usually remain open long enough

to allow a significant number of particles to escape.

These calculations suggest that our qualitative risk approach appears appropriate. It should be noted, however, that we have approximated only the effect on average concentration; local conditions near the box may be higher than the average for the room because air patterns play an important role in understanding the impact of pass-through boxes. A test of particle counts near the box during operation is a wise addition to a validation plan to ensure the validity of the approach.

VENTILATION

When pass-through boxes connect spaces of differing classifications, contamination risk can be reduced by ventilating the pass-through box interior. This reduces the particle count within the box as well as the probability that particles will escape or enter the box.

Even in the highest risk situations, ventilated boxes can reduce contaminant ingress when the box is opened in a clean space that adjoins a less clean space. Ventilated connections can also bridge unclassified to classified spaces with low risk.

Passive ventilation

Passive ventilation relies on internal mixing and airflow patterns to provide air transfer for the enclosure, since openings on the clean side are often at a higher elevation than those on the other side. Time delays can further reduce particle counts by flushing the box with 3-4 air changes before the box is reopened. These delays should be indicated by SOP or controlled by interlocks.

Filtered leakage paths can also provide passive ventilation with containments and inhibit the passage of pests. In this design, panel-style filters (usually H-13 or better) are mounted over the openings in the box.

Active ventilation

The risk of contamination can be further ameliorated by active ventilation of the pass-through box. Active ventilation schemes fall into three categories:

Exhausted

Exhausted boxes have extraction systems to remove particulate; this helps prevent particles from exiting through the doors. To prevent particle emissions effectively, air velocity greater than 40 fpm is recommended through an open door. Operators should be aware that this can negatively affect room pressure relationships when the doors are cycled.

Supplied

Supplied boxes have an attached air-supply system that is intended to prevent particulate from entering. Airflow velocity through an open door should exceed 40 fpm to prevent particle entry. Operators should be aware that this can negatively affect room pressure relationships when the doors are cycled.

To allow the doors to open easily, both exhausted and supply boxes must allow air from one or both rooms to leak in. Variations use HEPA^{*} relief ports to admit air into the box, or HEPA extraction fan/filters to return air

from the box to an adjoining room. While the box is closed, optional air inlets can reduce the particle concentration when the door is opened. In supplied boxes, a return duct can send excess air to the building air-handling system, similar to personnel or material airlocks.

Internally recirculated

Recirculated boxes have an internal air-supply system that reduces particulate concentration within the box. Recirculated boxes do not require a leak path, making them easily cleanable and well suited to containment applications. Variations utilize airtight door seals and interlock timers to allow sufficient dilution before a door can be opened. HEPA supply fan/filters normally recirculate air within the box. Depending on the application, it may be necessary to introduce conditioned air from the building HVAC system to overcome heat gain from the internal fans, then recirculate the air back to the air-handling system. This type of box does not negatively affect room pressure relationships when the doors are cycled.

Pass-through space temperature

In some instances, materials may remain inside the pass-through for an extended time. Space conditions in ventilated pass-through boxes will be approximately equivalent to the room conditions, unless heat gain is realized from the material being held. Conditioned air to support material stability is typically not required.

CONCLUSIONS

Numerous pass-through box configurations and options are available. Their small size and lack of particle-generating sources make them a low risk for bridging different space classifications. Passively ventilated boxes are appropriate for bridging 1-2 log differences in particle concentration; actively ventilated boxes can handle more robust particle concentrations and provide lower risk. <>

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^{*} High-efficiency particulate air (HEPA) filter: A mechanical filter that forces air through a mesh to trap particles.



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EXPERIMENTAL CONDITIONS DEFINE THE ATP INFERENCE SPACE

Brent Harrington and Kimber Barnett, PhD

This article illustrates the importance of experimental conditions to evaluate analytical methods. Italicized text is used throughout the article to emphasize key points and illustrate formula variables.

Analytical method validation characteristics accuracy and precision, as defined in ICH Q2,¹ are key components in demonstrating the appropriateness of an analytical method. If chosen correctly, a joint metric that considers accuracy and precision criteria together²⁻⁵ will provide a pragmatic criterion for inferences from the analytical method results.

The measurement source used in the assessment against an a priori criterion must be defined carefully. An accuracy or recovery experiment that is part of a method validation exercise, for example, can use measurements of carefully characterized (known) spiked amounts of the active pharmaceutical ingredient (API) in solution to provide an estimate of the measurable amount of the true (spiked) value.⁴ When measuring API in the drug product (final dosage form), however, there may also be an effect attributed to other components (e.g., excipients) upon complete extraction of the API from product samples.

Without examining representative product samples (in addition to the usual ICH Q2 accuracy validation assessment), the uncertainty of reportable drug product values may not be estimated completely. The interplay between the drug substance, excipients, and drug product manufacturing process can affect the complete drug substance recovery when assaying the dosage form; this can increase the uncertainty of the final result or reportable value.⁶ If the primary intent is to ensure high quality in the decisions made from the results of drug product samples, then the assessment against a joint accuracy and precision criterion should include evaluation based on experimental units containing drug product (i.e., real) samples.

A staged approach can illustrate the difference in viable inferences between experiments using drug product samples and those that use spiked amounts of API. First, defining an analytical target profile (ATP) can determine the required performance criteria (parameters). Next, method conformance is executed against criteria based on observed data.^{2,4}

ATP DEFINED FOR METHOD TRUENESS

In an ICH Q2 validation exercise to assess method accuracy, experimental units can be prepared as spiked API solutions. In addition to typical assessments

against individual accuracy and precision criteria, a company may choose to apply an additional criterion for accuracy or trueness by defining an ATP statement such as this one:

ATPI: The procedure must be able to accurately quantify *known concentrations of compound name* over the range 90%–110% of the nominal concentration with specificity, linearity, accuracy, and precision such that *measured concentrations* fall within $\pm 1.0\%$ of the true value with a 95% probability.

This ATP defines the characteristics for the analytical method to be considered acceptable.³ The range (90%–110% of nominal) and the risk (100% – 95% = 5%) of making an incorrect decision concerning both *concentration values* and (through the 95% probability) the tolerance statement ($\pm 1.0\%$) is an inherent expression of the true unknown total uncertainty. Because the ATPI statement attributes constitute unknown parameters, ATPI should be thought of as a criterion or acceptance domain that defines the maximum decision error of measured concentration values.

Decisions concerning an analytical method acceptance against the ATPI criterion are based on estimates calculated from real experimental data and serve as an additional internal accuracy validation assessment.

When evaluating the accuracy of an analytical method, spikes of very precisely measured or “known” compound amounts (Sp_i) are prepared as individual solutions (C_i), usually at three or more concentrations. Figure 1 illustrates such an experimental run. Preparation (C_i) may be an analyte spiked into a mix of product excipients to mimic a typical product sample.⁷

While other experimental factors may also be examined in the accuracy experiment (e.g., series, instruments, analysts) and their contributions to the total variability examined, the inference is on the accuracy (*trueness*) of the method, as the reported measurement consists of well characterized (known) concentrations and not real-life samples of the drug product.

As an example of qualifying an analytical method against the a priori-defined ATP criterion, consider the following accuracy validation experiment, which consists of three spiked amounts of well characterized (known) content, with concentrations increasing from level 1 to level 3.

Values in Table A show the recovered amount of known quantities of analyte dissolved in diluent and assayed for content. The three concentration levels represent different amounts of the dissolved known ingredient. Thus, the experimental variability from concentration to concentration represents variation among standard preparations with differing levels of analyte concentration. Variability within concentration levels represents the contribution of variability attributed to weighing the analyte and pipetting the known concentrations, as well as contributions from the separation, detection, and

data analysis. We can assess this data set against the criterion defined in ATP1 to say something about the method trueness or accuracy.

Table B shows the sums of squares (derived from the data in Table A) required to estimate the random effects of the precision components. The precision is then calculated as:

$$\hat{\sigma}_{IP} = \sqrt{\frac{1}{r} \times MS_{concentrations} + \left(1 - \frac{1}{r}\right) \times MS_{preps}}$$

$$\hat{\sigma}_{IP} = \sqrt{\frac{1}{3} \times 0.0043 + \left(1 - \frac{1}{3}\right) \times 0.0553}$$

$$\hat{\sigma}_{IP} = 0.196$$

The accuracy ($\bar{y} = 99.93$) and precision ($\hat{\sigma}_{IP} = 0.196$) estimates may now be used to assess method performance against the ATP1 criterion. Confidence in this assessment may be achieved by several techniques.

Using experimental data, two statistical procedures provide confidence of meeting the a priori ATP1 criterion: the gamma-content tolerance interval,^{3,8} and the large-sample joint confidence interval.⁹ The upper $100(1 - \alpha)\%$ confidence bound can also provide confidence of achieving the ATP1 criterion. This upper bound U_{GW} for $\hat{\sigma}_{IP}$ is presented by Graybill and Wang.^{3,8} The formula is:

$$U_{GW} = \hat{\sigma}_{IP} + \sqrt{H_1^2 \left(\frac{1}{r}\right)^2 MS_{conditions}^2 + H_2^2 \left(1 - \frac{1}{r}\right)^2 MS_{samples}^2}$$

where

$$H_1 = \frac{c - 1}{\chi_{\alpha, c-1}^2} - 1$$

$$H_2 = \frac{c(r - 1)}{\chi_{\alpha, c(r-1)}^2} - 1$$

and $\chi_{\alpha, df}^2$ is the α th quantile of the cumulative χ^2 distribution with df degrees of freedom.

For this example, $U_{GW} = 0.298$, the two-sided γ tolerance interval form is:^{3,8}

$$\bar{y} \pm Z_{\frac{1-\gamma}{2}} \sqrt{\left(1 + \frac{MS_{conditions}}{rc\hat{\sigma}_{IP}^2}\right) \times U_{GW}}$$

where $Z_{(1-\gamma)/2}$ represents the $100(1 - \gamma)/2\%$ quantile of the standard normal.

Similarly, a joint γ confidence interval for the mean and variance may be used to demonstrate acceptability.⁹ Graphically, this joint confidence interval is an ellipse centered at $(\bar{y}, \hat{\sigma}_{IP})$ of the (x, y) coordinates in the ATP graph.

The equations for this joint confidence interval are:

$$x = \bar{y} + \hat{\sigma}_{IP} \sqrt{2 \frac{F_{2, n-2, 1-\alpha}}{n}} \times \cos(t)$$

$$y = \hat{\sigma}_{IP} + \hat{\sigma}_{IP} \sqrt{4 \frac{F_{2, n-2, 1-\alpha}}{n}} \times \sin(t)$$

where t ranges from 0 to 2π radians, and $F_{2, n-2, 1-\alpha}$ represents the $100(1 - \alpha)\%$ quantile of the F distribution (Figure 2).

Indeterminate of the confidence interval applied, both the joint confidence interval (ellipse) and the tolerance interval (rectangle) illustrate acceptance against the a priori-defined ATP1 criterion.

Based on observed data, an interval allows for a statement of confidence (90% in the example) concerning ATP1 acceptance. In this example, the method may be judged as accurate, since data show that the method can

FIGURE 1: PRECISELY PREPARED CONCENTRATIONS FOR DETERMINATION OF ACCURACY

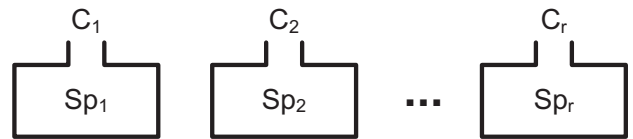


FIGURE 2: TWO STATISTICAL INTERVALS FOR RECOVERY VALUE CONFIDENCE ASSESSMENTS TO MEET AN ATP STATEMENT

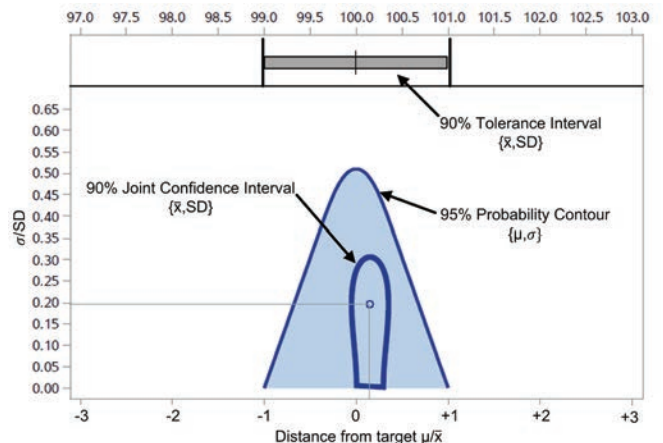


FIGURE 3: R PRODUCT SAMPLES, EACH CONTAINING K DOSAGE UNITS, TO DETERMINE A REPORTABLE ASSAY

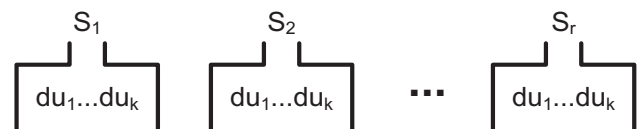
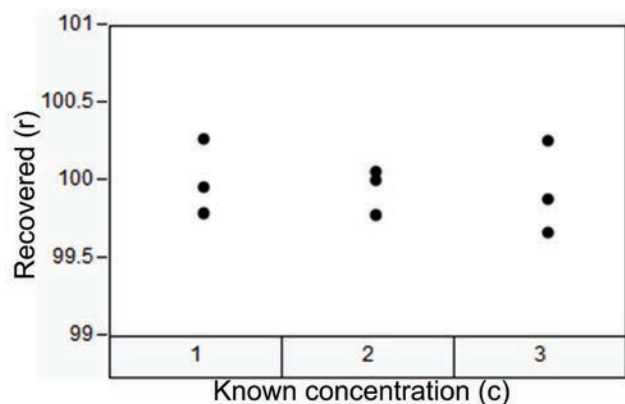


TABLE A: RECOVERED VALUES FROM SPIKED CONCENTRATIONS OF A KNOWN DRUG AMOUNT

Known* concentration	% Recovered
1	99.95
1	100.27
1	99.79
2	99.78
2	100.00
2	100.05
3	99.67
3	99.88
3	100.25

* While the true content is never really “known,” the exactness of API powder weighing and acquiescing affords an extremely precise estimate of the true content.



provide a measured amount of a well-characterized concentration within $\pm 1\%$ with at least 95% probability. Confidence in this statement, based on data generated by the experiment, is 90%.

While this example illustrates an experiment that applied an analytical method to a known drug substance, it is equally applicable to a synthetic mixture of the known drug substance and drug product excipients. In either case, a drug substance or drug product accuracy experiment, the accuracy of the method can be determined.

ATP DEFINED FOR REPORTABLE DRUG PRODUCT ASSAYS

When evaluating an analytical method to report drug product results, sample preparation includes not only the API and drug product excipients, but the dosage form itself. Therefore, any assessment used to infer method ability to elicit decisions concerning drug product reportable values should include the drug product sample. This differs from the validation exercise of assessing method accuracy as illustrated above.

DRUG PRODUCT SAMPLE PREPARATION INCLUDES NOT ONLY THE API AND DRUG PRODUCT EXCIPIENTS, BUT THE DOSAGE FORM ITSELF

The following is a hypothetical ATP statement, defined a priori to any experimental data analyses, for judging reportable assay values for a drug product.^{2,5}

ATP2: The procedure must be able to accurately quantify *compound name* in *dosage form* over the range 90%–110% of the nominal concentration with accuracy and precision such that *reportable assay values* fall within $\pm 3.0\%$ of the true value with at least 95% probability.

Like ATP1, ATP2 defines the characteristics by which the analytical method will be considered acceptable.³ The distinction is that ATP2 provides an a priori criterion to judge dosage form samples (drug product assay values) that incorporate the dosage unit sample preparation technique. Because the ATP2 statement attributes constitute unknown parameters, ATP2 should be considered a criterion or acceptance domain. ATP2 defines the maximum decision error of reportable assay values involved in lot release against specifications, stability trending assessments, and experimental outcomes in formulation or process development exercises of a finished drug product lot. Decisions concerning an analytical method acceptance against the ATP2 criterion are based on sample estimates calculated from real experimental data.

To enable inferences on reportable values,³ the precision estimate must consist of components inherent in the drug product sample and the method applied to it. Variability of the reportable drug product potency value is contributed by both the method and dosage-unit variability.^{7, 10} Other factors that may also contribute to the total variability can be assessed in an intermediate precision study, ultimately evaluating the method against the criterion defined in ATP2.

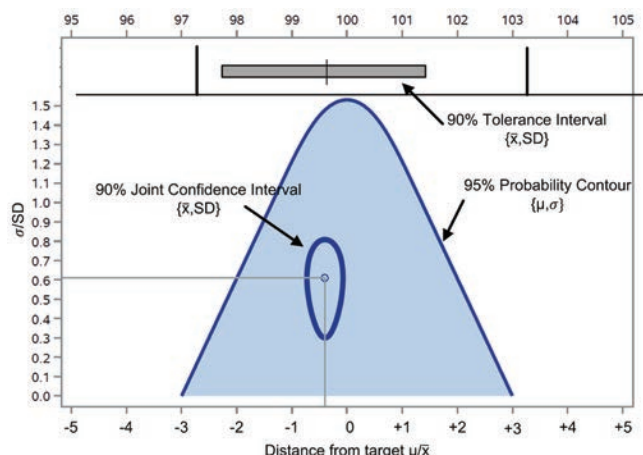
Figure 3 illustrates the sample replication component of this type of experiment. The variability of such an assay consists of the contribution of differences of the average of r product sample preparations (S), each comprising k dosage units (du).¹⁰

By replicating Figure 1 for any number of ICH Q2–defined intermediate precision components (e.g., series, instruments, analysts), estimates of these

TABLE B: SUMS OF SQUARES OF EXPERIMENTAL CONDITIONS

Source	Concentrations	Preparations	Total (corrected)
df	$(c - 1) = 2$	$c(r - 1) = 6$	$(cr - 1) = 8$
Sums of squares (SS)	$\sum_{i=1}^c (\bar{y}_i - \bar{y})^2 = 0.0085$	$\sum_{i=1}^c \sum_{j=1}^r (y_{ij} - \bar{y}_i)^2 = 0.3321$	$\sum_{i=1}^c \sum_{j=1}^r (y_{ij} - \bar{y})^2 = 0.3406$
Mean squares (MS)	$\frac{SS_{concentrations}}{c - 1} = 0.0043$	$\frac{SS_{preps}}{c(r - 1)} = 0.0553$	
Expected mean squares	$\sigma^2 + 3\sigma^2$	σ^2	

FIGURE 4: TWO STATISTICAL INTERVALS FOR REPORTED VALUE CONFIDENCE ASSESSMENTS TO MEET AN ATP STATEMENT



components can be partitioned from the total experiment variability along with the above assay method repeatability component to determine their contributions to total analytical variability.

Consider the experimental data shown in Table C, consisting of eight independent experimental conditions [combinations of analysts and instruments, (c)]; each with three product sample replicates (r). The values in Table C are the average of five dosage units dissolved in media and assayed for content. The eight experimental conditions represent different analyst and instrument combinations. Variability from condition to condition reflects variation among analyst and instrument combinations (an intermediate precision component). Variability within conditions represents variation from sample to sample. We can assess this data against the criterion defined in ATP2 to determine the method's ability to elicit risk-based decisions concerning reportable values (sample assays). This is achieved by estimating the overall average and the composition of the precision components.^{7,10}

Table D shows the sums of squares derived from the data in Table C required to estimate the random effects of the precision components.

The intermediate precision is then calculated from the random effect estimates:

$$\hat{\sigma}_{IP} = \sqrt{\frac{1}{r} \times MS_{condition} + \left(1 - \frac{1}{r}\right) \times MS_{samples}}$$

$$\hat{\sigma}_{IP} = \sqrt{\frac{1}{3} \times 0.128 + \left(1 - \frac{1}{3}\right) \times 0.466}$$

$$\hat{\sigma}_{IP} = 0.6$$

As in the first example, confidence in the analytical method's ability to produce results that adhere to the decision rule of the ATP may be calculated from experimental data.

The graph in Figure 4 illustrates the β -content tolerance interval^{3,8} and the joint γ confidence interval⁹ methods using 90% confidence as the experimental guarantee. Including the tolerance interval within the ATP2 bounds (± 3 of target) and the joint data confidence ellipse within the ATP2 probability contour parabola (shaded area in Figure 4) indicate at least 90% confidence of meeting the ATP2 criterion. Figure 4 also shows the average (\bar{x}) and standard deviation (SD) of multiple drug product samples. Since the true sample average is never known, \bar{x} inferences must incorporate knowledge gained from separate extraction studies to account for systematic method bias. Figure 4 illustrates this adjustment for an accuracy recovery estimate of -0.4% observed in a previous accuracy validation experimental exercise.

As in the previous example, the joint confidence interval (ellipse) and tolerance interval (rectangle) illustrate acceptance against the a priori-defined ATP2 criterion. This implies that a statement of confidence (90% in the example) concerning ATP2 acceptance for this method can now be made. That is, the method is capable of providing reportable values within $\pm 3\%$ label claim of the true, unknown sample value with at least 95% likelihood. Based on the data in this experiment, the confidence level is 90%. Of particular note is the proclamation concerning reportable drug product values, because the experiment was executed utilizing drug product samples, not a synthetic mixture.

While the statistical assessments in Figure 2 and Figure 4 are similar, the inference space changes. In the second example, the dosage unit variability estimates (Figure 4) reflect the contribution of the drug product sample variability to the reported potency assay variability. This indicates

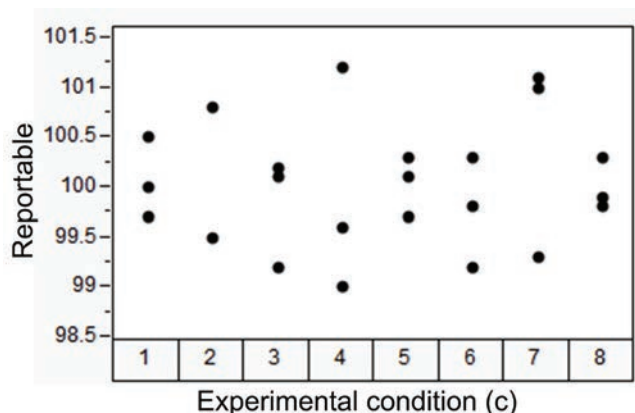
that evaluation against the ATP2 criterion helps infer risk-based decisions on the reported drug product assay value by assigning a risk threshold (probability) that the reported value will exceed a maximum distance from the true, unknown assay of the *sample*.

Conversely, the accuracy validation experiment (Figure 1) provides an estimate of variability about known spike amounts (Sp_i) that measure variability about analyte weighing and pipetting of known concentrations. Evaluating

EXPERIMENTAL CONDITIONS ARE CRITICAL FOR DETERMINING WHICH INFERENCES CAN BE MADE

TABLE C: REPORTABLE VALUES FROM SAMPLES OF A DRUG PRODUCT METHOD

Experimental condition	Sample number		
	1	2	3
1	99.7	100.5	100.0
2	99.5	100.8	99.5
3	100.1	99.2	100.2
4	101.2	99.6	99.0
5	100.3	100.1	99.7
6	99.2	100.3	99.8
7	101.0	101.1	99.3
8	99.9	100.3	99.8



the ATP1 criterion speaks to the inherent *trueness* (bias) of the method by assigning a risk of how much known standard *concentrations* may differ.

This distinction is necessary to ensure appropriate inferences concerning the measured results. The qualifying difference is the experimental conditions: By using known concentrations—as illustrated in the first example (ATP1)—the inference is to a measurement of accuracy or trueness, an ICH Q2 validation exercise to estimate method bias. This is an extremely useful exercise as the assessment of known concentrations provides the best estimate of method trueness or accuracy. While the accuracy assessment is critical to the method validation exercise, this experiment says little about the risk of inferences concerning a drug product reportable result value.³ It is equally important to assess reportable value variability as well via an experiment consisting of variance components of drug product samples, as illustrated in the second example.

CONCLUSION

The experimental conditions under which results will be generated are critical for determining which inferences can be made. Assessing measurements from known concentrations against an a priori-defined criterion (ATP) provides an additional validation assessment of the accuracy attribute defined in ICH Q2. For drug product assays in particular, evaluating drug product samples against an a priori ATP statement provides a pragmatic means for assessing the confidence (guarantee) that the analytical method will elicit reportable values capable of meeting a pragmatic decision rule—e.g., reportable values will remain with $\pm 3\%$ label claim of the true, unknown sample value. <>

TABLE D: SUMS OF SQUARES OF EXPERIMENTAL CONDITION

Source	Concentrations	Preparations	Total (corrected)
df	$(c - 1) = 7$	$c(r - 1) = 16$	$(cr - 1) = 23$
Sums of squares (SS)	$\sum_{i=1}^c (\bar{y}_i - \bar{y})^2 = 0.894$	$\sum_{i=1}^c \sum_{j=1}^r (y_{ij} - \bar{y}_i)^2 = 7.45$	$\sum_{i=1}^c \sum_{j=1}^r (y_{ij} - \bar{y})^2 = 8.34$
Mean squares (MS)	$\frac{SS_{concentrations}}{c - 1} = 0.128$	$\frac{SS_{preps}}{c(r - 1)} = 0.466$	
Expected mean squares	$\sigma^2 + 3\sigma^2$	σ^2	

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GETTING READY FOR PHARMA 4.0

Data integrity in cloud and big data applications

Toni Manzano, PhD, and Gilad Langer, PhD

The amount of data collected in a typical pharmaceutical manufacturing operation is staggering, yet research shows that much of this information is rarely used for anything more than compliance. New technologies such as big data, artificial intelligence, machine learning, and deep learning permit unprecedented analysis of real-time data and can even predict trends in processes and operations. Manufacturers can use these technologies and the information they provide to understand and improve their processes.

Machine learning (ML) can be described as a way of achieving AI through “brute force”—superfast, relentless calculation that gauges every possible option in search of a solution. Deep learning (DL) uses algorithms based on the structure and function of human learning to cascade and transform data through layers of processing. Big data technologies can store and retrieve huge volumes of data at high speeds. And artificial intelligence (AI), which can learn human activities such as planning, language comprehension, and problem-solving, offers advanced analytics to produce meaningful conclusions and predictions from these data sets. Together, these technologies deliver the information and intelligence needed for continuous improvement—one of the promises of Pharma 4.0.¹ But with them comes a question: How can we maintain data integrity, especially to support GMP operations?

Big data environments and their algorithms must be designed to follow data integrity guidelines. This requires a clear and well-coordinated effort to apply best practices to system design, including system architecture, data capture and storage, and data consumption. Of greater interest, however, is that these technologies permit a built-in, automated audit trail. This allows AI to analyze captured data and trigger alerts about noncompliance or data integrity issues.

Current pharmaceutical manufacturing has varied systems to manage GxP tasks, as well as the required data capture capability for analytics and real-time manufacturing intelligence. Yet research shows that 70% of all manufacturing data collected is not used, and that pharmaceutical manufacturing data capture operations in general have significant waste. Faced with increasing pressure to optimize, many manufacturers see the advantages of using already captured data to gain insights about processes and operations. The ability to use this data, however, given the multitude of monolithic systems, each with their own proprietary format, is not trivial. The

Industry 4.0 paradigm promises to solve many of these shortcomings with technologies such as big data and the Industrial Internet of Things (IIoT).

INDUSTRY 4.0

Industry 4.0, dubbed the Fourth Industrial Revolution, was first presented in 2011 at the Hannover Fair. This new paradigm, which began as the German government’s technology strategy, applies science- and risk-based approaches to manufacturing and process intelligence. An ISPE Special Interest Group has redefined it as “Pharma 4.0” for pharmaceutical manufacturing. Figure 1 illustrates its four main principles,¹ which demonstrate the importance of data and manufacturing intelligence.

Transforming current pharmaceutical manufacturing to Pharma 4.0 requires a new approach to manufacturing and process data capture. Big data provides a practical solution that does not require complicated integrated models and permits the use of cloud-based advanced analytical techniques for artificial intelligence. With enough information and quality content, these technologies can transform data into knowledge that supports critical activities, including process optimization, continuous improvement, operational excellence, and

FIGURE 1: PHARMA 4.0

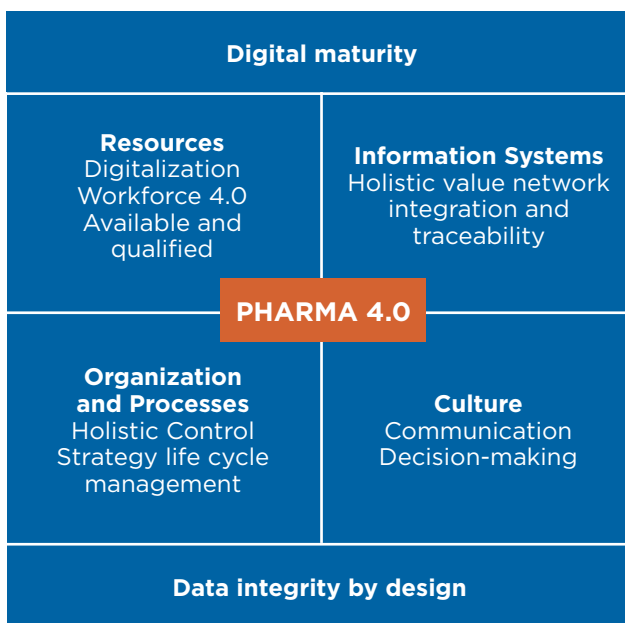


TABLE A: COMPONENTS INVOLVED IN CLASSIC IT AND XaaS SCENARIOS

	IaaS	PaaS	SaaS	Classic IT
Network	■			■
Storage	■			■
Servers	■			■
Virtualization		■		■
Operating system		■		■
Middleware		■		■
Data			■	■
Application			■	■

even real-time release. Pharma 4.0 also allows the potential for GxP decisions based on the results of AI algorithms. This makes compliance with data integrity guidelines critically important, specifically those from the US Food and Drug Administration (FDA);² the European Medicines Agency;³ as well as other relevant regulations, such as the US Code of Federal Regulations Title 21, parts 11,⁴ 210,⁵ and 211;⁶ and the EudraLex Annex 11.⁷

Other industries' progress toward Industry 4.0 has proven the value of a fully connected environment. It has shown how big data analytics can optimize operations and improve quality. The pharmaceutical and biotech industries should be able to reap these same benefits—as long as they can establish data integrity and manage it in a compliant manner.

WHY BIG DATA?

In Industry 4.0, manufacturing environments are fully connected, with every operation and piece of equipment transmitting data in real time. This includes the full plant, from devices to operational systems, across the entire manufacturing operation (work center, process cell, production unit, production lines, etc.). As a result, the amount of data collected is enormous and varied, from time series process data to complex data sets such as batch records.

Even a medium-size facility can collect between 500 terabytes to 10 petabytes of data per year. (As a means of comparison, 1 petabyte is four times the content of the US Library of Congress.) Although these numbers seem enormous, they are normal in a modern facility and will only increase as new equipment, systems, and devices are introduced. For this reason, a big data solution is necessary for storage and indexing, so that information remains accessible for historical and real time analysis.

Managing this amount and variety of data is not a trivial task, but traditional manufacturing intelligence systems are not able to do it in an effective way. The cost and effort required to maintain this volume of in-

formation along the entire data GMP workflow (acquisition, access, backup, retirement) can quickly become unmanageable. These increasingly large amounts of data require a substantial investment in data centers, backup infrastructures, and IT services. As data volume increases, periodic upgrades will incur additional costs.

But there's an alternative to these on-premise architectures: cloud-based big data services.

WHY THE CLOUD?

Cloud-based options depend on the services required:

- Infrastructure as a service (IaaS) outsources the physical hardware and the logic necessary to maintain it. Computing resources such as servers, hard disks, and the tools to manage them (regional location, data partitioning, scaling, security access, storage life cycle, and backup) are offered as a service.
- Platform as a service (PaaS) enables software development and deployment without the need to buy it. Companies such as Google, Microsoft, and Amazon are offering these types of ready-to-use components.
- Software as a service (SaaS) runs software applications on a cloud-based platform; no software is installed locally. This is very different from traditional on-site applications.

These "XaaS" alternatives provide new methods that can meet industry requirements for large data storage and computing resources at a reasonable price. They open a new way to use big data with global access, built-in security, and an inherent audit trail. They provide the necessary computation power and data storage to process huge amounts of data with AI algorithms, because they were developed for use with massive amounts of information, a critical requirement for Pharma 4.0.

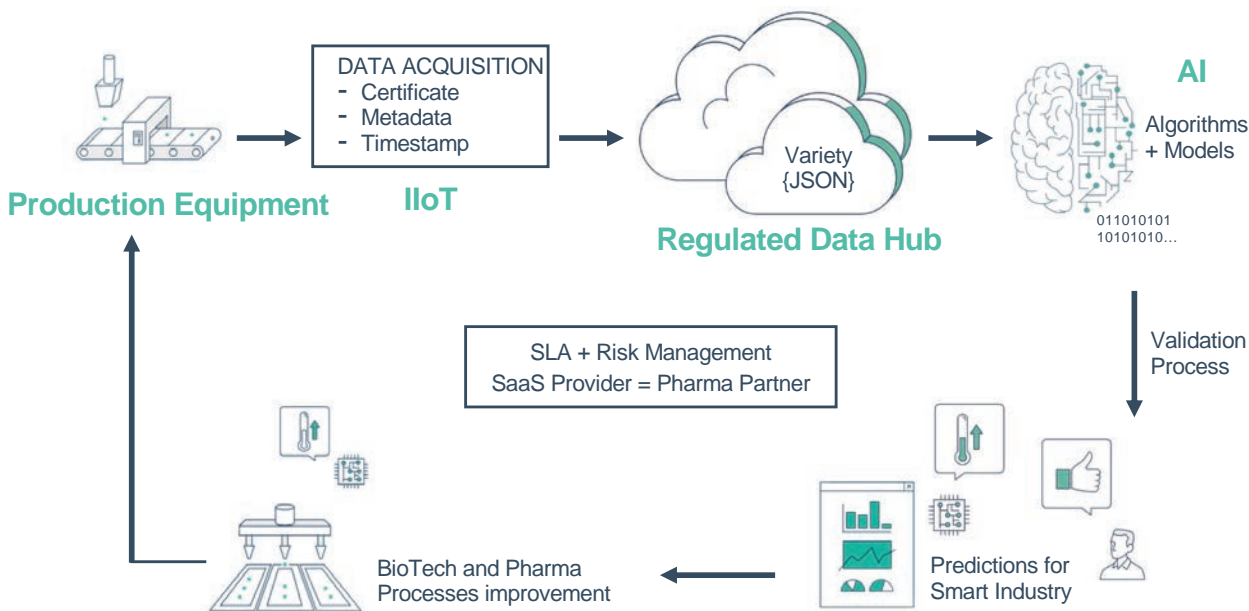
WHAT ABOUT BIG DATA AND AI?

Simply capturing data does not in itself give us knowledge. Data must be processed into information, which in turn is transformed into knowledge. This requires context and analysis:

- Big data keeps getting bigger. In the past, a terabyte was considered big data; now a petabyte is the norm.
- With growing volumes of data, classical statistical methods such as the student's T distribution, chi-square, and analysis of variance are not practical.
- The data is unstructured, with multiple formats (numerical, categorical, visual, document) that make traditional analysis methods impossible.
- The processing power required to analyze terabytes and petabytes of data is practically impossible to achieve in traditional server-based systems.

AI models, however, can analyze these huge volumes of nonstructured data using algorithms such as K-Means, Random Forest, or K-Nearest Neighbors. While these methods are not new (they were developed during the 1960s), they become incredibly useful when combined with modern cloud computing power and a vast amount of data. These three elements (big data, cloud computing, and AI) present a new way to apply science to understand the complex nature of modern manufacturing. They provide the ability to monitor production processes where equipment, devices, processes, systems, and

FIGURE 2: DATA AND DECISION FLOW IN BIG DATA ENVIRONMENT



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THE AMOUNT OF DATA COLLECTED IN A TYPICAL PHARMACEUTICAL MANUFACTURING OPERATION IS STAGGERING

operators are continuous data sources. They also set the stage for continuous process validation by making it more practical, achievable, and cost-efficient.

Current best practice pharmaceutical manufacturing analytics use statistical methods on specific control process parameters (CPPs) and control quality attributes (CQAs) to monitor product quality. In reality, however, these parameters are dependent on external and internal factors as well as their own behavior. To truly understand product quality, we need to adopt a holistic view that considers not only CPPs and CQAs, but all aspects of the manufacturing environment along with the inherent interdependencies of the process variables.

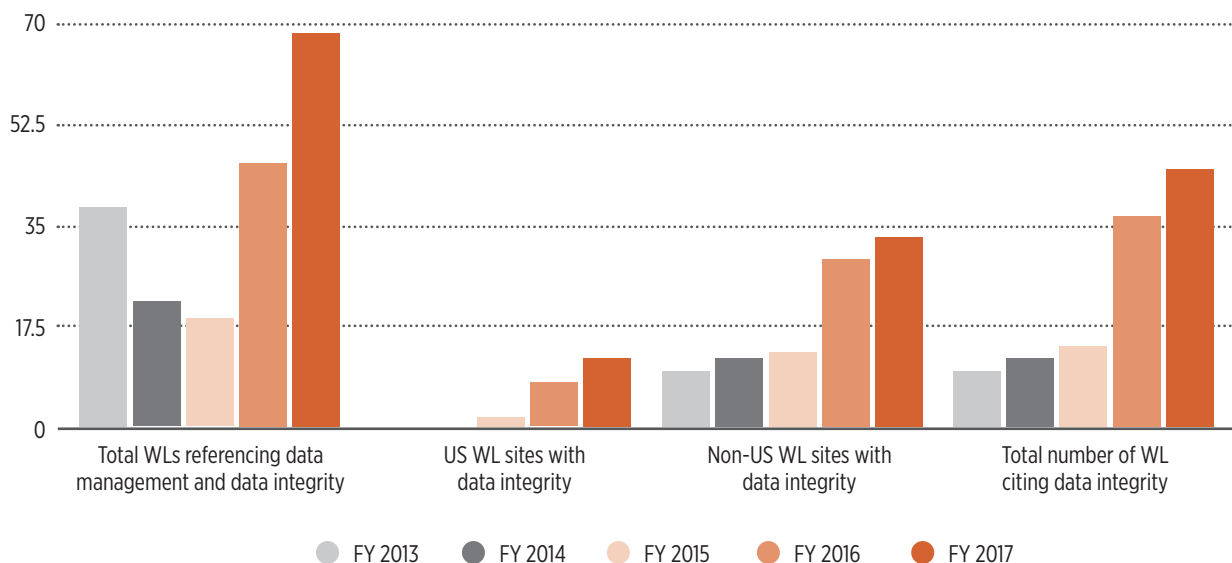
Big data with AI can support this holistic view. Their ability to find pat-

terns and dependencies beyond those that traditional statistical methods can supply provide an approach so powerful that they have been adopted in many manufacturing industries. The pharma industry already considers AI a valid tool to manage data in its research, development, and manufacturing processes. Both artificial neural networks and support vector machines have recently been proposed by the European Pharmacopoeia as valid chemometric techniques for advanced analytical methods.³

Until now, great effort has been expended to provide a common context—an integrated information model—for manufacturing intelligence solutions; this is typically based on International Society of Automation hierarchies ISA-95 and ISA-88. As noted previously, however, data stored in a big data environment is unstructured. Whatever context existed in the automation and manufacturing systems, therefore, is lost.

But unstructured data also means that there is no need to develop an integrated model. In fact, AI algorithms not only perform better with unstructured data, they can process data from multiple sources in different formats. Because context is still important to interpret the data and create AI models, future manufacturing intelligence solutions must be able to import contextual hierarchies from automation and manufacturing systems and build it as an overlay on the big data. These overlays do not restructure the data (in storage), they simply point to and set boundaries on the data. Overlays can provide multiple perspectives on data sets such as master recipe model, equipment model, product model, etc. It is remarkable, for example, how running AI algorithms to uncover causalities will detect patterns that reinforce traditional hierarchies and sometimes even point to relationships that would otherwise have been missed.

FIGURE 3: WARNING LETTERS THAT REFERENCE DATA INTEGRITY ISSUES FOR AMERICAN AND INTERNATIONAL SITES, 2013-2017



QUALITY AND SECURITY

SaaS and cloud-based solutions introduce a new paradigm for manufacturing information systems. Because there is no need to deploy and maintain on-premises IT infrastructures such as storage, servers, virtualization, operating systems, middleware, data, and applications, there is virtually no cost associated with deploying and maintaining the IT infrastructure. Table A compares the responsibilities of each component in the different scenarios.

Traditional IT applications, system architecture, data, and software are deployed on-premises, i.e., in a company’s IT physical infrastructure. In a XaaS environment there are no physical servers or storage devices; you cannot obtain a server’s serial number, and there is no need for a backup process. More importantly, the quality of the data that is captured, stored, and consumed cannot be measured or managed using the same classic IT systems approaches. Cloud computing technology can provide any required storage and computing capacity instantaneously. This concept, called “elastic computing,” offers unlimited storage and automatic scalability.

XaaS also introduces competitive elements such as pay per use, business focus, robust systems, well-protected infrastructures, automatic backups, and total workflow encryption. Current estimates predict that by 2021 more than half of the global companies currently leading in the adoption of cloud solutions will have moved all of their systems to a cloud-based infrastructure.⁸ Cloud-based solutions have demonstrated robustness and security that are far superior to traditional hardware and software designs. This is confirmed by the rapid adoption of these systems in a variety of industries such as finance, automotive, and health care—sectors that require a high degree of confidence in the technological tools.⁹

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TABLE B: ALCOA+ TECHNOLOGICAL CONCEPTS THAT WORK AS DATA INTEGRITY FACILITATORS

Attributable	PGP, certificates, MFA, geolocation, time stamp, blockchain
Legible	JSON, OCV-OCV, AI (sound, image, and text recognition)
Contemporaneous	NTP synchronization, MQTT protocol, 5G wi-fi, high data speed
Original	Data variety, encryption, self-replication across regions
Accurate	Metadata, regional settings detection, primary data acquisition
+ Completeness	No limits about data volume, unstructured information, VPC
+ Consistency	Automatic audits, full traceability, electronic inviolability
+ Enduring	Replication, persistence guaranteed by big data design
+ Availability	Internet bandwidth, geographic distributed cloud, multiplatform

Compared to other industries, however, the adoption of cloud-based solutions in the pharma and biopharma industries is lagging, mainly because of concerns related to security and quality. Qualification of these solutions (IaaS, PaaS, or SaaS, or a combination) requires a risk-based approach and reliance on the service provider’s quality systems and processes. This often challenges the traditional qualification mindset.

There is no physicality to these solutions; no system hardware, no server instances, no serial numbers, and no operator systems to verify. Operational aspects, such as the management and compliance of data and information storage or backup processes and their storage, should be delivered by the PaaS provider. Data storage and computing systems are provided on demand in a “serverless” environment. Disaster-recovery plans become simpler and faster with architectures that simultaneously replicate data and information in real time to different geographic locations (“geolocation replication”).

SERVICE LEVEL AGREEMENT

In this type of environment, where hardware and operational functions are delegated to the XaaS supplier, the service level agreement (SLA) is the end user’s—in this case the pharmaceutical company’s—control mechanism. Quality can be assured by supplier certification, audits, and periodic reviews. Using XaaS suppliers that have established life sciences business and relevant compliance practices provides a significant advantage. Not only does this

transfer most of the compliance work, but it presents less potential quality risk.

The ISPE GAMP® guidelines on risk-assessment analysis for computerized systems address some of these topics.¹⁰ The World Health Organization¹¹ also addresses cloud-based service provider quality agreements. Britain’s MHRA¹² was the first agency to dedicate an entire guidance section on managing cloud-based services. All of these organizations recommend using suppliers with specific life science certifications and governing them via an SLA. Naturally, it is also important that the pharmaceutical companies have a solid program in place to confirm compliance.

Cybersecurity, another point of major concern, often makes companies reluctant to trust cloud-based systems. Cloud technologies have gone through focused development, however, and are now considered more secure than on-premises infrastructure.¹³ They have also adopted the latest security technologies and employ legions of security experts for continuous improvement. Many of these advances have been driven by industries that take data security and privacy very seriously, such as the finance and health care sectors, when they adopted cloud-based systems.

DATA INTEGRITY IN A CLOUD XaaS MODEL

Just as the traditional qualification process must be rethought in a cloud-based XaaS model, so must the approach to data integrity. This requires a holistic quality approach based on ALCOA and GAMP principles.

ALCOA—an abbreviation for the data properties *attributable*, *legible*, *contemporaneous*, *original*, and *accurate*—is used in regulated industries as a framework to ensure data integrity. ALCOA is vital for good documentation practices (GDP), and should be considered in any cloud-based solution.

Attributable: Secured protocols and certification keys are pillars of cloud technologies. Encryption algorithms (pairs of keys, private and public keys, or the recent blockchain technologies) are designed to ensure the authenticity of the message source. Protocols such as hypertext transfer protocol secure (HTTPS) or message queuing telemetry transport (MQTT) further facilitate the attribution task by using security certificates or peer-to-peer architectures.

Legible: Big data is built on the structures that encapsulate the data. *Legibility* means that these structures are easy to interpret. A common implementation is JavaScript object notation (JSON), which organizes data in plain text based on pairs of keys and values. Because these structures include definitions of data types, they do not need additional markup as is common in XML. JSON offers a leaner interpretation mechanism that makes legibility easier and uses less computational power.

Contemporaneous: Typical manufacturing process data is collected in real time and in frequencies measured in milliseconds. Many instruments are used to ensure the high availability, precision, synchronization, and time localization of the measurements. Network time protocol, local configurations, and fast internet infrastructures ensure that the measurement is in the right “envelope” and marked correctly. Raw data can be recorded instantaneously and sent to the cloud stamped with the time at which it was collected. If connectivity is lost, communication protocols such as MQTT can delay storage while maintaining the original time stamp.

Original: Several electronic tools can verify data originality data, using encrypted certificates. Original records can be wrapped with specific metadata (e.g., unit of measure, regional settings, geolocation) that provide context. Data-transfer models such as peer-to-peer or socket communications can guarantee that data is original.

Accurate: Logic rules can check data quality at the point of capture and before storage in the data lake. The challenge is to control changes to the data, which is not available in all big data environments. Change management is critical, and features built into big data solutions should include full audit trail, e-signatures, and security.

When applying the ALCOA principles and defining risk profiles in a big data environment, it's important to understand the data flow and corresponding decision flow that are at the core of advanced analytics in this environment (Figure 2).

To support big data solutions for regulated environments, ALCOA principles should be enhanced with the additional principles *complete, consistent, enduring, and available*, a combination known as ALCOA+.

Completeness and consistency should be implemented with data definition schemas and verification protocols as part of the system design.

Enduring: Cloud platforms with automatic backup and data replication across geographies practically guarantee “eternal perdurability.” Data persistence is guaranteed as part of the data management system; each byte is triplicated in three different locations and on three different data storage systems.

Available: Data is always available within the defined retention periods, with no need for backups or data management.

Traditional checklists and assessments are not practical in a cloud-based services environment, since data technologies provide inherent mechanisms that comply with ALCOA+ principles by design (encryption, security, obfuscation, surveilled storage, access rules and rights, etc.), as represented in Table B. These systems can be qualified for a GMP environment in which data integrity is an inherent feature of the architecture. Every action and change in this self-monitoring system is stored in the GMP data lake. And here's the breakthrough promise: By applying AI algorithms to the data, the system can detect compliance levels and trigger an alert about any nonconformities. It is the same principle as continuous process validation, simply applied to the data itself.

IMPLEMENTING A CLOUD AND BIG DATA APPLICATION

Pharma and biopharma companies considering the switch to big data and cloud-based systems may be challenged by their lack of experience and best practices for these new technologies. They may also lack expertise with some of the more disruptive knowledge management features, such as AI. As a result, new strategies for qualifying and maintaining GMP and GDP have to be adopted:

- Start small to establish confidence with system quality and compliance. This is new technology, and probably unknown to most of the manufacturing organization. That makes the adoption and learning curve steeper.

TRANSFORMING CURRENT PHARMACEUTICAL MANUFACTURING TO PHARMA 4.0 REQUIRES A NEW APPROACH TO MANUFACTURING AND PROCESS DATA CAPTURE

It's critical that key stakeholders buy into the value that the new solution brings. A good practice is to start with low-friction deployments where the GMP impact is minimal. Applications for preventive maintenance, environmental monitoring, or energy savings are good candidates.¹ Other options are tasks that require repeatability and scalability. The FDA, for example, transformed report documents into digital data in a cloud-based solution with 99.7% accuracy, reducing costs from \$29 to \$0.25 per page.¹⁴

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- Establish a close and effective working relationship with the SaaS supplier. Because this is new technology for many organizations, it is imperative that all parties work together with a common goal in mind. The supplier must be fully transparent about the maturity, strengths, and weaknesses of the offered solution, understand the pharmaceutical business, and facilitate the tasks needed to qualify the infrastructure, platform, or service, as well as validate the processes. An SLA that supports a good working relationship with the SaaS supplier is important. While compliance remains a requirement, the implementation responsibility will shift to the provider.
- For services related to artificial intelligence algorithms, indexing, or aggregation processes that require specific data calculations, the provider should be ready to share the verification process used to qualify data operations. It may be valuable to consider new innovative methods for system qualification and the use of the ALCOA+ principles.
- A risk-based approach is a valuable tool when designing a big data, cloud-based solution. A good working relationship between the supplier and the organization is necessary to build trust; this is especially true for the QA organization.
- AI, ML, and DL tools must be considered standard for analytics with very large data sets, some of which have already been recognized by the European Pharmacopoeia. The results of these analytical techniques are models that can be validated with the same rules applied to traditional statistics.
- Make sure to utilize the automation and data integrity tools built into the cloud and big data infrastructure.

INDUSTRY ADOPTION

Cloud-based, big data analytics technologies are rapidly gaining acceptance in the biotech, pharmaceutical, and medical device industries. Industry 4.0 technologies have given rise to the Pharma 4.0 initiative led by ISPE. The promise of this new paradigm is consistent quality by use of a practical science-based approach. Predictions for 2020 and beyond⁸ describe the following scenarios for life sciences and manufacturing activities:

By 2020:

- Of the current AI proofs of concept in the top 50 life science R&D organizations, 20% will move into production.
- A major technology provider will provide independent digital health services directly to patients.
- Business function-led ML initiatives will be at least twice as successful as enterprise IT-led projects.

By 2021:

- Three-quarters of the top life science R&D IT organizations will create data connections and business partnerships with nontraditional ecosystems.

By 2022:

- Precompetitive, shared, and open research IT platforms will support at least 25% of life science distributed innovation environments to connect to an ever-growing R&D ecosystem.

XaaS ALTERNATIVES PROVIDE NEW METHODS THAT CAN MEET INDUSTRY REQUIREMENTS FOR LARGE DATA STORAGE AND COMPUTING RESOURCES AT A REASONABLE PRICE

Adoption is progressing at a rapid pace. There is a new energy in the industry based on data, not applications. These new technologies are not only easier to qualify, but can solve many of the industry’s current data integrity challenges. Figure 3 shows that FDA warning letters, both inside and outside of the United States, increasingly include references to data management and data integrity.¹⁵

CONCLUSIONS

As always, progress is unstoppable. Industry 4.0 technologies will facilitate a generational change in manufacturing. Digitalization with big data, AI, cloud computing, continuous connectivity, advanced analytics, and the IIoT is here to stay, and the digital manufacturing plant is becoming a reality. In the more conservative biotech and pharmaceutical industries, adoption of these breakthrough technologies is being tested cautiously. As this happens, the Pharma 4.0 concept will gain momentum, especially for the practical application of GMP within this new reality. The cloud, big data, and AI make data an asset; this offers great potential for process optimization, science-based approaches, continuous process verification, and more. The ability to move from reactive to predictive, from strict to adaptive process control creates “smart” manufacturing in which advanced information and manufacturing technologies add flexibility to physical processes.¹⁶

Current data integrity best practices and guidelines are applicable in the XaaS big data environment, where inherent data management technologies automatically monitor compliance. AI technologies that analyze manufacturing data also allow constant monitoring and risk analysis using advanced analytics to find and segregate suspect data. Continuous data capture gathers data from any manufacturing or production source with no overall structure or context. Neural networks and pattern-recognition algorithms are used to train the system about right or wrong scenarios. AI algorithms discover context and patterns to detect nonconforming behaviors, unexpected errors, and inconsistencies. Examples of these solutions have already been developed in the predictive maintenance field with successful results.¹⁷ The same predictive techniques are now being applied to detect and prevent data integrity issues.

The Pharma 4.0 paradigm has given manufacturing intelligence a new meaning. We can now truly achieve predictive and adaptive systems that manage the manufacturing process based on science. The future is here; climbing the steep part of the adoption curve should be our focus. <>

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