PHARMACEUTICAL ENGINEERING®

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TRACKING THE JOURNEY OF BARRIER TECHNOLOGY

2020 ISPE Aseptic Conference Regulatory Panel: Q&A with the FDA

Special Report: COVID-19 Impact and Preparing for the "New Normal"

Case Study: Facilitating Efficient Life-Cycle Management via ICH Q12

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2020 ISPE BARRIER SURVEY: TRACKING THE JOURNEY OF BARRIER TECHNOLOGY

For over two decades, the ISPE Barrier Isolator Survey has gathered meaningful data on the applications of barrier technology and has been a resource for the fill-finish pharmaceutical industry community. This article provides context for the latest survey, the first in several years, and presents its key results, which were first shared at the 2020 ISPE Aseptic Conference.

ON THE COVER The journey of barrier technology is represented by the concept of cleanroom hallways. Photo of an active, open RABS is courtesy of Franz Ziel GmbH.

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By Frances M. Zipp


Frances M. Zipp

The Next Normal:
Welcome to the Workforce of the Future

Since January, nothing has been normal. Nothing, especially when we try to compare it to anything we have experienced in the recent past. So how do we begin to move forward as the efforts of both the public and private sectors combine to offset the advance of the impact to businesses due to COVID-19?

As time passes, it becomes more evident to me that looking back and trying to faithfully recreate the past in hopes of finding a way forward as we emerge from the current pandemic is a recipe for failure. No, we have to prepare for the Next Normal and nimbly adapt to it as it takes shape—whatever shape that may be.

DEFINING THE NEXT NORMAL

First things first: What will the next normal be? What will it look like? How will we conduct business? How will we work together? And from where? As professionals, how will we in the life sciences move our industry forward into the future? And what will the workforce that takes us there look like?

These are important questions. And there are many more. A vast majority of them have open-ended answers. I consider a variety of possible solutions on a daily basis, especially because these questions seem to change on a daily basis as well.

What seemed a distant goal of achieving is here, right now, and for many it seems as if we are making it up as we go. And the reality of it is that, often times, we are. The idea that we could slowly and steadily begin to incorporate the principles of the "workforce of the future" into our long-term business plans has been completely disrupted in the course of a few short months. The faster and smarter we adapt and evolve, the more successful we will be.

Not coincidentally, a McKinsey & Company article published in April titled "Pharma Operations: Creating the Workforce of the Future" [1] addresses this key topic of preparing the new, next workforce and how "reskilling employees to address talent gaps can help a company retain the bulk of its operations workers and empower them to take advantage of a new world." In 2019 ISPE collaborated with McKinsey on the generation of the data and the study to support this article, long before COVID-19 was a household phrase.

The article notes note the unprecedented scale of technological disruption and how pharma is facing its own unique disruptions, such as new business models like direct-to-customer sales and personalized medicine, and new product modalities like cell and gene therapies. Their belief is that these disruptors "have created skills mismatches in more than 80% of pharma manufacturing companies."

MISSION CRITICAL

This gap, as noted by McKinsey, underscores the mission and importance of the ISPE. After 40 years, we are still fully committed to "the advancement of the educational and technical efficiency of its members through forums for the exchange of ideas and practical experience" [2]. At no time during our organization's history has it been more

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important for our community of professionals to support each other through interaction (in new and novel ways) and to share our knowledge, expertise, and experiences.

I encourage everyone throughout every organization and at every level to contribute to and utilize the resources that ISPE offers. We'll be doing our part. Although we are unable to physically gather as professionals, ISPE is offering a number of online events, including the 2020 ISPE Biopharmaceutical Manufacturing Virtual Conference "Vision for Biomanufacturing: Today's Challenges and Tomorrow's Therapies" held on 1–2 June—watch for information about other virtual opportunities, including online training courses and more ISPE webinars. These are just a few examples of the various resources available to help prepare our members and member organizations as we create the workforce of the future.

I could easily close this column by inserting an inspirational quote about the future, but that would be too easy and a cliché. Instead, I'd like to leave you with a recollection of a former colleague of mine who was always the most positive during the worst of circumstances. He viewed the predicament and uncertainty of the moment as an opportunity to evaluate his true mission and that of his organization, how well it was achieving that mission, and how to evolve in creating a more meaningful, relevant organization when all was said and done.

I see that same vision in our mission. In continuing to advance ISPE, I encourage you to join me in achieving the "next normal" for ISPE as we grow and ultimately thrive in 2020 and the years ahead.

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People for Process Automation

 By Jennifer Lauria Clark


Jennifer Lauria Clark

VIRTUAL CONNECTIONS

How is your calendar looking these days? As I write this, we have all been living a bit differently today than we were one year ago. I'll bet you have seen an increase in webinars, virtual trainings, and video conference calls, and likely having far fewer face-to-face interactions.

The ISPE Women in Pharma® (WIP) networking community hopes that you have some type of WIP event on your calendar at least once a month. Our volunteer and staff committee has been working very hard to put together programming and share lessons learned across the globe. The highly successful 2019 ISPE South Asia Pharmaceutical Manufacturing Conference on 25–27 September 2019 gave momentum to our model, and we had planned to continue the ISPE signature events in 2020. Given the change in circumstances, we have had to be agile and focus on how we can share the value of our community while remaining socially distanced.

MORE COMMUNICATION

One way to do this has been with the launch of a monthly newsletter called *The Bridge*. We are communicating information on ISPE Chapter and Affiliate successes, ISPE conference and training updates, and other career-advancing topics such as mentorships, sponsorships, and embracing workplace challenges.

Our Mentor Circles may not be happening in person, but we are in full force virtually hosting Mentor Circles around the globe. Prior to the pandemic, my company planned on starting a virtual ISPE Mentor Circle within our organization so we could include as many interested professionals as possible. We have hosted the first one, which then led to a weekly gathering of men and women to support each other through the challenging stay-at-home requirements of the pandemic.

WIP's reach has gone beyond the borders of our membership. We are touching lives of women and men globally who may not work in an environment that offers constructive feedback or shares with them why each person needs to know their value within their workplace. WIP is breaking down the barriers between continents with our virtually limitless global engagement and idea sharing.

WIP is breaking down the barriers between continents with our virtually limitless global engagement and idea sharing.

2020 GOALS

We made big plans in 2019 for 2020, and we continue our efforts to raise $25,000 for the ISPE Foundation to support other professionals looking to advance their careers. As of April, we have raised $10,000 toward our goal. If you are interested in supporting the Foundation, please reach out to me or visit the ISPE Foundation website (ispe.org/initiatives/foundation).

We are still working toward achieving 20 Mentor Circles in 2020. For more information about the value of mentorship and WIP's support through Mentor Circles, see Jeannine Hillmer's editorial in the May-June 2020 issue of *Pharmaceutical Engineering®*.

Overall, this has been a successful year for WIP. I hope you have seen an article we posted on the ISPE iSpeak blog, attended a conference (in person or virtually), or listened to our podcast. Perhaps one of our messages resonated with you, and you now have stronger knowledge of yourself and clearer understanding of the value of your network. Thank you to all our volunteers and ISPE staff who help make WIP a success. I look forward to seeing a WIP event on your calendar very soon.

Jennifer Lauria Clark is Executive Director, Strategic Development, for CAI, and the ISPE Women in Pharma® 2020 Steering Committee Chair. She has been an ISPE member since 2003.

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LeAnna Pearson Marcum

CAREER DEVELOPMENT GOES ON

I wanted to take a break from my usual column and highlight a few Young Professionals (YPs) around the world. These individuals have not let COVID-19, or anything else, get in the way of their career development. Each joined ISPE at a different time in their career and is using the ISPE Communities of Practice (CoPs) and other ISPE resources to continue their career development virtually.

CAROLINE KUSTERMANS

Senior Supply Chain Operations Consultant, PwC Belgium; ISPE Belgium Affiliate; Kustermans is YP Chair for the ISPE Belgium Affiliate and the European YP Co-chair.

How has ISPE helped shape your career? It offers me a wealth of knowledge sources for any topic in biopharma I want to dig into (webinars, conferences, *Pharmaceutical Engineering®* magazine, etc.). The ISPE family gives great opportunities for networking as well, and it has truly broadened my pharma network that I can reach out to in any situation.

How are you continuing your development during COVID-19? I'm listening to podcasts, completing webinars, studying new things in my interest field, and reading both fiction and nonfiction. What else to do with all the time, right? 🙂

Words of wisdom: Don't be afraid to "choose wrong." You'll have endless opportunities and plenty of time to explore what your true passions are and get acquainted with different functions, departments, and more within the industry. Just make sure that you have at least one "success cycle" and good learnings in every role, project, or job before exploring new horizons.

MONIQUE SPRUEILL

Senior Manager, Q&C Strategy, Insights, and Innovation, Johnson & Johnson; ISPE New Jersey Chapter; Sprueill is Executive Board Secretary for the ISPE New Jersey Chapter and an active member of multiple CoPs, including Biotechnology.

How has ISPE helped shape your career? ISPE helped with networking and meeting people who have become trusted friends. It has also helped me navigate through my career and shaped my career path.

How are you continuing your development during COVID-19? I am checking in with friends, colleagues, and associates via phone calls, text, email, Facebook, and LinkedIn. I am asking about their families and letting them know that I care about their welfare. I am also asking if I can help with anything. At this time, people need to demonstrate empathy and a genuine interest in how others may be feeling.

Words of wisdom: Build relationships with people before you need them. Get to know them and allow them to get to know you. If there is an issue you need help with in the future, you will have a network to tap into.

VAL RODRIGUES

Reaction Engineer II, Chemical Engineering Research and Development, Merck; ISPE New Jersey Chapter; Rodrigues is YP Representative on the GAMP® North America CoP.

How has ISPE helped shape your career? I have developed strong relationships with industry professionals that I have utilized throughout my career.

How are you continuing your development during COVID-19? I'm taking online webinars and tutoring online. I'm also utilizing the ISPE CoPs and literature to learn more about some of my favorite topics in pharma.

Words of wisdom: Make connections with people, not just groups, in order to learn more about subjects you are passionate about.

HEATHER BENNETT

Project Manager, ACCO Engineered Systems; ISPE San Francisco Bay Area Chapter; Bennett is Executive Board Vice President of the ISPE San Francisco Bay Area Chapter and YP North America Chair; she is also on multiple committees, including Women in Pharma® and YPs.

How has ISPE helped shape your career? I have gained and strengthened customer, business, and mentor relationships through ISPE. Mentoring helps me grow and be better able to serve my customers both in and out of ISPE.

How are you continuing your development during COVID-19? I'm checking in with friends and family more than I might normally, and reading articles and books that are beyond COVID-19.

Words of wisdom: Push yourself to have more opportunities to fail, and make sure you learn from those opportunities, regardless of the outcome.

DINA MANFREDI

Sales Engineer, GMP Systems; ISPE New Jersey Chapter; Manfredi has served as YP Chair on the ISPE New Jersey Chapter Board and as YP Representative for the 2021 ISPE Aseptic Conference.

How has ISPE helped shape your career? Making new contacts through networking and utilizing the Good Practice Guides and documents within the CoPs to aid my career development.

How are you continuing your development during COVID-19? I'm taking webinars—since most are free, it is a great time to learn new content from the safety of home.

ZEN-ZEN YEN

Head of Maintenance Operations, Bayer; ISPE Germany/Austria/Switzerland (D/A/CH) Affiliate; Yen is on the ISPE D/A/CH Board and serves as D/A/CH YP Chair, Europe YP Chair, and D/A/CH WIP Representative.

How has ISPE helped shape your career? Knowledge sharing and exchange.

How are you continuing your development during COVID-19? Webinars within the D/A/CH Affiliate.

Words of wisdom: Connect with others, share knowledge, and build your network.

LeAnna Pearson Marcum is a Senior Project Manager at PharmEng Technology and the 2019–2020 ISPE International Young Professionals Chair. She has been an ISPE member since 2009.

2020 ISPE Barrier Survey:

TRACKING THE JOURNEY OF BARRIER TECHNOLOGY

By Elizabeth J. Dorn, PE, Jessica Frantz, and Paul F. Valerio

For over two decades, the ISPE Barrier Isolator Survey has gathered meaningful data on the applications of barrier technology and been a resource for the fill-finish pharmaceutical industry community. This article provides context for the latest survey, the first in several years, and presents its key results, which were first shared at the ISPE 2020 Aseptic Conference in North Bethesda, Maryland, in March 2020 [1].

Unit operations involving aseptic processing are critical to product integrity and safety in the drug manufacturing process. The cleanliness of the environment surrounding these processes and adherence to associated standard operating procedures ensure that the drug delivered to the patient is sterile and essentially free of particulates. Aseptic processes include the filling of injectable products into final containers (in the form of vials, syringes, cartridges, ampules, and others) and aseptic formulation of suspensions or live virus vaccines that do not undergo subsequent sterile filtration. Given the current increase in other small-scale aseptic applications, including cell and gene therapy processes and 503A and 503B compounding pharmacies, aseptic barrier technology is needed now more than ever before.

ORIGINS OF ASEPTIC BARRIER TECHNOLOGY

Those new to the world of aseptic processing may take the now-mature solutions of today's robust barrier isolators and restricted access barrier systems (RABS) for granted. However, it is important to note the challenges the industry faced before arriving at the current state of barrier technology. A mix of innovation, failure, debate, improvement, and persuasion was required to overcome the obstacles impeding broad implementation.

Through the 1980s, aseptic processing for formulation and filling operations for injectable products was performed solely in traditional Grade A cleanrooms. Product protection in traditional aseptic processing relied exclusively on the unidirectional flow of HEPA-filtered air combined with good aseptic technique by fully gowned operators. Activity by operators in proximity to open processes sometimes led to product contamination.

When environmental monitoring revealed that operators were often the greatest source of process contamination, the concept of barriers emerged, starting in the form of machine guards, curtains, and other devices intended to separate people from processes. These early barriers still relied heavily on aseptic technique for nonroutine activities as well as many routine operational tasks. Thus, the initial attempts to enhance aseptic processing by implementing flexible curtains or simple guarding represented small, but inadequate, steps forward. Processes and equipment still frequently relied on operators to bypass the barriers. There had to be a better way.

By the late 1980s, barrier isolation technology for fill-finish processing was under development. It was thought this new technology could take the human factor out of this critical process step. However, obtaining approval from regulatory agencies for this novel approach could be difficult.

Trailblazing efforts involved struggles with defining appropriate and feasible levels of decontamination—i.e., sterilization

versus biodecontamination. Hydrogen peroxide vapor became the chemical agent of choice; however, in the early years of this technology, biodecontamination cycles were very long, with many lasting over 10 hours. News of the initial limitations, high cost, and challenging qualification efforts of barrier isolators led many to doubt the practicality and efficacy of the technology.

In parallel to the long-term development of barrier isolators, industry professionals recognized the urgent need to improve barriers for aseptic processing beyond curtains and simple guards. Without an isolator, how could operators be separated from the process during routine processing tasks and even during process interventions? Iterative design improvements enhanced simple machine guarding with glove ports, material transfer solutions, active air handling, and other innovations. With these improvements, a new name for a truly engineered solution was warranted: restricted access barrier system (RABS).

In the early 1990s, industry leaders worked within ISPE to establish a new platform for end users to discuss isolators and advocate for their adoption, which resulted in the formation of the ISPE Barrier Isolator Conference (now the ISPE Aseptic Conference). At this conference, the idea for a new industry group was formed: the Barrier Users Group Symposium (BUGS) [2–4]. This group—made up of representatives from Merck, Upjohn, Eli Lilly, Bayer, Sanofi, TL Systems, Despatch Industries, and the University of Minnesota—would lead the way in the adoption of barrier isolator technology in their final drug-filling operations.

To help ensure the US FDA would support barrier isolator adoption, a small subgroup emerged—LUMS. The companies involved in the LUMS subgroup (Lilly, Upjohn, Merck, TL Systems, Despatch Industries, and the University of Minnesota) worked together to build a model isolator system and generate data with media-filled containers [2–4]. In 1995, these media fill data were shared with the FDA and served as evidence that isolator technology could be used to significantly improve the cleanliness of the area immediately surrounding the drug final container closure (vial). Isolator technology increased drug safety for the patient while also reducing operating costs.

Barrier isolator technology has advanced significantly since then. Better air handling systems, shortened decontamination cycle times, and more complete validation packages are just a few of the notable advancements.

SURVEY HISTORY

Tracking the number of installed barrier/isolator systems and the evolution of barrier technology is important to end users and equipment manufacturers alike. Understanding this progression can help ensure the best technologies are considered and incorporated into all new fill-finish projects. Data about the application of the technology can also highlight gaps and areas for improvement.

The ISPE Barrier Isolator Survey, which was first established in 1998 by Jack Lysfjord and Michael Porter, has shown the trends of increasing adoption of isolator and RABS installations and evolution of the associated technologies. For 15 years, Lysfjord and Porter tracked various metrics and reported survey results at the ISPE Aseptic Conference on a biannual basis: isolator survey results were reported for 1998, 2000, 2002, 2004, 2006, 2008, 2010, and 2012; and RABS survey results were reported for 2005, 2007, 2009, and 2011 [5].

The survey results provided data on the progression of technology adoption and documented many technological and operational improvements related to the design of isolator and RABS systems. The current survey, now called the ISPE Barrier Survey, researched all barriers including isolators and RABS.

DEFINITIONS

As the design attributes of isolator and RABS systems took form, it became possible, and necessary, to refine their definitions to enable broader implementation. Understanding the key attributes of RABS and isolators, and the distinctions between the two, enables well-informed technology selection as well as interpretation of the survey data presented in this article.

RABS

An example of one of the first RABS applications in the early 1990s illustrates their role in separating people from the process for tasks that previously relied solely on aseptic technique by gowned operators.

The example operation involved collecting sterile stoppers at the discharge of a stopper processor. The discharge was located fairly low to the floor, causing the operator to lean over the discharge and block the "first air" as the stoppers were accumulated. The "first air" principle in aseptic processing is that no object shall be positioned in the unidirectional flow airstream between the HEPA filter and the critical process zone, thus ensuring that the critical process is exposed to "first air" [6]. Innovative designers provided a combination of guarding and strategic access points to keep the operator segregated from the discharge point and away from the first air while still installing a receiver chamber under the stopper processor. According to the story, when asked what this device was called, the originators said it was a restricted access barrier system, and RABS was born.

The example of the stopper processor was a step in the right direction, and the concept of RABS has progressed much further since then. The definition for RABS in the recently published draft of Annex 1 [7] is as follows:

> *System that provides an enclosed, but not sealed, environment meeting defined cleanroom conditions (for aseptic processing Grade A, but where used for non-sterile applications can be lesser grade) and using a rigid-wall enclosure and air overspill to separate its interior from the surrounding environment. The inner surfaces of RABS are disinfected and decontaminated with a sporicidal agent. Operators use gloves, half suits, rapid transfer systems (RTPs) and other integrated transfer ports to perform manipulations or convey materials to the interior of the RABS. Depending on the design, doors are rarely or never opened.*

Figure 1: An active, open RABS. (Photo courtesy of Franz Ziel GmBH.)

A well-executed RABS design emphasizes the system aspect—i.e., the RABS is an integrated and enabling part of the overall aseptic process. A RABS is not just rigid machine guarding that is opened during operation. Instead, it is a system that also includes glove ports, often rapid transfer ports (RTPs), and other features to provide operator segregation at all times and enable uninterrupted aseptic processing.

Risk assessment during RABS design determines required features and procedures that must be in place to permit nonroutine interventions. The system (machine and procedures) must enable intervention alerts and tracking, product tracking, and determination of product rejection or batch loss for various types of interventions.

The Annex 1 draft classifies RABS as opened or closed. The term "open RABS" can be misunderstood to mean that the doors of the barrier are routinely opened during operation. In fact, the word "open" refers to the way first air from the HEPA filter flows over the process and then out into the room. In an open RABS, the air typically exits the barrier through slots or grates at the bottom of the barrier. Figure 1 illustrates that the system is open in the way air flows downward from the HEPA filters through the barrier and out to the room through openings below the level of open containers. The doors remain closed during operation.

Two subsets of open RABS are active RABS and passive RABS, which are differentiated by the HEPA air supply sourcing. An active RABS includes fan filter unit(s), with fan and HEPA filters integrally mounted to the barrier frame (see Figure 2). The barrier system in a passive RABS uses the room HEPA filtration and first air supply. In a passive RABS, the top of the barrier is positioned closely enough to the HEPA supply to capture and channel the flow past the process (see Figure 3).

Figure 2: Active RABS with onboard air management [8].

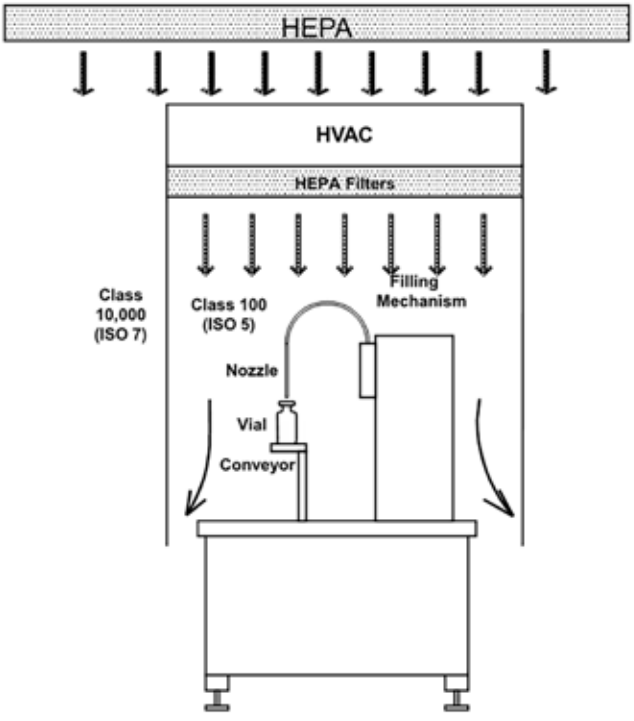


Figure 3: Passive RABS using unidirectional airflow coverage from the cleanroom [8].

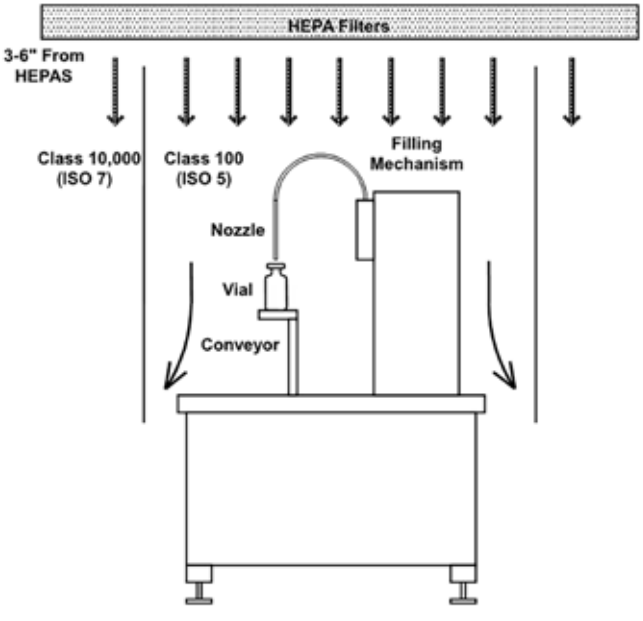


Figure 4: Example of a closed isolator. (Reprinted with permission of VanRx; photo of Emergent BioSolutions closed robotic workcell [gloveless isolator].)

Figure 5: An open isolator enabling flow of nested tubs and vials through mouseholes. (Image courtesy of Catalent. © 2020 Catalent, Inc. All rights reserved.)

Isolators

The 2020 Draft of the Annex 1 offers the following definition for isolator:

> *A decontaminated unit, with an internal work zone meeting Grade A conditions that provides uncompromised, continuous isolation of its interior from the external environment (e.g. surrounding cleanroom air and personnel).*

Annex 1 further identifies two types of isolators:

- "Closed isolator systems exclude external contamination of the isolator's interior by accomplishing material transfer via aseptic connection to auxiliary equipment, rather than use of openings to the surrounding environment. Closed systems remain sealed throughout operations." (See Figure 4.)
- "Open isolator systems are designed to allow for the continuous or semi-continuous ingress and/or egress of materials during operations through one or more openings. Openings are engineered (e.g. using continuous overpressure) to exclude the entry of external contaminant into the isolator." (See Figure 5.)

Each type of isolator has distinct advantages and specific uses. Closed isolators tend to be highly used for lower-speed, lower-volume applications, and where containment is a concern. They are operated in a batch operational scheme, and all materials for the aseptic process are either placed inside the isolator prior to biodecontamination or introduced afterward by a closed transfer process, such as an RTP or H2O2 airlock.

Open isolators allow higher-speed applications and continuous operational schemes, and can use air pressurization bubbles and sinks to accommodate containment. They typically involve integrated systems such as a vial-filling machine that receives components from a depyrogenation tunnel via a low-profile gate and discharges them to a capping/sealing machine via a small-profile "mousehole." Although the isolator is open to the tunnel and capper, proper pressurization and local HEPA coverage at the boundary openings ensure protection of the aseptic environment.

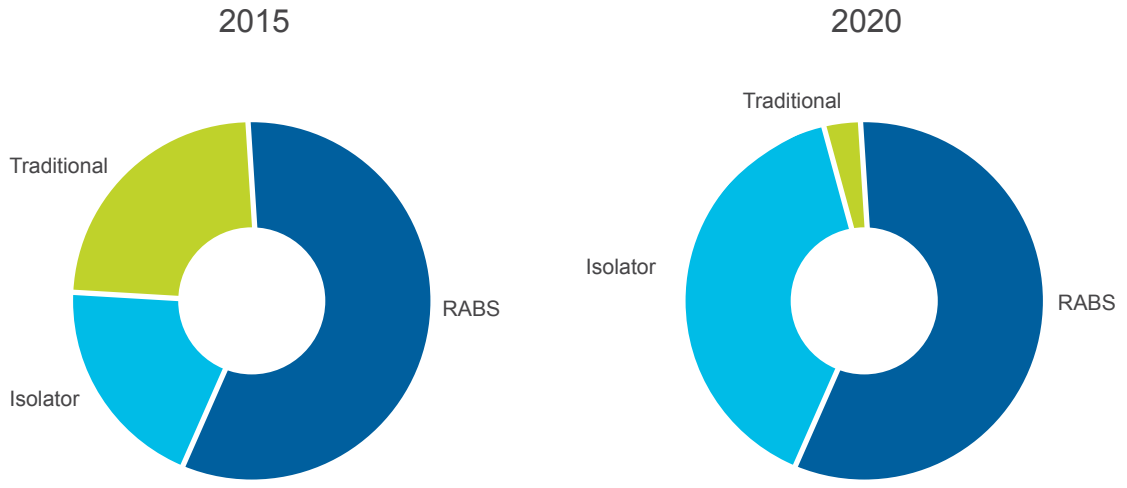
As noted previously, isolators have gained significant acceptance within the industry. Complete segregation of the process from operators and the surrounding environment, coupled with automated and validated biodecontamination processes, elevates them as the barrier method most likely to meet regulatory expectations. During FDA panel discussions at the conclusion of recent ISPE Aseptic Conferences, FDA representatives have repeatedly indicated that they expect facilities equipped with a minimum of RABS to receive less scrutiny than facilities with traditional aseptic processing setups. They said that facilities equipped with isolators are viewed most favorably.

NEW SURVEY DESIGN

Understanding the trends in both RABS and isolator designs and installations can help guide engineers working on current fill-finish projects in both old and new facilities, and help equipment manufacturers better understand market needs. Although the last survey by Lysfjord and Porter was conducted in 2012, interest in related trends continued. In 2019, a work group formed within ISPE to revive the survey and collect data from the past five years, with the intent to fill the gap and publish data on the equipment installations that occurred since 2012. The group had big shoes to fill, so its membership was composed of several industry peers with decades of experience in aseptic processing.

The current ISPE Barrier Survey group wanted the information they gathered to be as useful, accurate, and complete as possible. The group first met in May 2019 to discuss the objectives for the new survey and capture their goals in the following mission statement:

Figure 6: Installations of isolators, RABS, and traditional filling lines at the beginning and end of the survey period, showing a substantial reduction in traditional cleanroom applications.



To develop a thought-provoking survey on the implementation of RABS and isolator-based systems across a range of manufacturing scales in the pharmaceutical industry which contains relevant information to convey important trends and data to the ISPE community.

The group determined the best way to collect meaningful data would be to approach the equipment manufacturers directly, which would ensure that the collected data were representative of a broad range of applications. The group reached out to original equipment manufacturers (OEMs) known for supplying major markets across the globe. They assured the companies that data would remain confidential and would only be used to show trends, and the response from OEMs was very positive.

Once the survey group had buy-in from the OEM community, they compiled the survey questions, which asked for specific details related to the filling equipment, associated barriers, containers being filled, installation locations, and more. The group requested that survey participants provide these details for every individual project since 2015. Survey details and responses were captured and organized for analysis using a spreadsheet in late 2019. Even though this was a huge ask of the 13 participating suppliers, the response rate of over 90% was good, and data were collected on over 900 global installations.

SURVEY RESULTS

The results, representing over 900 filling applications from the participating industry suppliers, showed some interesting and welcome trends. The most relevant and intriguing results are outlined here. The presentation from the 2020 ISPE Aseptic Conference with all results has been posted on the ISPE Sterile Products Processing Community of Practice site and on the website for the 2020 ISPE Aseptic Conference attendees.

The most notable outcome was the clear trend toward the use of barrier systems and the near extinction of "traditional" cleanroom installations for aseptic filling (see Figure 6). Respondents indicated that, in 2020, virtually no systems would be delivered without a form of RABS or isolator, illustrating that the industry is decidedly moving to the use of barrier systems. This is great news for patients and product safety.

Reviewing the results, some may wonder why isolators were not used in a larger proportion of projects. The authors recognize that a contributing factor could be the common practice of retrofitting existing facilities, which frequently have Grade B infrastructures and height limitations. These projects tend to use RABS as the more economical and easily constructed alternative. Attributes of the product being filled and its associated manufacturing processes also impact the choice of RABS or isolator. Many factors should be considered when evaluating which barrier type is most appropriate to use for a project.

Trends related to fill speeds were also studied, and the data represented a wide range of unique fill speeds. Results were grouped into four general categories based on units of production per minute: less than 50, 50–199, 200–400, and greater than 400. These groupings were chosen to reflect representative industry offerings and applications. Between 2015 and early 2020, the proportion of equipment supplied by line speed remained fairly constant. Most of the applications fell in the 200–400 units per minute

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Figure 7: Installations by filling speed (units of production per minute) and region.

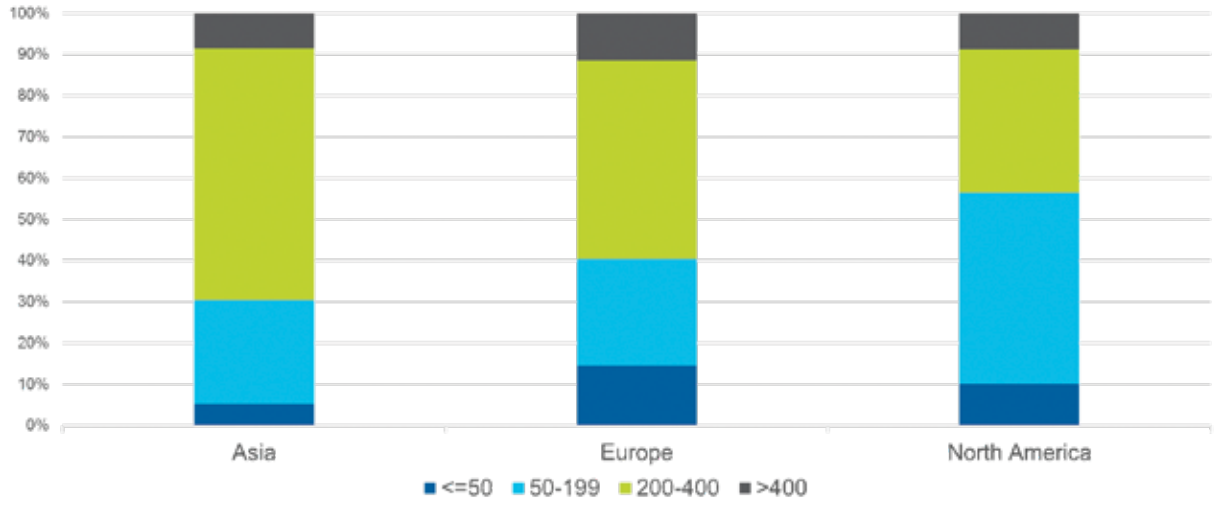
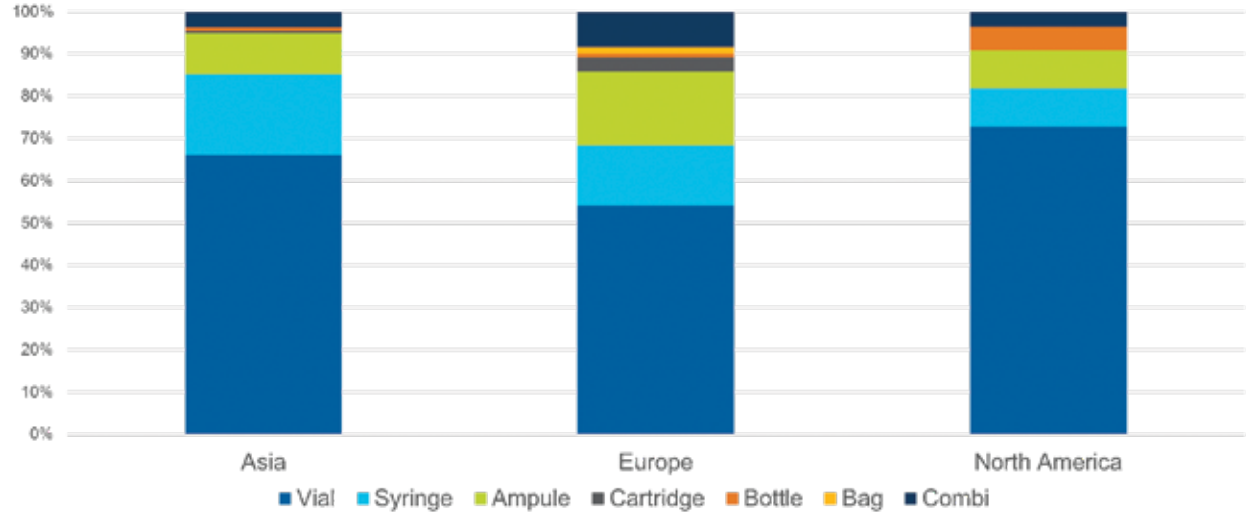


Figure 8: Container type usage by region.



range. Figure 7 shows that the North American market had a higher percentage of low-speed lines than Europe and Asia, and high-speed filling lines made up the majority of lines in the Asia market. The number of projects reported in the survey for Africa and South America were too few to include the graphing of region-related results.

The survey also evaluated final container type. Figure 8 illustrates that vials represented the majority of container types, with proportions varying slightly by region. In each region, syringes and ampules were used in about 10%–20% of the installations. Compared to the other regions, Europe installed a larger percentage of ampule fillers during the survey period. Although combination/flexible fillers, which are capable of processing more than one component type, are often discussed these days, the survey data did not include a significant number of combination filler projects.

Figure 9 shows the types of barriers used for different container types. Barrier technology was most often used for syringe applications, and isolators were used for a higher percentage of these applications compared to other formats. Syringe lines predominantly use presterilized, nested-format components in tubs that are contained in sealed bags. Use of isolators is ideal for these setups because isolators enable the tubs to be debagged in one

Figure 9: Barrier type used for vial, syringe, ampule, and combination filling lines.

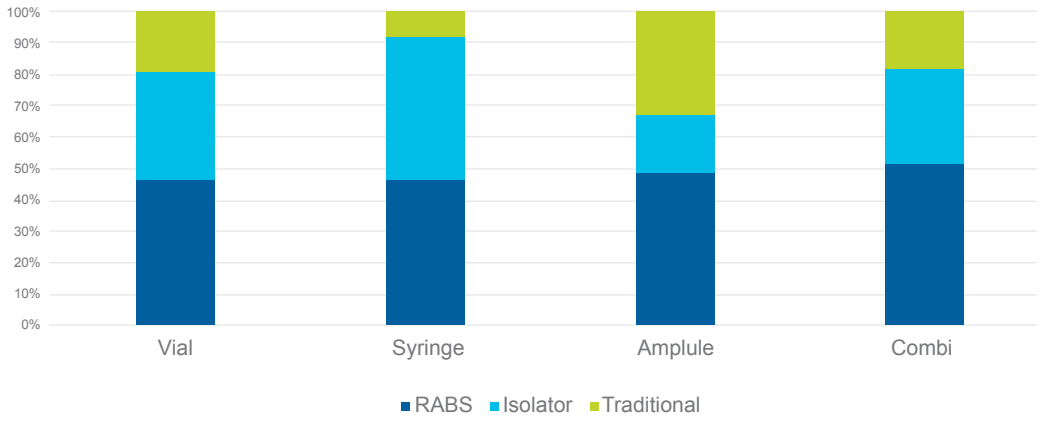
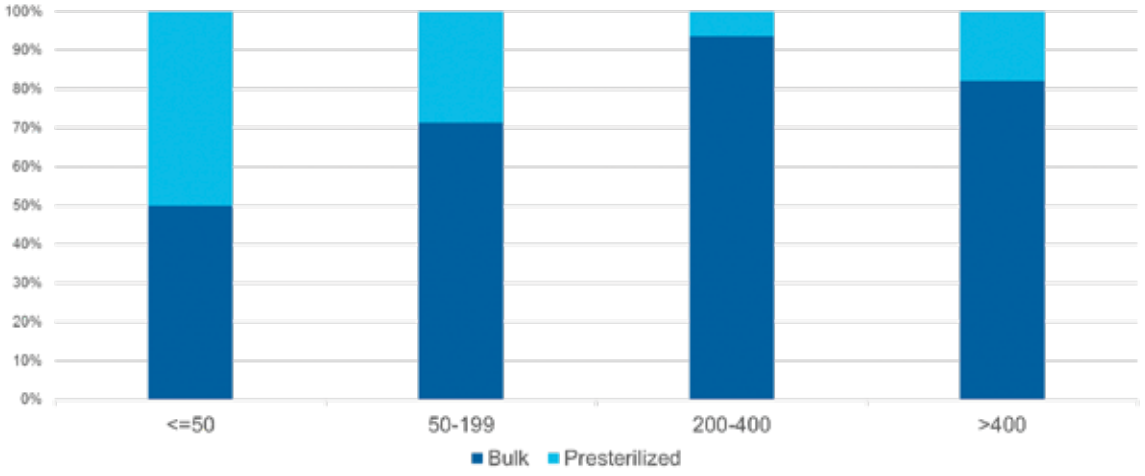


Figure 10: Incoming container treatment (bulk versus RTU) use for various ranges of filling speed (units of production per minute).



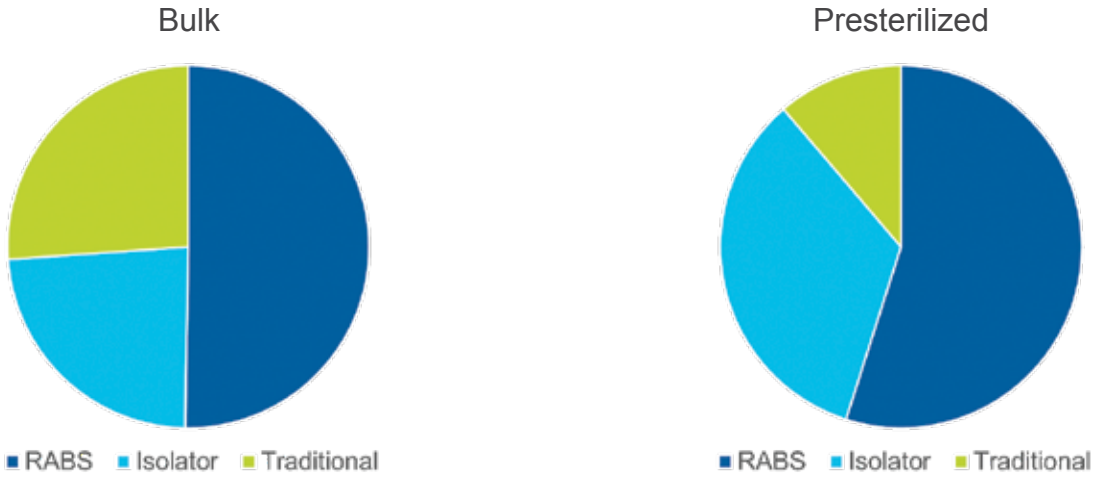
place, with the barrier technology keeping people out of the process and simplifying the transitions from Grade C to Grade B and from Grade B to Grade A.

Survey results indicated an interesting relationship between filling speed and the type of container supply format. Figure 10 compares the percentages of incoming container types—bulk containers (vials requiring use of vial washer and depyrogenation tunnel) versus ready-to-use (RTU), or presterilized, containers—for the four ranges of filling speed.

It is helpful to review several factors that influence the choice of bulk or presterilized components and also the type of barrier in which they are processed. Presterilized components cost more per unit compared to bulk components. Costs of either type vary largely by volume purchased annually. Bulk components run through a washer and depyrogenation tunnel prior to entering the filling line. Presterilized components are introduced by a controlled debagging, no-touch transfer process or through a decontamination process, such as e-beam or biodecontamination. Nearly all syringe filling applications use presterilized units, supplied in nested format. In evaluations for the choice of bulk versus presterilized components, cost implications for components, equipment, labor, utility, infrastructure, and material handling should be considered.

Considering the points above, it is not surprising to see that the highest usage of presterilized components occurs in the two slower

Figure 11: Barrier type use for production using bulk and presterilized containers.



speed ranges. Lower-speed filling lines with smaller batches and, typically, higher-value products are more often coupled with presterilized components. Bulk components were most prevalent in the 200–400 units per minute range. The increase in usage of presterilized components for the fastest range is certainly represented by filling of presterilized syringes, as it is not cost-effective or practical to run at high speeds with presterilized vials. Data also indicated that the use of bulk supplied vials remained fairly constant over the survey period, at about 80%–90% of the applications overall.

Figure 11 illustrates the tendency for production using presterilized containers to be installed in barrier systems. In comparison, traditional cleanroom installations were used for more than a quarter of for bulk component feed applications.

Results for terminally sterilized products were limited, but the available data indicated a much higher usage of RABS over isolators for terminally sterilized products. Due to different regulatory requirements for manufacturing terminally sterilized products, many manufacturers choose to operate with less-stringent microbial controls since the final process step assures product sterility.

Lyophilized products represented a small portion of the results. The data showed use of lyophilization for product preservation held steady at 20% of the applications over the survey period.

CONCLUSION

Taking part in the renewal of the Barrier Survey has been a privilege for the ISPE Barrier Survey team. The results of the survey indicate continually increasing application of barrier technology for advanced aseptic processing since 2015. Interrelationships between barrier type, line speed, region, container type, container processing, and other categories help us understand the current landscape of sterile drug product manufacturing.

Perhaps most notably, the renewed survey may have captured the approaching end of traditional cleanroom processing for new aseptic applications. Its data help us recognize how far the industry has come since the efforts of early implementers of barrier technology. This has been a journey with high hopes and some setbacks. The trailblazers in barrier technology development might be pleased with some of the survey results—and yet they would likely yearn for more, such as broader implementation of isolators, increased acceptance of data-driven strategies, and new methods for environmental monitoring. The survey team and countless industry colleagues also aspire for more.

Progress continues. Years ago, the most successful solution providers made a powerful transition, leaving behind their identity as machine builders to become innovation leaders. A select few suppliers initially gained the know-how to advance methods and offer robust solutions. Fortunately, the number of qualified suppliers continues to grow, allowing the global machine-building capacity and number of isolator installations to increase.

Progress often leaves someone behind. The impressive recent advancement in barrier technology sharpens the differences between new installations and older manufacturing technology in legacy facilities. Regulatory inspectors may observe a state-of-the-art isolator installation one week and a decades-old facility with a traditional Grade A cleanroom the next. Presenters on the FDA panel at the 2020 ISPE Aseptic Barrier Conference confirmed that legacy facilities receive a higher level of scrutiny because the

patient safety risks are inherently greater for traditional aseptic processing than for aseptic processing using barrier technology.

When some drug manufacturers implement new and improved capabilities, others feel pressured to maintain pace. Fortunately, a leapfrog opportunity is at hand for companies in need of modernizing their aseptic processes. Although the regulatory bar continues to rise, the hurdles for entering the world of advanced aseptic technology have been lowered. Thanks to work by predecessors, organizations can take advantage of budget-friendly, state-of-the-art technologies. New filling lines offer speed, accuracy, flexibility, and reliability. Isolator solutions come with well-developed H2O2 decontamination technology and glove-testing solutions, and because costs are lower, more drug manufacturers can afford to invest in barrier isolators. In addition, new compact designs enable the installation of lines in smaller spaces, including opportunities for cost-effective facility renovations.

During discussion after the presentation of the survey results at the ISPE 2020 Aseptic Conference, one attendee exclaimed, "Mission accomplished!" Indeed, the industry has achieved broad implementation of barrier technology and related process improvements. However, those passionate about aseptic processing still see great opportunity for continuous improvement. Here's to the next 30 years of innovation.

About the authors

Elizabeth J. (Lisa) Dorn, PE, serves as Director of Aseptic Technology at CRB. Completing over 28 years with CRB, Lisa is accountable as a Senior Project Manager and Subject Matter Expert. She has been active in ISPE for over 25 years and is recognized for her presentations at ISPE functions, ACHEMA, PDA, and international training courses. She pursues her passion for improving drug safety and delivery through holistic design approaches, and integrating the facility, equipment, and operational interactions. Lisa has lead projects in Asia, Europe, Russia, and domestically in the biotech and pharmaceutical industry. She holds a bachelor's degree in chemical engineering from the University of Missouri. Lisa has been an ISPE member since in 1993.

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Paul F. Valerio has spent his 27-year career in various engineering and operations roles in the chemical and pharmaceutical process industries. He earned his bachelor of science and master of science in mechanical engineering at Lehigh University in Bethlehem, Pennsylvania. Since entering the pharmaceutical industry in 2002, he has gained experience at Merck, Bristol Myers Squibb, and Telstar Life Sciences. Outside the US, he has also enjoyed conducting business in Canada, the Caribbean, Europe, and Asia. Now in his seventh year at IPS-Integrated Project Services, LLC, in Blue Bell, Pennsylvania, Paul is Director of Process Technology, where he leads a team of process technology experts and continues to directly support clients in applying state-of-the-art solutions for aseptic and high containment applications. He has been an ISPE member since 2005.

Acknowledgments

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2020 ISPE Aseptic Conference:

REGULATORY PANEL SESSION

Explores Key Aseptic Topics

By Matthew P. VonEsch and Susan Sandler

The 2020 ISPE Aseptic Conference was capped off on Tuesday, 3 March, by the Interactive Regulatory Panel session, which has been a popular feature of the conference during its 29 years. The session featured a panel of seven US FDA regulators who addressed a long and varied list of questions about aseptic processing issues, including isolator environments, glove integrity tests, artificial intelligence (AI) and deep learning effects on automated visual inspection, container closure systems, settle plates, and more.

Robert Sausville, Director, Division of Case Management, FDA/CBER, moderated the session and participated in the discussions. Other panel members were:

- Alonza Cruse, Director, Office of Pharmaceutical Quality Operations, FDA/ORA
- Richard Friedman, Deputy Director, Science and Regulatory Policy, FDA/CDER
- Christine Harman, PhD, Chemist, Review Branch 1, FDA/CBER
- Jie He, Facility Inspection and CMC Review Branch 2, FDA/CBER
- Brooke Higgins, Senior Policy Advisor, Office of Manufacturing Quality, FDA/CDER
- Zhihao (Peter) Qiu, PhD, Director (Acting), Office of Pharmaceutical Manufacturing Assessment, Division of Biotechnology Manufacturing, FDA/CDER

Sausville reminded attendees that the panel members' responses were their opinions, not the position of the FDA. Of 47 questions submitted to the panel for the session, 36 were addressed by the panelists. The following are highlights from the questions and answers.

Do you accept isolator surrounding environment to be below Grade C (CNC, Grade D equivalent) for process isolators such as for cell therapy?

Higgins referred the questioner to the FDA "Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice" [1]. One of the principles in the guidance is that the classification of the room surrounding the isolator should be based on the design of the isolator and the kind of material transfer ports or systems used. Class 100,000 in operation (dynamic) is a commonly used classification and the minimum expectation, she added.

Can FDA please reconfirm its position on PUPSIT [preuse, poststerilization integrity testing of filters] as compared to that put forward in the commenting of Annex 1 in 2018?

Friedman said that the PUPSIT position in the FDA aseptic guidance is not in disharmony with Annex 1 [2]. The FDA guidance states that PUPSIT of filters can be done prior to processing, but a postuse integrity test should always be done. The draft Annex 1 (current version) indicates that pre- and postuse testing should be done, but, based on risk assessment and practical considerations, the manufacturer may be able to justify only postuse testing. "Guidance documents can be equivalent, but they will not necessarily be identical,"

Friedman said. Expectations are that the FDA's guidance and the Annex 1 currently out for comment will remain in harmony.

How does FDA control accuracy of glove integrity testing? Which hole size should be tested?

The FDA expects a robust testing device to be used, Friedman said. A specific hole size is not necessarily prescribed, but the device needs to be sufficiently sensitive (50 or more microns is used by some vendors; efforts should be made to use a lower sensitivity, if possible). Automated integrity tests are better than the human eye and more reproduceable, he said. "It is important to have a robust glove integrity testing device that will reliably detect holes in gloves, as nonintegral gloves can pose a critical risk to product sterility."

FDA participants at the Interactive Regulatory Panel session (left to right): Zhihao (Peter) Qiu, Alonza Cruse, Jie He, Brooke Higgins, Christine Harman, Richard Friedman, and Robert Sausville.

Qiu added that it is really important when using automated equipment that the equipment is qualified to detect leaks.

FDA will update the 1999 guidance on container closure systems. Will the updates provide guidance [on] container closure integrity testing and when it should be done in development and manufacturing?

Mr. He said the FDA began to develop new high-level guidance for container closure systems late last year, and work continues on this high-level guidance that will replace the current guidance, "Container Closure Systems for Packaging Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Documentation" [3].

Mr. He noted that subguidances will be addressed after this is completed, and the high-level guidance will provide recommendations regarding the data to be provided to support the container closure system, including data to demonstrate container closure integrity.

Harman added that the umbrella guidance will provide general information and will have limited information regarding container closure integrity testing for specific products, and that the purpose of the subguidances will be to supplement the high-level guidance, providing additional recommendations with regard to container closure systems for specific products that are out of the scope of the high-level guidance.

With the advancements in AI and deep learning on automated visual inspection, do you believe it is plausible that groups could use virtual libraries for teaching equipment or training inspectors?

Sausville responded that these developments could be used for training, but the FDA still expects operators to visually inspect real vials as part of the training before they are qualified to do it in-line with actual product.

Friedman noted, "As a general statement on AI, software is designed by humans. Different circumstances and combinations of variables are considered by software developers in simulating or predicting situations. This is a higher-level comment on AI, but there still is no substitute for the human element of quality management when it comes to knowing what software is doing, understanding algorithms, and what decisions can be made under conditions not predicted or practically simulated by modeling. AI will most definitely advance manufacturing in many respects. But for qualifying or validating personnel practices, there generally will be nothing better than final evaluations of the operation in practice in the actual production environment—this will ultimately be the most direct study and measure of true capability." With that said, Friedman continued, the FDA would like to see AI leveraged for training. "AI is very promising—and machine learning is, too—for atypical interventions, for example. But for qualification and quality management, you cannot cede the responsibility to software."

Sausville added, "One of the most compelling things that came to my mind had to do more with small-scale [products] we are seeing at CBER and visual inspection of those. Not necessarily AI, but the optics used for AI could be used to enhance the human visual inspector to visualize what's in that vial. Less eye fatigue could be a good way to enhance that."

Qiu noted that a lot of unknowns can come up that the system is not used to seeing. "How are you able to teach the [AI] system how to catch the unknowns?"

What do you think about an opinion that settle plates are not meaningful for environment of UDAF [unidirectional airflow] and active air samplers are suitable for effective monitoring considering the recovery rate?

Sausville said that the FDA has allowed the use of settle plates for many years, and continues to do so. "Would active air samplers be

> "Guidances do not have to be the same to be equivalent and in harmony."

more effective? Probably so. We would rather see those as long as they don't impact the environment of the filling area, the aseptic area." See the FDA aseptic processing guidance [1], section X.A.4, for more detailed information on the preferred use of active air monitoring devices and discussion of settle plates.

What do you think about employment of video recording in isolators for process control? There's a company that utilizes video recording of glove operation, environmental monitoring, etc., for ris[k].

Higgins said, "Video recording is only going to help you. We want to encourage the use of it. We've seen it aid firms in investigations if something has gone wrong; it is easy to pull the video and see what operators were doing. Beyond the isolator, it is also helpful in sterility testing in isolators and investigating cleaning issues."

What are the expectations for lyo[philization] process validation in terms of at-scale lyo runs requirements? Can the boundary studies be performed at lab scale instead of manufacturing scale?

Harman said the expectation for process validation is ideally three runs at the maximum load and one run at the minimum load performed at target operating parameters (shelf-temperature, chamber pressure) and with extended sampling. Regarding boundary studies performed at small scale, these studies could be used to leverage the at-scale process validation, provided that there is a comprehensive understanding of the differences in the lyophilizers and the scale-up. The scale-up can be affected when considering different lyophilizers (lab scale vs. commercial scale); these changes include changes in the vial heat transfer coefficient as a result of the changes in the ratio of center to edge of vials on the shelf (geometry of the lyophilizer) and differences in the radiation of the walls of the lyophilizer (differences in the materials of construction and thermal history). Additionally, the design of the lyophilizer in relation to water flow capability and differences in process parameters should be considered. She indicated that the FDA is amenable to the use of leveraging boundary studies performed at small scale to support process validation, provided there is extensive supporting information (i.e., modeling that takes into account the effects of scale-up between lab-scale and commercial-scale lyos).

Annex 1 draft has been released. As part of PIC/S [Pharmaceutical Inspection Co-operation Scheme], how will FDA consider implementing this GMP document in the US?

Friedman said the FDA is on the work group at PIC/S that inputs into the EU's Annex 1. "Through that venue, we have endeavored to maintain equivalency, and I think our group has been successful. As mentioned, guidances do not have to be the same to be equivalent and in harmony. The aseptic guidance covers topics that are not found in Annex 1, and vice versa. Annex 1 also addresses terminal sterilization. But they are complementary guidances. Regulators can provide more specificity on certain topics that they have found need further articulation of GMP expectations, but while there may be differences in depth of coverage of some topics, the two guidances work hand in hand. They are interchangeable. We'll be on the committee through PIC/S for further input as Annex 1 ultimately moves to the finalization stage."

Can you please share your experience with the Mutual Recognition Agreement (MRA) between the US and the EU up to now?

Cruse noted that the FDA signed the MRA with the EU in November 2017. Capability assessments were undertaken from then through July 2019 with 27 countries (originally 28 because the United Kingdom was part of the EU at that time), and the EU did a capability assessment of the FDA. Cruse said that since November 2017, the FDA has been requesting reports for sites from its risk-based selection model. "We are performing analytical review of the inspectional reports. We are using the reports from EU countries for decisions on things like on classifying an inspection or whether a site is cleared for application for marketing products." Only surveillance inspections are included now, he said, but future uses under consideration are preapproval inspections and possibly vaccines and biologics at some point. Progress is good, he noted—the program is maturing and starting to take a deeper dive into more provisions. "I should add that as we are reviewing and classifying, [we are] also sending classification letters back to the companies that we deem acceptable" based on the inspection results of the local European authority.

What is the current regulatory expectation for 02 headspace monitoring? Is the expectation that 100% of vials are monitored? Is high stopper detection required/expected?

Most firms are monitoring headspace, but 100% monitoring is not generally a requirement, Mr. He noted.

However, stopper position should be checked during 100% visual inspections. Further, automated stopper height detection devices are also common.

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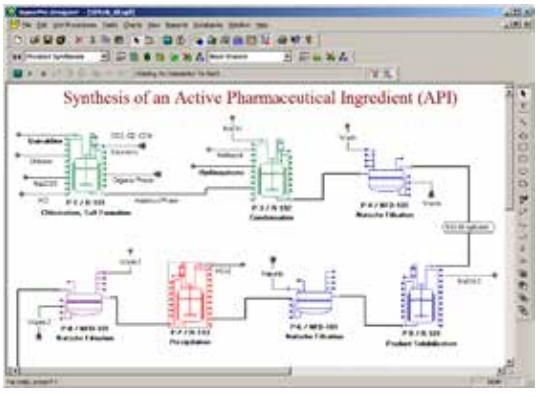

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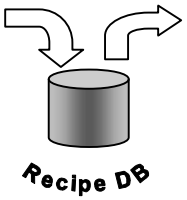

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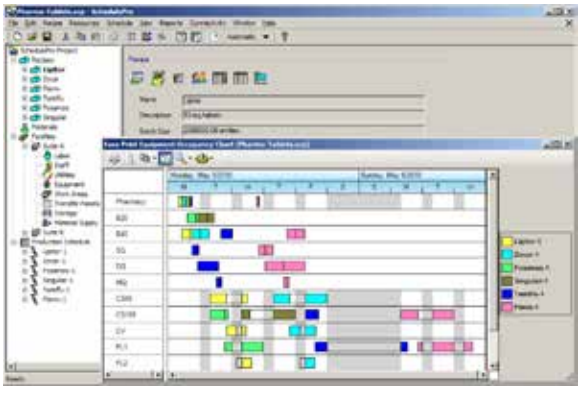

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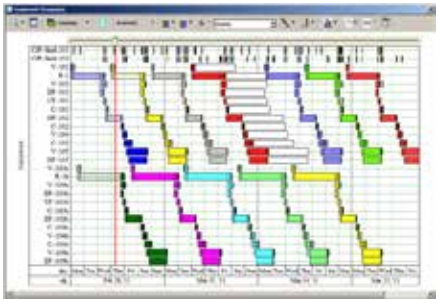

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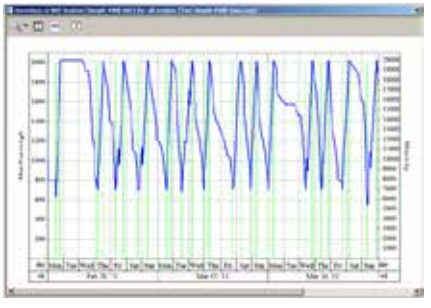

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Qiu added that in measuring for syringe stopper positions, it is also important to assess stopper position after shipping, especially if air shipping, because the stopper may move and could impact the sterile boundary.

Particle recovery in low concentrations makes recovery at >5 microns inappropriate. In Annex 1, this is recognized in classification but not in monitoring, hence no alignment with FDA guidance. Is this an issue?

"We were not seeing a lot of problems with 5 microns, so we were silent on the matter in the aseptic guidance," Friedman said. "Industry in the EU believes that the original 5-micron particle value in Annex I was too stringent and triggered too many investigations, so ultimately the limit changed. I know that folks struggled with coming up with an exact number. At your company, 29 or 10 or 15 might be highly abnormal. Bottom line: the overarching position is aligned between regulators—the HVAC system must provide for highly controlled environmental conditions that prevent contamination." He added that significant levels of 5-micron particles would be abnormal and could signal that there is something to worry about.

What are requirements for use of surrogates in DP [drug product] fill-finish process? Specifically, if surrogate is used for lyo studies, mixing studies, etc., due to limited availability of drug substance (DS).

Sausville noted that for fill-finish processes, media simulations are nothing but surrogates.

For the second part of the question, Higgins noted that surrogate usage may be allowed during early development activities; however, "once there are PPQ [process performance qualification] batches, we expect actual drug product would be used."

Qiu added, "In CDER, when we are observing the manufacturing process during an inspection, in general we prefer to have actual product. But if you have justification, and the surrogate has a similar manufacturing process, we will consider it to support an inspection. In supporting data as part of process validation for commercial, we expect actual product. Early on, you can use a surrogate. When you submit the application, you must submit validation data to support commercial manufacture of the product. I'm not sure how a surrogate could be used if it is not the product you intend to license."

Can you give an update on the New Inspection Protocol Project (NIPP)? How are the protocols working? Will they result in different ways the agency reports inspection data?

The new protocol has been in use for about two years, only in sterile dosage forms, both domestically and internationally, Cruse said, although other dosage forms are being worked on. He added that he hopes there will be pilot testing of these later this year. The use of an intelligent questionnaire, a dynamic tool to help gather and structure data, is part of NIPP; however, Cruse emphasized, it does not replace the investigator role in searching for and looking at critical information.

"Our inspections tend to look for deviations or things that are out of place. NIPP will allow FDA inspections to highlight areas that may exceed quality best practices or a new way of achieving higher levels of compliance."

Through the entire process, including pilots and every time an inspection is done, the process seeks feedback from the investigator to make NIPP more useful. The number of questions has been reduced, and the FDA is looking at using the questionnaire in conjunction with a tablet.

"Where we are now, it is moving quite well, and we are looking forward to additional feedback from investigators," Cruse said.

What is considered a robust validation strategy for validation of a process with the option of using 1 of 3 identical lyo units? Is one run per a lyo required?

Harman said the expectation is to perform three runs at the maximum loads, and one run at the minimum load in one lyophilizer, and one run at the maximum load in each additional lyophilizer, provided that the lyophilizers are demonstrated to be identical. However, the FDA is open to discussion on this validation strategy on a case-by-case basis.

The 2020 ISPE Barrier Survey [findings were shared with Aseptic Conference attendees] indicates that filling lines sold [from] 2015 to 2020 predominantly use barrier tech. Will FDA continue to encourage modernization of legacy facilities? How?

Friedman noted the FDA's commitment to innovation and applauded the industry for the strides it has made. "When you look at innovation and modernization, and the objectives of ETT [the FDA's Emerging Technology Team], one can be generally optimistic if you view the sterile drug industry evolution over the last 20 years. The uptake of innovative approaches is largely a success story. Twenty-five years ago, maybe 1% of manufacturers were implementing isolators. Here we are in 2020, and the majority of companies now have RABSs [restricted access barrier systems] and isolators," he said. "Although there are still some antiquated processing lines that need upgrading, industry has done a nice job overall at modernizing," he continued, recognizing ISPE's contributions via the conference and other work. "The FDA has not stood in the way of innovation, and we have all shared practical experiences, so folks were aware of new considerations and possible failure modes. Our transparent discussions have demystified the new technologies over the years, and they have helped promote wide implementation."

Friedman said the FDA seeks to provide consistent information through this panel and other means. "The transparency has made a big difference on both our parts—you share your practical, scientific, and business learnings with the FDA, and with each other, at these conferences. This has been the single most important conference in the industry for isolators and RABS technology. And we share our perspectives, and continue to encourage modernization of legacy facilities. We have had recent warning letters

following 483s by our investigators that show that legacy aseptic processing facilities continue to have some major manufacturing problems."

The FDA's compliance program for sterile process inspections, which can be found online, is a good resource to understand the FDA's risk-based inspection approach at sterile facilities. This program says most inspectional scrutiny will be afforded to manually intensive processes that have less automation, as well as those without contemporary barrier technology. Inspectors will also look for indicators of sterility, line performance, and other factors as they evaluate line capability. Overall, there will typically be more time spent inspecting the legacy lines.

When will FDA prohibit use of traditional cleanroom fill-finishing facility [facilities] and make at least RABS mandatory?
"Anything that does not demonstrate robustness will get a lot more attention," Friedman said. "Open lines that allow direct manual intervention are risk laden." He added that in the early days, industry was not sure if RABSs and isolators could work for the smaller niche operations, but the technology has evolved to the point where basically any aseptic operation can be done using these barrier technologies.

At what clinical trial phase is final filter validation appropriate in cell and gene therapy manufacturing? In many cases, there is very little product available to do something like this too early.
"I can't imagine filter validation for cell therapy," Sausville said. "In gene therapy, clinical trial begins and we expect product to be GMP compliant; this is going into people, so we want to be sure they are not put at risk by the product."

Harman said, "Typically with these type of products, early in IND stage we would expect sterility of product whether or not sterile filtered or performed aseptically from beginning to end. Safety is priority in Phase 1."

If a batch passed inspection with low reject rates, does the FDA require particle analysis/identification if a single particle is found during AQL [acceptance quality limit] inspection?
Friedman said, "Whenever possible with visible particles, you want to know what that particle is. Hard to prescribe here—we don't know the whole story when you ask these questions. We don't know the scenario. AQL is hopefully going to give you a pass with flying colors. So the aim is, of course, for the final AQL check to not find units with visible particles in your injectables." This would indicate manufacturing and 100% inspection were successful. But, with that said, there may be some low tolerance for intrinsic particles, and that is discussed in USP <790>.

Qiu added, "How your company handles particle identification is important. Extrinsic/intrinsic? 100% ID? If you found particles during AQL, ask, 'Is this intrinsic or extrinsic?'" Particle size and why it was missed during visual inspection are key considerations. He noted that the FDA is working on a draft guidance on visual particles. Friedman noted that GMPs and USP <790> do not consider extrinsic particles (e.g., cardboard, skin, and other worrisome foreign particles have been identified in recalled injectables in some unusual cases) in an ISO 5 environment to be equivalent to "intrinsic." Intrinsic particles are inherent to the product, while foreign particles have infiltrated the ISO 5 environment or container-closure system and should be strictly avoided.

"There will be clear efficiencies and advantages with well-designed robotics. But don't change expectations on asepsis."

Is it necessary to autoclave stopper bowls and tracks when using an isolator filler, where bowls and tracks are sterilized via VHP [vaporized hydrogen peroxide]?
Sausville noted that FDA guidance says that if something can be autoclaved or dry heat–sterilized, it should be. Friedman added there is need for justification if you do not do this.

Is it necessary to autoclave gloves in open RABS after each batch operation or change over for aseptic filling?
Some firms do, although a few days between sterilizations could be justified in some instances, Friedman said. He added that some factors that can be considered in determining appropriate procedures would be whether that door is opened at all, and whether the RABS is kept closed after aseptic equipment setup or the ISO 5 zone is accessed through doors during operations, since this will affect exposure and risk. So, definition of appropriate practices can be determined case by case, depending on how the RABS is operated. Because of cumulative risk, the manufacturer may have to justify not sterilizing each batch, and you will be decontaminating between batches no matter what.

How concerned is the FDA about robotic end-effectors (robot "hands"), which are autoclave sterilized, which break first air over sterile product or components? Does the FDA care?
"You wouldn't want to break first air; you would want to use aseptic technique," Friedman said. "There will be clear efficiencies and advantages with well-designed robotics. But don't change expectations on asepsis. People should not have a false sense of security that robotics, or isolators, will prevent contamination no matter what you do. There are specific considerations that apply to robotics. With

robotic arms: Are they sterile? How well are the arms maintained to be sure they aren't contaminated?" Friedman and Sausville agreed that more details would be needed to respond to the question.

What is the status of FDA Quality by Design and process analytical technology initiatives? Are we still 20 to 30 years behind other process industries?

Friedman observed progress with these initiatives and acknowledged ISPE's Facilities of the Year awards as highlighting innovation. "Industry has made some major progress with designing quality into facilities and processes in recent years," he said. He also mentioned, in addition to sterile operations, there have been several exciting approvals for continuous manufacturing. "There is still a long way to go for all dosage forms in this industry. But the journey continues! Sterile in particular has seen a lot of innovation. Please keep it going."

What is the FDA position on media fills for different fill-finish sizes but the same product? Is matrix approach acceptable? Or is FDA expectation 3 media fills per presentation?

A bracketing approach covering the smallest and largest vial sizes is acceptable with justification, Mr. He said. Harman added that the bracketing approach should include three runs per representative vial size considered as the worst case. Typically, this includes the smallest and largest vial sizes (i.e., containers with widest diameter openings or containers requiring increased manual intervention due to instability in line operation). After the initial validation, the vial presentations can be used on a rotating basis in the semiannual media simulation run. See the FDA aseptic processing guidance [1], section IX.A, for more detailed expectations.

When will aseptic guidance be updated?

"We wrote the guidance to be technology independent as much as possible to accomodate future innovations," Friedman said. "We did an annex on isolators because industry asked for it to help to establish clarity on the basic GMP standards for that technology. But our intent in general was to include principles and practices that can be widely applied and that accommodate a lot of new technologies and beneficial approaches. Right now, our priorities are the annual agenda: Microbiological considerations for nonsterile drug products is the subject of one of the guidances that we hope to issue by the end of 2020." He encouraged attendees to let the FDA know about what updates are wanted in a future aseptic guidance revision; he predicted that robotics could bring an update in coming years as they start to be more frequently used.

For plunger rod placement in syringes, there is always the question of potential stopper/plunger movement or rotation. What is the FDA's view on this point?

Qiu said that the manufacturer needs to demonstrate that movement and condition do not impact the sterile boundary; some movement is expected, but the manufacturer needs to show this will not impact the sterile boundary.

Follow-up question in regard to the plunger rod placement in syringes: Should the media simulation incorporate plunger rod placement?

The panel said it depended on whether this had an aseptic impact. Qiu said, "If we are talking about stopper movement, there should be separate studies because boundaries are defined by stopper and syringe size."

Can you give an update on program alignment? How is it progressing, lessons learned, and plans for future?

Cruse provided the response, noting that since May 2017, the FDA in its drug program has been "working to integrate in all aspects of the pharma space in what we do. A number of committees are working together, joint problem-solving, working on creation of things like site-selection modeling, integrating and working on user-fee negotiations and other things, and working to build content of operations to define roles, responsibilities, and more-efficient operation in the pharma space." He said a lot of progress is being made, and a number of key performance indicators are monitored for continuous improvement.

DISCLAIMER

This is an abridged, unofficial summary of US FDA regulators' responses during a panel discussion at a conference. While individual panelists have reviewed this content, the content of this article does not represent official guidance or policy of the FDA.

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Pharmaceutical Engineering® COVID-19 Impact Survey:

HOW THE INDUSTRY IS RESPONDING TO THE PANDEMIC

By Susan Sandler

As the COVID-19 pandemic continues, pharmaceutical companies are taking steps to address the short-term consequences while also preparing for what may be the long-term effects for the world, individual nations, and the pharmaceutical industry. In late April and early May, *Pharmaceutical Engineering* surveyed over 50 ISPE members who hold leadership positions within the Society about the pandemic's impact. This article shares highlights from their feedback.

Respondents included members of the ISPE International Board of Directors, Chairs and Co-chairs of Communities of Practice, and Chairs and Co-chairs of major committees such as the Guidance Documents Committee, Regulatory Steering Council, Knowledge Network Council, and *Pharmaceutical Engineering* Committee. They were asked to complete an email survey about COVID-19's impact on their organizations to date as well as thoughts about what may lie ahead for the industry. Almost 40% of those invited to participate responded. *Pharmaceutical Engineering* thanks the respondents for taking time to share feedback. (Note: Some participants asked that their comments not be attributed to them by name or company.)

The survey questions were:

- How has business changed for you because of the COVID-19 pandemic?
- What are your biggest concerns coming out of COVID-19 pandemic isolation/social distancing protocols?
- What are the greatest concerns you hear about from your teams?
- What changes for the better do you see as a result of lessons learned from the pandemic?

OVERVIEW

Respondents shared views from both a personal and a leadership perspective in their organizations and the pharmaceutical industry. One clear trend from their responses is the deep commitment of the industry to helping patients worldwide. Manufacturers, equipment providers, and consultants are not only dedicated to the development of COVID-19 tests, treatments, and vaccines, but also focused on ensuring that all medications continue to be available under these most extraordinary circumstances.

Concern for team members who are working remotely and those who must remain in manufacturing and lab settings was another common theme in the respondents' feedback. They are prioritizing communication with both remote and onsite staff and looking for ways to address the work, home, and health pressures of the pandemic on all employees.

BUSINESS CHANGES

Employees working remotely, postponed or canceled travel, and meetings via various technology platforms have rapidly changed how work is done by many respondents and their organizations. Although some respondents reported declines in business, others saw new opportunities and appreciated the efficiencies available from virtual operations. Many noted longer work hours for themselves and their teams, and some found that remote work increased focus and productivity. As respondents adjust to the new work arrangements, they are paying close attention to supply chains and strategies to meet demand for pharmaceutical products.

"The current crisis has changed how we do business, for both the good and the bad," said Vivianne Arencibia, President, Arencibia Quality and Compliance Associates, Inc. Starting with the positive, she noted, "The crisis has opened new avenues, businesses opportunities not traditionally thought possible or at least preferred. Working from home was always part of the model, but business from home is entirely different. Meetings, discussions, and learning opportunities are virtual but no less effective. I am in contact more often with associates and colleagues than previously."

Arencibia also pointed out some of the negative effects: Although expenses have fallen, short-term business changes and a decrease in onsite activities have impacted the bottom line. Additionally, workdays are longer, and lines between work and home have been blurred. And, although virtual communication is effective, it takes effort. "Relationships have changed, conversations need to be planned."

Remote work has been a welcome way to keep business moving, with some organizations swiftly adopting remote work and others making a slower transition. One respondent noted an IT upgrade in their organization made the move to virtual operations much easier, with remote meetings and sharing and collaborating on documents. Another respondent said that their organization has made this adjustment even though "we did not have a playbook for this type of event (no one did). We learned to focus on critical items only at this point."

The pandemic has accelerated the move to remote work for some organizations that previously had just started with it. Nik Krpan, President, Cheme Engineering, Inc., said, "As an engineering service provider, we are almost all working from home, something we were taking baby steps toward for a while and now have taken a huge leap."

Frances Zipp, President/CEO, Lachman Consultant Services, Inc., said the "focus on working remotely to support clients has been the main change. However, the transition has been seamless and has availed many novel opportunities within the industry."

Despite reprioritizing activities, which can slow some work, communications may be enhanced by the current situation. Keith Beattie, Director, EECO2 observed, "It is easier to reach people to speak with, as many are working from home and not in meetings. They are also thinking about the future and planning for work post-COVID."

Other business impacts reported by survey participants include halted site installations; delays in contracts for new work; canceled audits or virtual/remote testing to replace in-person physical audits; use of remote testing to allow factory acceptance tests to continue uninterrupted; supply chain adjustments, including shipping changes, to ensure availability of products; and stepped-up emphasis on risk management.

One respondent reported that a focus on employee safety, well-being, and livelihood is most essential at their company. This includes an extra bonus to essential employees, rerouting traffic into plants for temperature checks, and asking questions about health recommended by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO).

Steps underway at another respondent's organization ranged from the strategic (business continuity in global regions hardest hit by the pandemic to continue essential work while keeping employees safe) to the practical (manufacturing hand sanitizer for donation to hospitals and the company's employees).

Though all industry members are committed to patient safety and ensuring that needed medications remain available, those who have been working on COVID-19 products and solutions have demonstrated exceptional commitment. Lou Kennedy, CEO, Nephron Pharmaceuticals Corp., noted, "Our company has been on the frontlines of the response to the pandemic. We are proud manufacturers of respiratory solutions that treat symptoms associated with COVID-19, and we also produce sterile injectable drugs used to sedate and wake patients on ventilators. This dynamic has given our entire team an even stronger sense of purpose."

Sartorius Stedim Biotech's manufacturing sites have remained fully operational, said Katell Mignot-Moraux, Subject Matter Expert on Single-Use Technology at Sartorius. The company implemented a risk mitigation plan in early March to address the pandemic's impact on supply chain and logistics; identify and resolve bottlenecks with increased stock levels and raw material safety stocks; maintain production capacities; and establish safety measures for employees' well-being, she explained. Many of the company's products are being used for treatment or vaccine development initiatives, so the company is supporting this work by prioritizing the needs via a COVID-19 task force. "Surprisingly, digital communication with our clients, many of them also being in lockdown, has strengthened the relationship," she noted. Weekly communications to clients and from the board and human resources to all employees have been additional steps.

Another respondent commented on the meaning of the term "essential" in the pharma industry under the current circumstances. "We are not a pharma company, but our equipment supports pharmaceutical companies. So, we both have both clearly essential roles."

Regulatory changes and other far-reaching changes have been notable, said Roger Nosal, Vice President and Head, Global CMC, for Pfizer Global Product Development–Global Regulatory Affairs. "There have been adjustments in regulatory approaches and expectations. Many of the regulatory accommodations are intended to expedite development and approval of products to prevent the spread or reduce the symptoms and secondary effects of COVID-19. Regulatory authorities have also adjusted regulatory processes intended to reduce potential for drug shortages for essential medicines for other therapeutic priorities." He said that the industry has leveraged regulatory opportunities and accelerated development for treatment and vaccines for COVID-19 and for supply chain continuity of medicines.

"In addition, many companies have embraced the opportunity to develop and work in collaboration to understand the science that causes the virus to infect and spread among individuals,"

Nosal said. To meet increased demand for some medications in the wake of COVID-19, "the industry has responded by working with regulatory authorities to enhance and increase production. Consequently, the industry has absorbed the increased demand on capacity to maintain business continuity, and that has significantly increased individual work schedules, effort, and time. In general, the pharmaceutical industry has demonstrated an unwavering commitment to patients during this period."

In her assessment of how the industry has been affected by COVID-19, Avril Vermunt, Strategic Technology Partnership Leader at Cytiva (formerly GE Healthcare Life Science), pointed out a clear change in interactions and relationships. "I heard someone say, 'During this [pandemic] you cannot overdo communication,' and I tend to agree with this. I think it is the same for emotional intelligence, too—you cannot extend too much grace during this time. All in all, I think everyone is doing an amazing job making the most of technology to maintain connection, even building relationships, and keeping our industry moving along."

ISOLATION/SOCIAL DISTANCING EFFECTS

The pressures of isolating and social distancing—as well as how to slowly emerge from these restrictions in different locales—were issues of concern cited by many survey respondents for their own organizations, the industry, and the world. Long-range changes may well include a permanent element of remote operations, according to predictions by multiple respondents. Participants also expressed fears that reopening economies too swiftly could lead to resurgence in infections.

"The fears I have are that we may not be ready to accept the change that managing through this crisis will entail," Arencibia said. "The discussions tend to center around getting back to normal [but need to be] thinking through what the new normal needs to be. For example, will we or should we as a society engage in large events, concerts, classes, etc.? I am not sure the implications are fully understood."

Kennedy agreed that complacency in addressing the risks from coronavirus could impact both health outcomes and the economy. "We can't afford to relax social distancing efforts prematurely because that risks reversing the progress we have made in the fight against the virus," she said. "For our company specifically, we must remember to follow all CDC guidelines regarding COVID-19 from the executive offices to our cleanrooms. In addition to social distancing, we must also keep in mind that COVID-19 testing is imperative to get this country back to work."

Other observations included the ongoing need to maintain communications; understand that the return to office work will be a gradual process; recoup lost or delayed business opportunities; continue focus on supply chain maintenance; and deal with uncertainties about travel and face-to-face meeting resumption.

Several respondents expanded on the need to keep focus on employees' well-being. Krpan said the mental health of his staff, especially those who live alone, and the well-being of those at higher risk for COVID-19 infection, are top of mind. Gunter Baumgartner, Senior Vice President, Head of Global Engineering at Takeda Pharmaceuticals, said regular meetings with team members are key, as is considering that return to offices will be different with physical distancing; he predicted that fully occupied offices will not be seen for a year.

Christian Wölbeling, Senior Director Global Accounts, Werum IT Solutions, agreed that attention to employee well-being must continue. "Virtual 'coffee corners' are one instrument with which we are fighting social isolation. Accepting the flexibility of the working day is a nice side effect, as IT and programming services can be done at any time of the day, except when you have to synchronize with other organizations." Flexibility also helps those with families to manage their time, he added.

Nosal focused on future risks, such as "the potential for the etiology of COVID-19 to change or mutate at a rate [that] may exceed the industry's ability to sustainably and effectively prevent or treat manifestations of the virus and secondary infections." He continued, "While several pharmaceutical companies have expeditiously introduced preliminary and putative tests for the COVID-19 virus, improving analytical accuracy and precision as well as access to simple, rapid, and direct assessment should be a priority."

Nosal also expressed concern that some legislative initiatives appear to be "politically motivated and protectionist rather than grounded in scientific and technical necessity." He stressed that science should drive both the development of new medicines and the sustainability of "medicines with consistent quality and well-demonstrated quality assurance globally."

Jeff Odum, Global Lead, Design, Technology, and Standards for Sanofi Biologics, voiced a related concern: "That people will forgo 'common sense' and will continue to place restrictions on organizations due to overreaction to false or biased data and information."

Vermunt pointed out the importance of timely information that is shared. "On a humanitarian level, the big question is what does the pandemic look like months from now, and how effective are our monitoring, response, and control measures, especially with differences region by region," she said. "At a macroeconomic level, the question is what does our industry recovery look like." This question is a top priority for the industry, and she noted that timely sharing of ideas and information is being seen. With respect to business, she believes future office hours, travel, and production will look different. "So having the most up-to-date information is key to devising strategies to address what we can control within our organizations." Finally, she noted, "At the individual level, these strategies also have to account for staff health, well-being, and productivity. This industry has good insight into safety related to infectious disease, and the decisions I have seen take personnel safety in the highest regard. That will continue, and hopefully we can set an example for other industries."

Keeping an eye on the positive opportunities is important as well. "Changes in our industry's supply chain have already begun,

and the distancing protocols put in place to support manufacturing during these isolation times may lead to a new way of working," said Zipp. "This is a great opportunity for our industry, and we can never return to pre-COVID-19 times."

Mignot-Moraux noted her company has needed some adaptations in manufacturing sites to allow for social distancing while maintaining production capacity. "Overall production capacity remains intact and spare capacity is available. Sufficient personnel are in place and necessary actions are taken to limit the infection risk for our operational staff. In addition, we are in the process of hiring additional personnel to further increase production capacity for critical items," she said.

TEAM CONCERNS

Respondents shared the concerns that their teams have expressed to them. Not surprisingly, these concerns often echoed those of the industry leaders who answered the survey: the uncertain future of the pharma business, potential risks as restrictions on social distancing are reduced, how to balance work and family while remote work continues, coping with greater workloads, and lack of social interaction.

"It's really mixed how people are personally taking this situation," one respondent said. "For many, it's business as usual, but for others it is extremely stressful." Krpan noted that concerns may vary by demographics: Younger staff are more concerned about financial impact, whereas older staff are more focused on health.

Burnout and stress management are emerging as significant concerns, Nosal said. "Most of my colleagues and teams are working longer hours and weekends, balancing familial and social demands while simultaneously navigating increasingly complex issues and uncertainties. This pandemic and the industry response to it have had a significant impact on planning and prioritization, particularly for life-cycle management of products." Companies have taken some measures to balance immediate versus long-term priorities, he said.

Another respondent described specific steps to provide support for team members under the stresses of the pandemic, including keeping employees safe; communicating often and listening; providing well-being assistance; supporting work from home with ergonomic aids, activities, and conferencing tools; being patient with remote workers juggling work responsibilities alongside home schooling and other family needs; and understanding that everyone will have both good and bad days.

The issue of mobilizing an "immobile" workforce deserves attention, Vermunt said. "Now people are dealing with different aspects of disruption and managing it differently and on different time frames. Most people in our industry want to help and are looking for opportunities to work with like-minded people. Be open to letting teams work in different ways and with different partners. Lean on the principles of trust, even in virtual settings, be you, be honest, and follow through."

Team members are also wondering about how the industry will meet changing needs in the market, particularly around the supply chain. For example, Zipp reported, "My teams have expressed some concern about availability of product for the US market and potential gaps in the ability to manufacture to meet the demands."

"Most people in our industry want to help and are looking for opportunities to work with like-minded people. Be open to letting teams work in different ways and with different partners."

"The biggest concern I hear—not just from our team, but from people across the country—is about the way this pandemic exposed the country's dependence on foreign sources of API [active pharmaceutical ingredients] and PPE [personal protective equipment]," Kennedy said. Making sure that these are manufactured locally is an important consideration, she said.

Survey participants indicated that their teams did not expect to experience job losses that have affected other business sectors. "As we are working in the pharma industry, people are not concerned for their jobs, even though some parts of projects have slowed down," one respondent said. "We seem to have a healthy and strong growing pipeline of new projects coming in. But there are growing concerns about unemployment for family and friends." This is a stressor in addition to not being able to see family and friends in person because of isolating and social distancing.

The risk of coronavirus exposure and infection is a serious concern, particularly for team members working in manufacturing settings and those who travel for work under ordinary circumstances and may be traveling again soon. As Ferdinando Aspesi, Senior Partner, Bridge Associates International, LLC, noted, "In the manufacturing area and critical jobs, if somebody becomes infected, it might create a full shutdown of the manufacturing line or of product testing and release." Proper testing of personnel "is paramount" for employees in manufacturing plants, he added. Several other respondents stated that team members who used to travel for business are leery about resuming travel while the virus is still active in many areas of the world.

For more information on COVID-19

ISPE provides information and resources about COVID-19 for the pharmaceutical industry at ispe.org/covid-19-coronavirus-pharma-industry-resources

What will the pharmaceutical industry look like in the months and years ahead? The future of COVID-19 will affect the answer. "While there have been positives, the positives are not enough to outweigh the losses should the virus not get under control," Arencibia said.

LESSONS LEARNED AND THE ROAD AHEAD

The challenges of COVID-19 are providing opportunities for the industry to learn, adapt, and be better prepared for the future. Respondents noted changes happening now that will be helpful for the industry in the long term, including embracing the opportunities presented by remote work such as greater efficiencies and focus. Other changes that may have a long-term impact on the industry include more planning to address risk and supply chain issues, less demand for travel due to efficiencies and technology, increased focus on effectiveness in meetings, greater work flexibility, better and more efficient manufacturing and supply chain processes, environmental gains from less commuting and less pollution, new opportunities for remote audits, and more opportunities for the workforce of the future because more remote work can make hiring in varied locales a viable option.

The industry has shown how adaptable it can be when necessary. "We all were forced basically overnight to think and work differently, and innovation and creativity resulted," Zipp said. "Additionally, the importance of personal connections and compassion has been highlighted."

The focus on supply chain issues could bring industry improvements for years to come. "Organizations now see the value in supply chain control and maintaining continuity in both operations and logistics," Odum said. "The industry has had an awakening in terms of 'disaster response' that will bode well moving forward."

Enhanced collaboration with regulators and among the pharma industry and other companies from the development of treatments and vaccines to helping produce supplies for testing and PPE is a short-term trend that several respondents hope will be a long-term change. Nosal noted that increased transparency and improved collaboration among companies and regulators offers "the possibility of improving global convergence on risk-based, scientifically justifiable standards and consistent regulatory expectations," which could become "a 'new normal.'"

"I believe we have an obligation to collectively assess and learn from this pandemic and its impact on our capacity, capabilities, collaborative boundaries and opportunities, development paradigms, regulatory expectations, and risks," Nosal said. He pointed to a recent statement from the International Coalition of Medicines Regulatory Authorities (ICMRA) [1] as offering a "compelling" acknowledgment and endorsement of collaboration. "Patients are much better served when the pharmaceutical industry is able to collaborate and the regulatory authorities are aligned on harmonized approaches, expectations, and standard criteria for product approval," he added.

Partnership is a word that may increasingly be in the industry's vocabulary to help solve the present challenges as well as future ones. "Companies looking to strategic partnerships means that when a therapeutic or vaccine is identified, it has the highest likelihood of being manufactured, entered into clinical studies, prepared for regulatory review, and distributed globally successfully," Vermunt said. "Next, we're seeing capacity of manufacturing being addressed through our strong CDMO [contract development and manufacturing organization] networks. Finally, funding, discovery, and development are coming through a number of academic, government, philanthropic, and industry consortia."

When Vermunt spoke about Moderna, Inc., the 2019 FOYA Facility of the Future category winner [2], at the 2019 ISPE Annual Meeting & Expo, she said the company "recognized patients needed not one weapon, but an arsenal against complex disease." In her survey response, she noted that this perspective is akin to the pharma industry's approach today. "What we're seeing is organizations deploying an arsenal against this pandemic based on their strengths. I'm not sure we go back to addressing modern treatment in the previous way after this."

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ENGAGE WITH HEALTH AUTHORITIES

to Mitigate and Prevent Drug Shortages

By Deborah Tolomeo, PhD, JD, Karen Hirshfield, RPh, and Diane L. Hustead, MS

When faced with large-scale disruptive events such as the COVID-19 pandemic, the emergency and business continuity plans of drug manufacturers and event-specific actions of health authorities may not always be sufficient to prevent shortages of critical medical products. However, early, transparent engagement with health authorities is a powerful opportunity for drug manufacturers to potentially mitigate or avoid drug shortages. This article offers an overview of the pathways for a drug manufacturer to notify and collaborate with health authorities to minimize the impact of a drug shortages, whether or not there is an ongoing pandemic or large-scale disruptive event.

With the early public reaction to the COVID-19 pandemic resulting in bare shelves at grocery stores, it has become easier for all of us to understand the struggle healthcare providers experience when they cannot obtain critical medical products. Drug shortages can have significant impacts on patients and the healthcare system, including delays or rationing of care, difficulties finding alternative drugs, increased risk of medication errors, higher costs, reduced time for patient care, and hoarding or stockpiling of drugs that are in shortage [1]. Depending on the length of the shortage, providers may have to cancel or delay procedures or patients may go without medicine, leading to significant, detrimental effects on patients and public health.

Drug manufacturers typically have emergency and business continuity plans to ensure the continued supply of critical medical products. Nevertheless, an actual or potential drug shortage may occur for a variety of reasons, some of which are unexpected and not within the control of the drug manufacturer. Figure 1 illustrates several factors that contribute to drug shortages.

Drug shortages may result from issues occurring at any node within the overall supply chain of a drug product. Figure 2 provides a high-level snapshot of common nodes within a supply chain for a pharmaceutical product.

Over the course of the past several years, many health authorities have developed sophisticated tools and practices to address actual and potential drug shortages. Each of these tools relies on drug manufacturers having full and transparent communication with the relevant health authority as early as possible to obtain timely, tailored support to mitigate a drug shortage. Janet Woodcock, MD, Director of the US FDA Center for Drug Evaluation and Research (CDER), described the FDA's proactive approach toward shortages as follows:

> *We have the most success in all of this by working closely with manufacturers to help prevent shortages actually before they occur. This means we need to know about potential supply disruption before it happens, not when hospitals start calling us [2].*

Additionally, health authorities may find it necessary to quickly modify or enhance regulations and pathways in response to large-scale events that significantly affect the overall supply chain. For example, in response to the COVID-19 pandemic, the US CARES Act, which became law in March 2020, expands requirements for notification of drug shortages, with new requirements to report on (a) shortages for any drug that is critical during a public health emergency, and (b) shortages or discontinuations of an active pharmaceutical ingredient (API) [3]. Similarly, the European Commission and the European Medicines Regulatory Network created a task force and published guidance on adaptations to the regulatory framework to address challenges arising from the COVID-19 pandemic [4, 5].

Figure 1: Factors contributing to drug shortages.

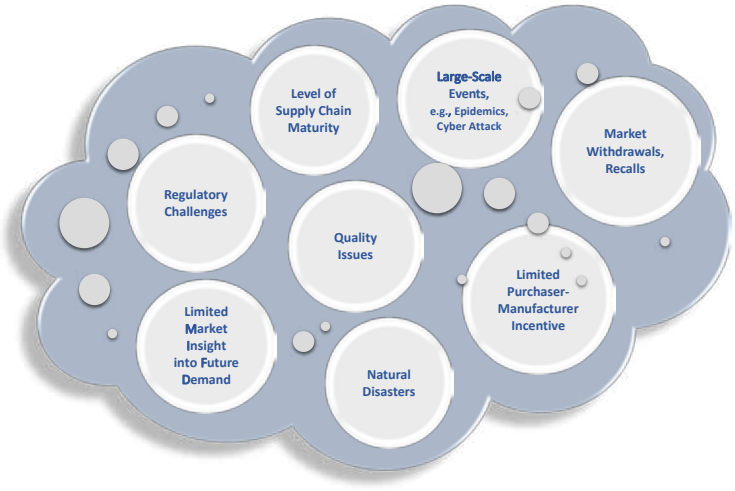
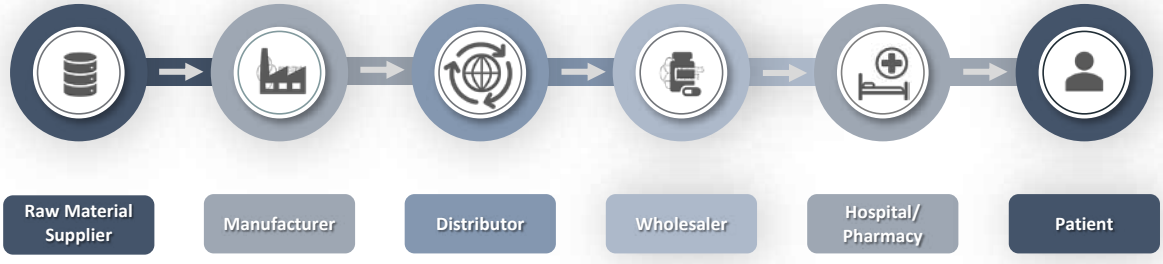


Figure 2: Common nodes in supply chains for drugs.



DRUG SHORTAGE NOTIFICATIONS

Once the potential for a drug shortage has been confirmed, drug manufacturers may be required to take expedient action to notify the health authority and implement mitigation actions to maintain continued supply. In many markets, regulations mandate that manufacturers report specific elements as part of the health authority notification of an actual or potential drug shortage.

Depending on the situation, drug manufacturers may also choose to include additional information in drug shortage reports. The aim should be to provide information that allows the health authority to support the manufacturer and reduce the duration of shortages, find alternative solutions to make treatments available to patients, or prevent some shortages altogether.

When engaging with a health authority, it is important for a drug manufacturer to be prepared to discuss the following information, as applicable:

- A summary of the reason for the actual or potential shortage
- A full description of the product(s) involved, including the name, dose, strength, packaging configuration, and any tracking or tracing information, such as the stock keeping unit (SKU) and National Drug Code (NDC) numbers
- The approved indications for use of the product, including nonapproved uses that are established or known in the medical community
- A general description of the supply chain
- A timeline of when the shortage is expected to occur, how long it will last, and when all existing product will be exhausted
- A description of the level of inventory that may be impacted, and the estimated volume of historic monthly sales, usage, or demand, as applicable
- A description of estimated market share for the product and whether the entire market share may be affected by the issue creating the shortage
- A description of what the drug manufacturer is currently doing to mitigate the shortage and resupply the market
- Ideas about how the health authority may assist in addressing a drug shortage, where and when appropriate

Figure 3: **Health authority tools to prevent or mitigate drug shortages.**

- A communication plan for informing healthcare providers, pharmacies, distributors, patients, or other health authorities, if needed
- A draft of any external notification of the shortage to the general public, if needed

If some of the drug shortage information described here is not yet available early in an event, drug manufacturers should notify the relevant health authorities with the information that is available and provide subsequent updates as the details emerge. Additionally, manufacturers should share other important information with the health authorities to assist with evaluating appropriate mitigation strategies, such as information on whether there are generic or alternative treatments available for each indication, and potential product surpluses in other markets.

Other products, such as APIs, personal protective equipment, medical devices, and diagnostics have historically not been subject to requirements for health authority notification. However, regulations are evolving rapidly; some jurisdictions now require reporting shortages for these product types during a public health emergency such as the COVID-19 pandemic or require this expanded reporting at any time. Even when notification is not required, health authorities are open to receiving notification of actual or potential shortages of all products and are willing to provide support and guidance to mitigate any critical impacts on patients and the public health.

An example of market-specific guidance on health authority notification may be found in the FDA-issued guidance, "Notifying FDA of a Permanent Discontinuance or Interruption in Manufacturing Under Section 506C of the FD&C Act," which was implemented as part of the agency's response to the COVID-19 pandemic [6]. The guidance provides information regarding the "who, what, when, where, and how" of notifying the FDA of actual or potential shortages and, importantly, expands the reporting obligations to include products that may be needed in response to COVID-19. This document is applicable for the duration of the COVID-19 public health emergency, and it will be important to watch for any revisions or replacements of this guidance that may occur after the public health emergency has concluded.

HEALTH AUTHORITY TOOLS AND PRACTICES

After a health authority has received the manufacturer's initial notification, the health authority may partner with the manufacturer to prevent or mitigate a drug shortage. Depending on the medical necessity of the drug, the availability of generic or alternate therapies, and the root cause of the actual or potential drug shortage, health authorities may use several tools to tailor their response to the underlying root cause. See Figure 3 for examples of actions health authorities may take [7].

Enforcement discretion is one of the most impactful, yet often misunderstood, tools that a health authority has to address drug shortages. The term "enforcement discretion" pertains to the ability of a health authority to determine whether to enforce select regulatory provisions as they currently apply to certain manufacturing entities or activities. Health authorities exercise enforcement discretion on a temporary basis when other tools or practices are insufficient to mitigate or prevent the shortage of a medically necessary drug. It is important to note that this tool is only used when (a) the patient benefit or necessity outweighs the potential risks associated with exercising the enforcement discretion, and (b) the proposed temporary solution is timely enough to mitigate or prevent a shortage.

For example, health authorities may use enforcement discretion or regulatory flexibility to develop risk mitigation measures to allow individual batches of a drug product to be released even when quality assurance requirements or the registered dossier requirements have not been met. Historical examples of enforcement discretion include:

- Allowing additional product testing prior to release
- Extending the expiry of select product batches on the market
- Temporarily allowing distribution of products with outdated or modified labeling and packaging
- Supplementing product distribution with accessories such as filter needles or other administration components to remove particulate matter

In the specific case of expiry dating, manufacturers may also consider submitting a postapproval change to extend expiry for all future manufacturing batches to alleviate shortage events. Depending on the scenario, the health authority may support expediting a submission of this nature to minimize the current shortage event or to prevent future shortages.

Manufacturers are encouraged to engage in an open dialogue with the health authority regarding all potential options to mitigate the shortage. As a part of the dialogue, manufacturers should

collaborate with the health authority and identify any potential assistance that the health authority can provide (see Figure 3).

COMMUNICATION WITH STAKEHOLDERS

When a drug shortage occurs, timely and effective communication is an important tool to ensure that all stakeholders are aware of the current drug supply status and remediation efforts in place to address the shortage. Both drug manufacturers and health authorities may wish to communicate regularly with customers (e.g., healthcare providers, wholesalers, distributors, hospitals, pharmacies, patients), and other stakeholders (e.g., professional organizations, the general public) until the shortage has been resolved [8].

The drug manufacturer should notify the relevant health authority before any necessary public communications are released. This approach helps ensure that the health authority and manufacturer can coordinate actions to prevent or mitigate a drug shortage and to make consistent information for customers available. In some cases, a drug manufacturer may be able to coordinate with the health authority to redirect patients or purchasers to locations where adequate supplies of the drug product are available.

Any external communication to the general public issued by a drug manufacturer about an actual or potential drug shortage may need to be reviewed by the health authority prior to distribution. In Europe, EMA guidance includes a template for such communications, which has also been translated into multiple local languages by National Competent Authorities [9, 10]. Some health authorities, such as the US FDA and EMA, may also recommend or require that drug manufacturers obtain health authority review of specific communications to healthcare providers about a drug shortage (i.e., a "Dear Healthcare Provider" letter).

Some drug manufacturers may be wary about reporting actual or potential drug shortages to health authorities because they are concerned that the health authority will share the information publicly without working with them. This hesitancy may result in delayed health authority notifications, which in turn could affect the ability of the drug manufacturer to partner with the health authority to mitigate an impending shortage. Based on experience to date, drug shortage information provided by a manufacturer to a health authority is not automatically communicated publicly without prior discussion with the drug manufacturer. Additionally, health authorities typically only communicate shortage risks publicly when there is a need for the end users or prescribers to do something differently to manage the shortage situation. Thus, it is in the best interest of drug manufacturers to communicate as early as possible with health authorities to allow more time to mitigate shortages and decrease the likelihood that an external communication is needed.

If a drug manufacturer decides that they would like to communicate externally, they may wish to coordinate with the relevant health authority to publish the information on the health authority website at the same time that it is made available through other communication channels. Health authorities may maintain websites (e.g., www.hma.eu/598.html) and mobile apps that list of ongoing drug shortages to facilitate the availability of accurate and reliable information for healthcare providers and patients. In some cases, manufacturers are able to use these tools to provide information about where their drug product can be obtained or list contact information to provide additional support to patients or healthcare providers.

CLOSURE OF DRUG SHORTAGE COMMUNICATIONS

After initiating communications with the relevant health authority, drug manufacturers should continue to track the progress of the event closely, update the health authority as needed, and ensure external communications and websites remain current. An ongoing update process is generally expected until the supply disruption is resolved and a closure communication is made to the health authority, customers, and other stakeholders.

Furthermore, once normal inventory has been achieved and all back orders for the product addressed, the drug manufacturer should evaluate the event and take any appropriate measures to prevent future shortages, including follow-up with relevant health authorities, if appropriate. Per the ISPE Drug Shortages Plan, which may be found on the ISPE website, lessons learned from the event should be used to improve product design, quality systems, and facilities so as to prevent future drug shortages [11].

Manufacturers may need to share their findings from the evaluation and their plans for preventive actions with the health authority. Companies should also use this information to improve business continuity plans, employee practices, and drug shortage processes and procedures.

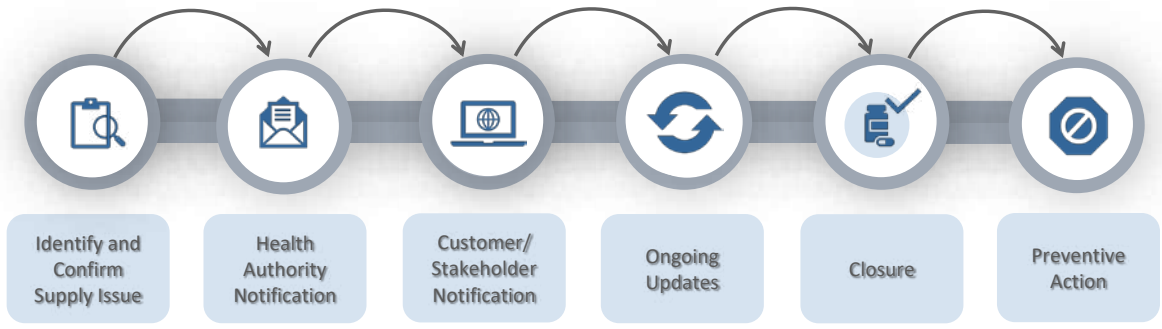
Figure 4 summarizes all the steps described in this article for effective health authority communication and mitigation or prevention outcomes.

CASE STUDY

In September 2017, Hurricane Maria devastated Puerto Rico, creating a shortage in the United States of a significant number of critical medical products manufactured on the island, including human drugs and components. In particular, normal saline and sterile water for injection were subject to extended shortages that lasted several months. These shortages affected hospitalized patients who needed life-saving medicines that rely on normal saline or sterile water for injection as a solvent or diluent vehicle for parenteral administration.

To mitigate the public health impact of the shortages, the FDA worked with drug manufacturers to approve new facilities and temporarily import product from other countries. The FDA also used data provided by drug manufacturers to extend expiry dates and issued guidance to provide alternate treatment and conservation strategies [12]. By increasing supply, managing existing inventory, and communicating frequently with the public, the FDA was able to partner with drug manufacturers to protect the public health and to provide a timely and impactful response to Hurricane Maria.

Figure 4: Life cycle of drug shortage communications.



Additionally, the impact of Hurricane Maria and other recent large-scale events inspired active global dialogue on the topic of drug shortages. This dialogue has become heightened during the COVID-19 pandemic, which has had a worldwide impact on all types of medical products, including human drugs, medical devices, personal protective equipment, biologics and blood supply, nutritional products, and animal drugs. The discussion is putting a spotlight on systemic vulnerabilities associated with drug supply and how health authorities and industry may better prepare for continuous supply of critical medicines for patients. ISPE encourages all manufacturers to stay current with the developing initiatives and potential for new regulations related to drug shortages.

CONCLUSION

Full and transparent communication with the relevant health authority is essential to obtain timely, tailored support to mitigate a drug shortage. The earlier a drug shortage can be identified, confirmed, and reported, the more likely the health authority can assist in providing expedited action to prevent the shortage and maintain continued supply. With robust business continuity planning and effective communication practices, drug manufacturers will be in the best position to collaborate with health authorities and minimize the impact of an actual or potential drug shortage on patients and the public health.

ISPE has had a longstanding commitment to preventing and mitigating drug shortages. For more information on successful interactions with health authorities, as well as in-depth information regarding other significant dimensions for preventing drug shortages, we refer you to the ISPE Drug Shortages Prevention Plan [11] and Drug Shortage Assessment and Prevention Tool [13] as key resources.

The ISPE Drug Shortage team is actively monitoring developments with drug shortages and is available for any related questions. We welcome input on best practices to support continuity of supply and decision making in the case of an actual or potential drug shortage.

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PANDEMIC PREPAREDNESS and Business Continuity

By Wendy Haines, PhD, DABT

This article updates a 2006 *Pharmaceutical Engineering*® Online Exclusive article titled "Avian Flu—Is My Company Prepared?" by Wendy Haines and Martin Rock [1]. Although that article focused on preparation for an influenza pandemic, its key points are relevant to any type of epidemiological threat—including COVID-19.

Several months prior to the publication of the 2006 PE article, the World Health Organization (WHO) stated that companies should identify pandemic teams, develop plans, and run drills to ensure preparedness [2]. It may be hoped that such recommendations have helped stakeholders in the pharmaceutical, biotechnology, and medical device industries successfully prepare for the challenges of COVID-19. However, as the trajectory of this pandemic remains uncertain and new pandemics may emerge, industry members must continue to vigilantly evaluate and refine their preparedness strategies.

COMMUNICATION IS KEY

The importance of communication is critical in a pandemic. Emotions are likely to run high, and clear lines of communication help people follow a scientifically sound path forward. In particular, it is essential to combat rumors by communicating correct, reliable information that helps individuals make intelligent, rational decisions about behaviors that spread infections.

While COVID-19 was emerging as a worldwide threat, how many people went to work or boarded airplanes even though they were sick? How many caregivers let children who were under the weather go to school and daycare? How many healthy and asymptomatic individuals took unnecessary risks such as ignoring public health recommendations for social distancing, using

There is no financial or business benefit in waiting until the last minute to prepare.

disinfectants improperly, or not routinely practicing hand hygiene? Many people seemed to not understand that these individual events can have a "snowball" effect, hastening the spread of infection.

Particularly in times of crisis, members of the pharmaceutical, biotechnology, and medical device industries should make sure that their communications effectively convey high-quality information to regulators, employees, patients, healthcare providers, and others. For example, to control the spread of COVID-19 and maintain safe working conditions, it is important to be proactive in educating employees about hygiene standards and procedures, what to do if exposed to sick people, and working from home when possible.

As part of preparedness efforts and throughout crises, companies should use credible resources to inform their communications and also share these resources with others. Among the best resources for information about COVID-19, other infection threats, and how to respond are international and national health authorities, such as:

- WHO: www.who.int
- US Centers for Disease Control and Prevention: www.cdc.gov
- US FDA: www.fda.gov
- US Environmental Protection Agency (EPA): www.epa.gov
- US National Institute of Allergy and Infectious Diseases (NIAID): www.niaid.nih.gov
- EMA: www.ema.europe.eu/en
- Health Canada: www.canada.ca/en/health-canada.html

ADAPTIVE PLANNING

Let us use Y2K to illustrate the value of preparedness planning. As the 20th century drew to a close, businesses of all types faced the possibility that an established practice of programming computers using two-digit codes for years (e.g., "77" for 1977) would lead to chaos on 1 January 2000 (e.g., software calculating ages from birthdates might interpret the date "1/1/00" as the first day of 1900). Once the potential "year 2000" (Y2K) threat was identified, individual organizations, industries, and governments all had to initiate strategies to prevent the problem and plan for contingencies if prevention efforts were not fully successful. From a business standpoint, early investment in planning was generally the most cost-effective strategy. Well before Y2K, computer programmers earned decent salaries, but as Y2K drew closer, their salaries rose astronomically due to the basic law of supply and demand. Therefore, the organizations that hired or contracted programmers at the end of the decade had to pay more than those that started sooner. Even though the worst fears about Y2K did not manifest, we can still learn something from this event: There is no financial or business benefit in waiting until the last minute to prepare, and you cannot adequately prepare for this type of contingency when it is already upon you.

As an essential first step in their COVID-19 response, companies can "arm" themselves with the knowledge of the pandemic, using guidelines and mandates set forth by WHO, CDC, EPA, NIAID, and other health authorities to help with planning and strategic actions.

If an organization does not yet have a pandemic risk management group, they should create one. Business leaders also need to ensure guidance on pandemic preparation is up to date in their business continuity plans. If these plans are to succeed, they must be flexible so they can be adjusted to appropriately handle whatever develops. In 1996, Nitin Nohria, the Richard P. Chapman Professor of Business Administration at Harvard Business School, wrote that the avian flu pandemic would be characterized as "survival of the adaptive" [3]. He suggested that companies would have to rely on decision makers capable of applying "new ways of problem solving in an unpredictable and fast-changing environment."

In January 2020, Nohria, who is now the Dean of the Harvard Business School, revisited these themes in an update to his 2006 article, stressing that risk management teams and contingency plans are "necessary but not sufficient. In the complex and uncertain environment of a sustained, evolving crisis, the most robust organizations will not be those that simply have plans in place but those that have continuous sensing and response capabilities" [4].

People throughout the pharmaceutical, biotechnology, and medical device industries are highly innovative and often "think outside the box," and they can troubleshoot problems in real time. These are essential skills during a global pandemic. Nohria has suggested we consider Marine expeditionary forces to be a model for pandemic preparedness: The Marines are highly effective in mission-critical situations because they practice as a team until everyone on the team can lead the team [3, 4].

Collaboration plays an important role in strategic business planning and operations during and after a global pandemic. A combination of cross training, an adaptive risk management group, and support by all employees and contractors aids in honing the effectiveness of preparedness planning. During strategic planning, companies should conduct a self-evaluation, asking key questions such as the following:

- What keeps us running and successful?
- What are our supply chain issues?
- Who are our critical staff, and how they can serve their clients during a pandemic?

Overview of COVID-19 and Other Recent Coronavirus Infections

According to the Centers for Disease Control and Prevention (CDC), symptoms of coronavirus disease 2019 (COVID-19) may appear two to 14 days after virus exposure. These symptoms can range from mild to severe and include fever, cough, shortness of breath or difficulty breathing, chills, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell [1].

The symptoms can be similar to those of seasonal influenza, and some people with COVID-19 are asymptomatic. These factors, in addition to early difficulties in diagnosis through lack of adequate testing materials, may have resulted in misdiagnosis and increased the community spread of the infection.

COVID-19 is caused by the SARS-CoV-2 coronavirus, a novel virus first identified in humans in January 2020 in Wuhan, China, where it caused an outbreak of viral pneumonia [2]. Coronaviruses are part of a family of viruses that are common in people and animal species, including cattle, camels, cats, and bats, and it has been theorized that COVID-19 was initially spread to humans from bats [3].

COVID-19 is thought to spread mainly from person to person through respiratory droplets from sneezing and coughing of infected individuals [1]. Droplets expelled from those who are infected can land in noses or mouths of nearby people or potentially be inhaled into lungs, or people may touch surfaces contaminated by droplets and then become infected by touching their hands to their face. Transmission is most likely to occur when people are within close proximity (six feet) of an infected person. Symptomatic COVID-19 patients are thought to be most contagious; however, asymptomatic people can transmit the virus.

Basic strategies to protect everyone from COVID-19 include hand hygiene, respiratory hygiene/cough etiquette, avoiding close contact with people while sick, and proper use of disinfectants; extra precautions may be warranted for older adults, people with immunocompromised status, and others at elevated risk of severe illness [4].

As the quality of laboratory testing improves and testing frequency increases, researchers are learning more about the community spread of COVID-19. The collection of accurate and detailed data will permit better comprehension and tracking the scope of the outbreak and bolster prevention and response efforts.

As many know, COVID-19 is not the only coronavirus infection to emerge in recent years. Severe acute respiratory syndrome (SARS) is also caused by a coronavirus, SARS-associated coronavirus (SARS-CoV). This viral respiratory illness characterized by high fever, respiratory symptoms/pneumonia, headache, and body aches was first reported in Asia in February 2003 [5]. In a few months, it spread to 29 countries in North America, South America, Europe, and Asia, with transmission occurring through exposure to respiratory droplets from an infected person [6]. The WHO officially declared the SARS epidemic to be contained on 5 July 2003 [7]. No specific treatment or vaccine was developed, and no new cases have been reported since 2004 [6].

Middle East respiratory syndrome (MERS), which is caused by Middle East respiratory syndrome coronavirus (MERS-CoV), is characterized fever, cough, and shortness of breath. The mortality rate in MERS patients is reportedly between 30% and 40% [8]. The first known case of MERS occurred in Jordan in April 2012, and all cases have been associated with individuals who have traveled to or lived in countries in and near the Arabian Peninsula. The largest known outbreak of MERS outside the Arabian Peninsula occurred in South Korea in 2015; it was associated with a traveler returning from the Arabian Peninsula [8]. Like COVID-19 and SARS, MERS-CoV is transmitted through exposure to virus-laden respiratory droplets.

Because information about COVID-19 symptoms, treatments, and preventive strategies is still developing, readers should always refer to the latest guidelines and mandates set forth by the WHO, CDC, Environmental Protection Agency (EPA), National Institute of Allergy and Infectious Diseases (NIAID), and other public health agencies.

—Wendy Haines, PhD, DABT

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With proper planning, the defensive or preventive strategies designed for a major crisis scenario also may enhance normal operations.

ESTABLISHING THE BUSINESS CASE

A balanced and sober analysis of strategic and business management issues is an essential part of pandemic preparedness. An organization should have both an "offense" strategy to advance its business interests and a "defense" strategy for protecting business continuity and cushioning the enterprise while managing or coping with contingencies.

During pandemics and other crises, a company's business opportunities may include increased sales to meet market demands for products and services, and this may in turn lead to other benefits—for example, a company's response to customer demands during a pandemic could spin off to new market segments, particularly if the organization strives to achieve robust operational flexibility.

With proper planning, the defensive or preventive strategies designed for a major crisis scenario also may enhance normal operations. For example, as part of the pandemic preparedness plan, the organization may strengthen communication networks between facilities in different countries and then reap ongoing benefits in improved day-to-day collaboration of personnel across facilities. Similarly, the organization that has planned well for major crises may find greater success and viability during relatively minor crisis scenarios, such as a short-term labor shortage in one region of the world.

CONCLUSION

Tackling a problem such as pandemic preparedness can build strength at all levels of our industry. As we have seen, a global pandemic does not honor or abide by the organizational chart or stop at the doors of the executive suite. The need for cross-functional training and backup leadership is as strong in our current world situation as it is on the battlefield. Although business continuity will depend on flexibility and adaptive creativity, building this flexible character can also create additional benefits for the organization. When key people clearly understand the functional requirements of their coworkers and supervisors, they can become more proactive and productive; and fewer items are likely to "fall through the cracks." This type of thinking can be applied throughout the supply chain and product delivery. The results are positive: Even normal operations become more effective and more adaptable to business fluctuations and unanticipated circumstances.

We have made many advances as a society since the last major pandemic, and the continued expansion of our knowledge, new technologies, and harmonization efforts will be critical to managing the current one. Pharmaceutical, biotechnology, and medical device companies, consultants, contractors, health authorities and other public agencies, university researchers, physicians, and healthcare workers all over the world are contributing to vaccine development and antiviral therapies to combat COVID-19. During this unprecedented time, we should feel confident that a successful vaccine will be developed, antiviral approaches and rapid and effective testing methods will be deployed, and best-treatment practices for patient care will be implemented.

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HOW VACCINES ARE DEVELOPED

By Frieda Wiley, PharmD

Vaccine development is an intricate undertaking, which may involve numerous challenges from the initial process of identifying an antigen to the final steps of delivering and administering the licensed product. The COVID-19 pandemic has put a spotlight on the science of vaccine development. As the world awaits a vaccine for the coronavirus, manufacturers face unprecedented pressure to respond quickly and deliver a safe and efficacious product.

According to the World Health Organization, as of 11 April 2020, three COVID-19 vaccine candidates were in clinical evaluation and another 67 candidates were in preclinical development [1]. Just a few weeks later, the Milken Institute reported that more than 120 coronavirus vaccine candidates were in development [2]. Although the final number of vaccine candidates that will be investigated for COVID-19 specifically can't be predicted, Dennis M. Gross, MS, PhD, SSYB, SFC, CEO, and Professor of Pharmacology, Pennsylvania Drug Discovery Institute, Doylestown, Pennsylvania, anticipates that the current surge in demand for vaccine development will continue long after COVID-19 vaccines come to market.

"There will be an increased need for many types of vaccines as the number of infectious diseases continues to rise," said Gross in an interview with *Pharmaceutical Engineering®* following his 22 April 2020 webinar presentation, "Vaccines 101," sponsored by the ISPE Delaware Valley Chapter. The webinar was part of a three-lecture lunch-and-learn series: "Immunology 101," "Vaccines 101," and "Anti-Virals." Information from the presentation on vaccines is shared in this article. He explained that one reason to expect more types of infectious diseases to emerge is the growing risk of zoonotic transmission. Though the origins of COVID-19 remain unclear, the novel coronavirus may have initially been transmitted from animals. Gross noted that contact between animals and humans becomes more likely as the unprecedented deforestation in regions such as the Amazon and sub-Saharan Africa uproots wild animals from their habitats.

TYPES OF VACCINES

In his presentation, Gross classified vaccines in four general categories: whole pathogen vaccines, subunit vaccines, toxoid vaccines, and nucleic acid vaccines. Each type is uniquely formulated to "train" the immune system to respond when exposed to a particular pathogen to ward off disease. The techniques used to create vaccines and their specific formulations affect the products' safety and stability profiles.

Whole Pathogen Vaccines

Two types of vaccines are classified in the whole pathogen category: live attenuated vaccines (LAVs) and inactivated whole-cell vaccines. As the name indicates, an LAV contains a pathogen that has been "attenuated," or weakened, but is still alive. LAVs generate an immune response that is similar to the immune response a person's body would launch when infected with the wild-type pathogen [4]; however, the weakened pathogen in the vaccine typically causes only mild disease or no disease at all. As a result, the vaccinated person can usually gain immunity without serious illness. There is some risk that an attenuated pathogen could change back to its original form and cause disease, and LAVs may not be effective or safe for immunocompromised individuals or pregnant women [3, 4].

Inactivated whole-cell vaccines use pathogens whose living properties have been chemically or physically destroyed. These types of vaccines tend to be more stable than LAVs. Also, because they contain no live components, inactivated whole-cell vaccines cannot cause disease. However, these vaccines may not cause an immediate immune response, or the initial vaccine response may not confer lasting immunity. Therefore, individuals may require multiple vaccine doses or periodic boosters [4].

Subunit Vaccines

Subunit vaccines contain only the portion of the pathogen that produces an antigenic response. Because these vaccines do not contain

"One of the biggest pitfalls in vaccine supply chain management relates to the predictability and reliability of output."

live pathogens, they are safer than LAVs. However, they are especially difficult to develop due to the challenges of determining which parts of the pathogen are needed to create lasting immunoprotection. Also, multiple vaccine doses or boosters may be required because subunit vaccines use inactivated pathogens [4].

Toxoid Vaccines

Manufacturers have used weakened toxins (i.e., toxoids) produced by certain bacteria such as diphtheria or tetanus to formulate vaccines against the infections caused by those bacteria [3, 4]. Toxoid vaccines cannot cause disease or revert to a virulent pathogen, so they are considered safer than LAVs. They are also relatively stable products because they are resistant to environmental changes in temperature, humidity, or light [4].

Nucleic Acid Vaccines

Types of nucleic acid vaccines under investigation for use in humans and animals include DNA plasmid vaccines, recombinant vector vaccines, and mRNA vaccines [5, 6].

- DNA plasmid vaccines introduce plasmids containing genes from the pathogen that causes the infection into the host tissues to spur an immune response that leads to immunity.
- Recombinant vector vaccines are created by inserting a pathogen's DNA into a different, deactivated pathogen. Gross explained in his presentation that these vaccines rely on the DNA's instruction-giving behaviors to direct cells to make proteins that resemble those of the infectious pathogen, causing the body to respond by producing antibodies.
- mRNA vaccines use messenger RNA to instruct cells to build antigenic proteins that the immune system will recognize, triggering it to create antibodies against the pathogen.

VACCINE DEVELOPMENT STRATEGIES

The strategies manufacturers select to develop vaccines are dictated by a range of factors, including which microorganism strains are available for investigation as well as the company's previous experiences and areas of expertise, according to Gross. Organizations tend to gravitate toward strategies where they have had some success, he said. For example, Merck has past experience with recombinant vector vaccines, whereas Moderna was already focusing on recombinant mRNA encapsulated in nanoparticles prior to the emergence of COVID-19.

Preclinical Research

In the initial preclinical stages of vaccine development, researchers undertake a series of exploratory steps to select the type of vaccine they want to develop, identify and cultivate potential antigens, assess the immune response desired from the vaccine, and begin planning a manufacturing process that will create a safe and consistent product that can be used in clinical trials and eventually released to the market [7, 8].

Preclinical investigations also involve experimentation with adjuvants—substances that amplify the antigen's immune response—as well as stabilizers to improve shelf life, preservatives to prevent microbial growth, and other vaccine elements [4]. In his interview with *Pharmaceutical Engineering*, Gross explained that adjuvant selection has limited room for innovation because manufacturers want to minimize the potential for unknown variables, such as the possibility that the adjuvant could be an irritant that causes adverse reactions.

After researchers derive a formulation for a vaccine candidate, that candidate undergoes rigorous preclinical testing to begin the evaluation of its safety and efficacy, Gross said. A key priority at this stage is to determine a plausible dosing regimen to generate an immune response. This step includes in vitro and in vivo analysis

If the candidate shows promise, researchers use animal models to help estimate the appropriate approach to human dosing [8]. However, sponsors may struggle to find a suitable animal model for testing the vaccine candidate.

"You want to try to get the same immunity response in the animal model as you would in a human to determine the appropriate dose for humans," Gross explained. "Animal modeling in vaccine development is not the same as using animal models in drug development because you're dealing with the immune system, which is harder to model than other human systems, such as the endocrine or cardiovascular system."

Clinical Trials

If preclinical studies of the vaccine candidate successfully meet scientific standards and produce sufficient evidence that the candidate seems safe for human use and could provide immunoprotection, researchers can begin clinical trials. Vaccines usually must undergo three phases of clinical trials before regulators will consider them for market approval [9–11].

Phase 1 trials evaluate the safety of the vaccine in a small number of low-risk subjects (typically, 10–100 healthy adults), Gross explained. This phase also provides information about how dose-response properties contribute to side effects, as well as immunogenic data useful for evaluating the efficacy of the vaccine [9–11].

A vaccine candidate that is well tolerated and has enough evidence of safety and efficacy in Phase 1 can advance to Phase 2 trials, in which the product is tested in several hundred participants who represent the target population to further evaluate its safety profile and appropriate dosages [9–11].

If the vaccine candidate passes Phase 2 trials, testing can progress to Phase 3 randomized controlled trials. To help investigators more fully understand the protective efficacy of the candidate, the number of participants tested tends to be quite large (e.g., in the tens of thousands), the populations studied are more heterogeneous than those studied in Phases 1 and 2, and the trial duration is longer than in the earlier phases [9–11]. Testing continues to focus on the candidate's immunogenicity, protective efficacy against the target disease, and safety. The use of a control group is important to evaluate the candidate's protective efficacy, which may be calculated as follows [12, 13 (p. 24)]:

$$\text{Protective Efficacy} = \left(1 - \frac{\text{Incidence of disease in vaccine group}}{\text{Incidence of disease in control group}}\right) \times 100\%$$

Assessment for immunogenicity involves measuring the amount of protective antibodies a vaccine candidate produces in the test participants. This may indicate the degree of protection the candidate offers [12]. In addition to evaluating the efficacy of the vaccine candidate, investigators use Phase 3 trials to continue to monitor the candidate for adverse effects as well as its behavior in specific populations.

Assuming the clinical trial evidence supporting the candidate is strong, the sponsoring manufacturer applies for market approval of the candidate. In the US, vaccine manufacturers submit a Biologics License Application (BLA) to the FDA [10].

Postapproval Surveillance

If regulators grant a license for a vaccine, the vaccine enters the postapproval stage [10]. At this point, the manufacturer may conduct Phase 4 trials and other forms of postmarketing surveillance to collect and analyze data on the long-term risks and effectiveness of the vaccine, associated health outcomes, and a range of pharmacoeconomic parameters, Gross noted in his presentation.

In some cases, the manufacturer may conduct large postmarketing studies with thousands of participants. Known as "megatrials," these studies can potentially help the manufacturer identify concerns about the vaccine or additional indications for the product. National regulatory authorities also have surveillance apparatus to help track the effectiveness and safety of licensed vaccines [10].

SUPPLY CHAIN HURDLES

Vaccine manufacturing and distribution is an intricate process, and whatever is produced can expire relatively quickly. However, perhaps no obstacles are more challenging than those involving supply chain management.

"One of the biggest pitfalls in vaccine supply chain management relates to the predictability and reliability of output from your manufacturing organization," said Nitin Goel, MBA, Senior Manager, Early Portfolio Commercial Strategy (Global Vaccines) at GSK in Washington, D.C., in an interview with *Pharmaceutical Engineering*.

Goel explained that vaccines often require long manufacturing times and can have high batch-failure rates and brief shelf lives. These issues limit the amount of product manufacturers can make and distribute. "It takes a long time to manufacture product, and whatever you produce can go bad pretty quickly," he said.

The challenges of manufacturing stable and reliable vaccine batches constrain the flexibility and adaptability of the supply chain and can have deleterious downstream effects. Historically, manufacturers have sometimes struggled to respond promptly to changes in vaccine demand. Although manufacturers may have good information to reliably predict short-term demand for routine vaccinations, they cannot fully anticipate how stochastic incidents such as large disease outbreaks or large batch failures might dramatically alter the balance between supply and demand.

Manufacturers may try to forecast the long-term demand for vaccines based on information from various national immunization schedules. However, because vaccine manufacturing capacity requires a significant amount of capital and time to develop, such investment decisions come at great risk. If the forecast is off, the manufacturer might over- or underproduce the vaccine, leading to a surplus or deficit of millions of doses.

Moreover, the lack of globally standardized product specification requirements (e.g., for quality control or labeling) can impair a manufacturer's ability to shift already-produced doses from one country to another. In such situations, manufacturers may require many months to adapt the supply chain. Until vaccine supply chain issues are resolved, populations are more vulnerable to communicable diseases and the company's reputation may be damaged.

Goel noted that one way to help ease supply chain headaches is to maintain significant stock at every step of the supply chain to maximize the manufacturers' flexibility to respond to unexpected events. Another important strategy for vaccine manufacturers is sustaining good relations and transparency with key external partners such as public health authorities in countries where the manufacturer supplies vaccines. When manufacturers and external partners have a shared understanding of the facts regarding production capabilities and the supply chain, they can better cooperate to lessen the risks posed to patient health and well-being.

LOOKING AHEAD

Vaccine development is usually a lengthy process. According to Gross, successful vaccines have typically taken 10 to 15 years to move from preclinical research to market approval, and some have taken even longer—for example, Merck's Varivax vaccine for varicella infection (chickenpox) took 23 years to be brought to market.

Sponsors of COVID-19 vaccine candidates hope they can dramatically shorten the typical development timeline. However, Gross warned, "You can't neglect safety by going too far too fast." Even if some vaccine candidates, such as those using mRNA, are developed quickly, scalability will present a challenge. It is uncertain what would be required to scale a vaccine created for research

to mass production sufficient for an entire country—or the world. Access to an approved vaccine is very likely going to become another issue in the pandemic.

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CASE STUDY:

Facilitating Efficient Life-Cycle Management via ICH Q12

By Connie S. Langer, Michael J. Cohen, Lindsey Saunders Gorka, Megan E. McMahon, Roger Nosal, and Timothy J. N. Watson

The latest ICH guideline, ICH Q12 [1], introduces regulatory mechanisms, such as established conditions (ECs), to simplify and expedite postapproval product variations and enable continual product improvement. As illustrated by this case study for a small molecule product, the appropriate use of ECs can successfully narrow the technical and regulatory gaps that limited the realization of flexible regulatory approaches promised by the application of Quality by Design (QbD) principles.

The implementation of QbD as a science-driven, risk-based approach to expand product knowledge and process understanding was intended to serve as a foundation for and encourage continual improvement, and thereby increase assurance of quality for pharmaceutical products. The QbD approach has been a paradigm shift for industry and regulatory authorities because it formally focuses on (a) prospectively characterizing quality risks to patient safety and efficacy, and (b) developing an appropriate control strategy to mitigate those risks [2–5]. Though the adoption of QbD as a development paradigm within the industry has been widely acknowledged as successful, the implementation of QbD to support regulatory applications through the product life cycle was incomplete because there were no provisions for how postapproval changes and improvements would be acceptably submitted and effectively approved. With the advent of ICH Q12, regulatory mechanisms have been introduced to simplify, enable, and expedite postapproval variations and supplements. The appropriate execution of those concepts will validate the principles of QbD. The concept of ECs has emerged as one of those enabling mechanisms.

THE VALUE OF ECs

In conjunction with a robust pharmaceutical quality system (PQS), ECs describe and present in a regulatory application a comprehensive control strategy for the product through its life cycle. According to ICH Q12, ECs "are legally binding information considered necessary to assure product quality," and they reflect a company's commitment to manufacture and control the drug product and ensure appropriate, consistent, and sustainable quality, safety, and efficacy for the patient [1]. In essence, ECs represent the company's "license to operate," by which decisions on postapproval changes are made.

Tools available in ICH Q12, such as the Product Lifecycle Management (PLCM) document, enable the company to distinguish the ECs from supportive information. The system of risk-based reporting categories also facilitates the use of the Post Approval Change Management Plan (PACMP), which enables predictability in planning for future changes to ECs. (Note: A PACMP is not included in this case study.)

Historically, when planning for a postapproval change to the chemistry, manufacturing, or control (CMC) of a product, the sponsor would have assessed all information in module 3 of the common technical document (CTD) with regard to the specific regulatory commitments and postapproval obligations of each relevant region and then would assign region-specific actions. Following the concepts within ICH Q12, all changes—irrespective of the proposed reporting categories—would still be formally assessed using the site change assessment process and managed within the PQS. The site change management system would continue to ensure that changes are fully documented and progressed through the change management procedure. The change would be assessed to determine its impact on regulatory compliance, quality, and product control strategy, as well as the necessity to revalidate the process. The advantage to implementing the concepts contained within ICH Q12 is that, in accordance with this

assessment, the required reporting category for a change to each EC is defined prospectively in the PLCM.

Given the level of scientific understanding of the process and control strategy, and the rigorous assessment of the impact of postapproval changes on the quality of the drug substance and drug product, some changes to ECs may be managed within the PQS without being reported to the regulatory agency. In addition, reduced reporting categories may be scientifically justified, resulting in a shorter time prior to implementation of the change. This prospective life-cycle management planning can enable a company to manage and implement postapproval CMC changes in a more predictable and efficient manner.

CASE OVERVIEW

The Prior Approval Supplement (PAS) submission discussed in this case study was included in the US FDA Office of Policy for Pharmaceutical Quality's ECs Pilot Program [6] and was submitted less than a year after the initial product approval. The approved original New Drug Application (NDA) for the specific product provided a detailed description of how a science- and risk-based approach was used to define the product control strategy. (The strategy for the product used the enhanced approach per ICH Q8 and Q11 [2, 5], along with an explanation of how the regulatory application was aligned with the company's change management system to ensure appropriate quality throughout the product's life cycle.) The active ingredient was a small molecule manufactured using standard batch process techniques, and the drug product used compendial excipients, direct compression, and a standard tableting process.

During the time when ECs were prepared for this product, ICH Q12 was at Step 2 draft [7], and the FDA specifically requested Pfizer to include the term "key," which was subsequently omitted from the final version of ICH Q12 [1]. Although the term "key" is used in this case study, the choice of ECs and their respective proposed reporting categories would not have changed if the term had not been used. The outcome, regardless of the term "key," remains aligned with the intent and guidance provided in the finalized ICH Q12, which recognizes a continuum of risk and criticality [1].

In November 2019, the FDA approved the PAS proposal that defined product-specific ECs and associated regulatory reporting categories for all aspects of the CMC commitments in the registration application. The discussion provided in this article is intended to share the strategies used to identify ECs for this program and the results of a successful interaction with regulators, and to encourage open communication around the opportunities provided in ICH Q12.

The identified ECs spanned the full scope of manufacturing and included items such as established name, structure, formula, molecular mass, description and composition, batch formula, manufacturing sites, manufacturing procedures, material specifications, critical process steps and intermediates, excipient specifications, release specifications analytical performance, container closure specifications, retest period, and shelf life. The following principles were applied in identifying ECs and assigning reporting categories, in accordance with the Step 2 ICH Q12 draft [7]:

- All changes, including those to non-ECs, were to be managed within the company's robust PQS and appropriate documentation was to be available during inspection.
- ECs associated with the analytical procedures were defined based on the potential risk to the quality of the product using the knowledge obtained during the development of the methods as well as the sample and its matrix.
- Relationships between process parameters/material attributes and product critical quality attributes (CQAs) were well understood and demonstrated through risk assessments and experimentation.
- All critical process parameters (CPPs) and key process parameters (KPPs) were considered ECs.
- Changes to ECs required either prior approval or notification.

Postapproval changes to ECs required different reporting categories depending on the level of potential risk associated with the change. For each EC, the risk to product quality associated with a change was quantified through a robust risk assessment, taking into consideration the overall control strategy. The original criticality assessment was completed using two criticality categories: (a) noncritical process parameters or material attributes that do not impact CQAs, and (b) CPPs or material attributes that are known to have an impact on a CQA and require control to ensure quality. Based on a request from the FDA, the criticality assignments were retrofitted to align with the ICH Q12 Step 2 draft guideline [7]. In the PAS, "key" was defined as "a process parameter or material attribute that may have a relationship to a CQA but has a reduced risk of impacting the safety or efficacy of the product compared with a critical process parameter or material attribute." This definition was used instead of the definition provided in the Step 2 guideline, which was based on process consistency.

Reporting categories were assigned either in alignment with FDA guidelines [8–10] or justified based on reduced risk to quality supported by appropriate development data. Table 1 shows the linkages for the PAS of ECs to criticality/risk to product quality as well as reporting categories for ICH Q12 and several regional guidelines [8, 11]. The terminology used for ICH regulatory reporting category was defined in the PAS in alignment with the ICH Q12 Step 2 guideline [11]:

- Prior approval (PA): Changes that are considered to have sufficient risk to require regulatory review and approval prior to implementation
- Notification Moderate (NM): Moderate-risk changes that are judged not to require prior approval and generally require less information to support the change
- Notification Low (NL): Minor changes that have minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product
- Not Reported (NR): Lowest-risk changes to non-ECs that do not have a potential impact to quality and are managed and documented only within the PQS

Table 1: Relationships among ECs, criticality, and reporting categories [8, 11].

EC	Criticality	Approach	ICH Q12	United States	European Union	Japan	Canada	WHO
Yes	Critical	Implementation after Approval	PA	PAS	Type I	Partial Change Application	Supplemental New Drug Submission	Major Variation
	Critical/Key	Implementation after Submission and Waiting Period	NM	CBE-30	Type 1B	Minor Change Notification	Notifiable Change	Moderate Variation
	Key	Implementation after Submission	NL	CBE-0	Type $1A_{IN}$	Non-approved Matter	Level III (annually)	Minor Notification
		Submit after Implementation		Annual Report	Type 1A			
No	Noncritical	Managed in the PQS	NR	NR	NR		Level IV	With no impact (on-site/GMP record)

Typically, changes to noncritical parameters disclosed in the process description require notification (e.g., in the annual report), at a minimum. When following ICH Q12 guidelines[1], all items that are not ECs do not require postapproval reporting; instead, they are managed within the PQS. This approach allows operational flexibility and the potential for continual improvement.

DISCUSSION

An abbreviated PLCM document, which was abridged to protect the proprietary nature of the information, is presented in the Appendix to this article (available online, see the box on page 58 with the link). The Appendix captures many of the same elements summarized in the pharmaceutical development control strategy tables. Like the control strategy tables, the PLCM contains the parameters and criteria (many criteria were redacted from the Appendix); beyond that, the PLCM contains associated regulatory reporting categories. Reductions in reporting categories compared to the current US guidelines [8–10] that were justified for this product are highlighted in the following sections.

Drug Substance Manufacturing Process

The drug substance synthesis included three chemical steps from the starting material to the drug substance. The synthesis included an isolation of the Step X intermediate and an isolation and recrystallization of the Step Y intermediate. In addition, there was an isolation and recrystallization of the crude drug substance at Step Z. The three isolations/crystallizations were very efficient at purging a variety of impurities other than the one that was specified in the release specification. To aid the risk assessments, the three chemical steps were further divided into a total of 12 focus areas. Based on the risk assessments, each process parameter was assigned a criticality and associated reporting category. Within the wide ranges in which the process parameters were studied, all parameters that were identified as having a functional relationship with a CQA were assigned either the "critical" or "key" criticality classification and categorized as ECs. All process parameters that were identified as having no functional relationship with a CQA were assigned as noncritical and categorized as non-ECs.

The PLCM document for drug substance is shown in rows 4–8 of the Appendix. A comparison of the reporting categories in the PLCM versus current FDA guidance [8] reveals several instances where the PLCM and the guidelines are aligned, as well as many ECs that have reduced reporting categories. The latter are described as follows:

- Omission of the recrystallization at Step Y from the manufacturing process will be reported as NM (Appendix row 5). The recrystallization of the Step Y intermediate was included in the commercial process as an opportunity to purge impurities. However, data collected to date have demonstrated that the recrystallization is not required to ensure drug substance quality. To improve the efficiency of the drug substance manufacturing process, Pfizer may look to remove the recrystallization via a postapproval submission. The change will be formally assessed using the manufacturing site's change management process within the PQS. The process will be revalidated to demonstrate that there is no impact to drug substance quality. Based on this rationale, the removal of recrystallization was accepted as a NM, which is a CBE-30 in the United States, as opposed to a PAS that would otherwise be required based on FDA guidance [8].
- Eight CPPs will be reported as NM rather than PA (Appendix row 6). The justification for this downgrade in reporting category is that the control of the process parameters is not the only component of the overall control strategy for the associated CQAs. Other elements of the overall control strategy, such as the drug substance specification, still mitigate the risk. Although these CPPs have an impact on a CQA, the material can be recovered through reprocessing, as allowed in ICH Q7 [12], because of the efficient purge of all impurities through the normal crystallization unit operations.

- Three KPPs that have very low risk to impact quality attributes that are not listed on the drug substance specification will be reported as NL (Appendix row 7). The reporting category was reduced from NM because these quality attributes are well controlled by the process and the process parameters' limits are not the only components of the overall control strategy.
- Twenty-four noncritical process parameters in Steps X and Y will be not reported (NR) but will be managed within the PQS. Through the enhanced development, it was demonstrated that these parameters lacked both a functional relationship with any CQA over a wide range and an identified edge of failure. These parameters would otherwise be reported as NM based on FDA guidance [8].
- Eighteen Step Z noncritical process parameters that do not impact any CQAs will be not reported but will be managed within the PQS. These parameters had an absence of a functional relationship with a CQA over a wide range and an absence of an identified edge of failure. According to the FDA guidance [8], any changes made after the final intermediate processing steps should be reported as PA.

Drug Product Manufacturing Process

The film-coated tablets were manufactured using a standard manufacturing process, which included blending, compression, and film coating, and used conventional pharmaceutical manufacturing equipment. The process parameter ranges identified through the development process produced tablets that met the proposed acceptance criteria of the drug product within the operating ranges evaluated. All of the parameters assessed produced tablets that met the acceptance criteria of the specified quality attributes of the drug product.

The manufacturing process remained largely unchanged throughout development, and significant experience at the proposed commercial manufacturing site, on the proposed commercial manufacturing equipment using the same common blend formulation, was available. Blend and lubrication revolutions were designated as CPPs based on their potential to affect blend and tablet uniformity. Screen size, film-coat weight gain, and tablet weight and hardness in-process controls (IPCs) were designated as KPPs based on their low risk or potential relationship to the CQAs. The PLCM document for drug product manufacturing and controls is summarized in the rows 27 and 28 of the Appendix.

A comparison of the reporting categories in the PLCM versus current FDA guidance [8] reveals several instances where the PLCM categories are aligned with current guidelines, as well as several examples where reduced reporting categories have been approved:

- For the drug product process description, the reporting categories for screening, blending, compression, and film-coating equipment are aligned with FDA guidance [8] if the equipment is changed to a different operating principle (Appendix row 27). Reporting categories for CPPs and for the tablet hardness IPC are also aligned with FDA guidelines (Appendix row 28).
- Changes to the equipment using the same design and operating principle will not be reported but will be managed by the PQS change management process. These changes do not have a significant impact on product quality, and this eliminates annual reporting responsibilities for five equipment items (Appendix row 27).
- Changes to tablet weight and film-coating IPCs will be reported as NL (Appendix row 28). The downgraded reporting category for tablet weight was justified because weight was monitored throughout compression to allow adjustment if required. The lower reporting category for the film-coating IPC was based on extensive prior knowledge with the equipment and coating system at the commercial manufacturing site and because the film coat is nonfunctional. These parameters would otherwise be reported as NM based on FDA guidance [8].
- Changes to screen aperture will be reported as NL because the screen is used for de-lumping and does not impact particle size. If screening impacted particle size, a change to screen aperture would be reported as PA based on FDA guidance [8].

Analytical Performance

Regulatory metrics associated with changes to analytical methods in the US are somewhat more nuanced due to the particular verbiage in the FDA guidance on changes to an approved NDA or abbreviated NDA (ANDA) [8], which states that alternative analytical methods may be added or revised via an annual report (a Minor Change) as long as this "alternative analytical procedure [...] provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application." This represents a useful path for industry as a way of making modifications to methodology via a low reporting category. However, for purposes of determining compliance, regulatory analytical procedures (i.e., not alternative procedures) are used. Consequently, the unaltered analytical procedure is still "on the books." Furthermore, designation of an alternative analytical procedure as a regulatory procedure is categorized as a Major Change, requiring a PAS. The FDA guidance [8] indicates that changes to an approved regulatory procedure can be prosecuted, by inference, via a CBE-30, as long as the revised procedure provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested.

The ECs for the purity methodology to support the quality evaluation are outlined in rows 17–21 of the Appendix. The ECs ensure the methodology will effectively separate and quantify specified degradation products in the drug substance. The purity method is a standard reversed-phase high-performance liquid chromatography (HPLC) procedure using a C18 column and an acetonitrile-buffer solvent system with gradient elution and ultraviolet (UV) detection. The analytical methods to assess the purity of the drug substance and drug product included ECs based on the method principle, method-specific performance criteria, and

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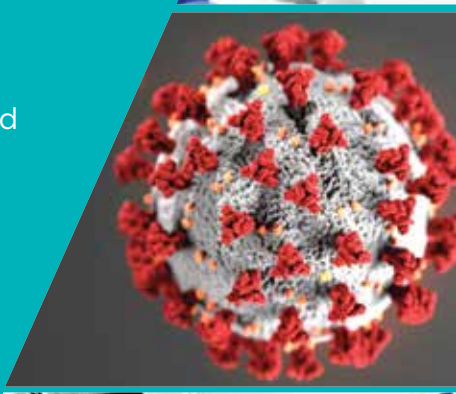

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higher-level method parameters. This performance-based approach was grounded on enhanced understanding of the method and the sample matrix. The ECs were focused primarily on performance attributes of the method (e.g., validation criteria per ICH Q2), but they also included key method parameter acceptable ranges rather than set points. This set of ECs will ensure that any method revisions will result in performance that continues to be aligned with the requirements of the method. Although not all method parameters are reported as ECs, parameters are selected to provide a boundary for what parameter changes may be implemented within the company's PQS. Defining the performance criteria as ECs further ensures any minor parameter changes will provide equivalent or better results than the original methodology.

By indicating specific categories of changes as defined in the PLCM document, the use of ECs helps alleviate whatever ambiguity these multiple options for prosecuting changes impart in terms of the appropriate reporting category to be used. In addition, by applying science- and risk-based assessments of the nature of the change, it is possible to downgrade the reporting category significantly, in some cases to the point where regulatory notification is not required. This can be illustrated through the following analysis. For the purposes of this analysis, it is assumed that the desire is to revise the approved regulatory analytical procedure, not merely introduce an alternative procedure. Six analytical procedures were included in the PAS that defined ECs. They included three liquid chromatography procedures, one using gas chromatography, one using laser diffraction for particle size, and one for dissolution of the drug product with UV end analysis.

- For each of the six procedures, the method principle (e.g., reversed-phase chromatography or spectroscopy) and the validation criteria as outlined in ICH Q2 [13] were defined as ECs, with the highest risk associated with the quality of the product. The method principle and performance criteria, a total of 65 ECs in all, will be reported as PA.
- For each of the six procedures, several of the higher-level operational parameters (e.g., solvent system for HPLC) and the system suitability criteria, 35 ECs in all, will be reported as NM (i.e., CBE-30); this is consistent with the FDA guidance [8], in that changes could be made to these parameters and criteria while still maintaining the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the approved analytical procedures.
- Six slightly more detailed parameters (e.g., the wavelength of the analysis) were still considered ECs but will be reported as NL (i.e., in an annual report). Because these parameters would otherwise have been reported as NM based on FDA guidance [8], they represent additional flexibility.
- As outlined previously, changes to non-ECs (65 parameters) are handled entirely within the PQS, with no reporting to FDA necessary. These parameters would otherwise have been reported as NM based on the FDA guidance; therefore, they represent the largest component of additional flexibility in the area of the analytical procedures.

Specifications

A safety-based approach was used to identify reporting categories for specification ECs to support the overall control strategy. The overall control strategy for ensuring product quality relies on upstream specifications established in conjunction with process understanding. For example, an impurity may have a specified limit in a drug substance starting material at a level that is known to be well purged by the first two steps of the drug substance manufacturing process. Given the purge knowledge, this impurity and its fate product may not be listed on downstream specifications (e.g., intermediate or drug substance) in addition to the starting material specification. The EC reporting categories for upstream specification limits (starting material and intermediate) are therefore based on how a change to that EC would ultimately impact the quality of the drug substance and/or drug product.

The reporting categories for changes to the quality attributes listed on the drug substance specification largely align with the FDA guidance on changes to an approved NDA or ANDA [8]. However, a safety- and risk-based approach was approved for changes to impurity ECs, as shown in the Appendix row 16. For this case study, the drug is approved for treatment of a specific subset of patients with metastatic non-small-cell lung cancer (NSCLC), an indication that falls under the scope of ICH S9 [14]. Both ICH Q3A [15] and ICH S9 [14] guidance on development of anticancer pharmaceuticals provide for some modification of control strategies to be proposed for such pharmaceutical products.

- Because the drug substance is used for the treatment of advanced cancer, quantitative structure–activity relationship (QSAR) findings for potential genotoxicity would not require low-level controls. Given this safety-based risk assessment, impurities in the range of 0.10% to 0.15% can be added to the specification via NM with appropriate validation data in line with the ECs. If an impurity above 0.15% were to be added to the specification, the appropriate supporting toxicology package would be assembled and submitted with the proposed specification change via a PA mechanism.
- Using a safety- and risk-based reporting approach, an increase to an impurity limit in a starting material or the addition of a new impurity to the starting material specification would not necessarily require PA to implement, as shown in row 10 of the Appendix. If it is demonstrated that raising an impurity limit in a starting material does not result in a change to drug substance quality, that starting material limit change should be made via a NM, with the relevant supporting data. Changes to starting material limits that would also result in a necessary change to the drug substance specification would be filed as PA in conjunction with the drug substance specification change.
- A similar approach was taken with the raw material specifications, as shown in row 11 of the Appendix. Special consideration was made for ECs that could impact the safety of the drug

Figure 1: Reporting categories for changes in the drug substance (DS) and drug product (DP) process and analytical methods per FDA guidance [8, 9].

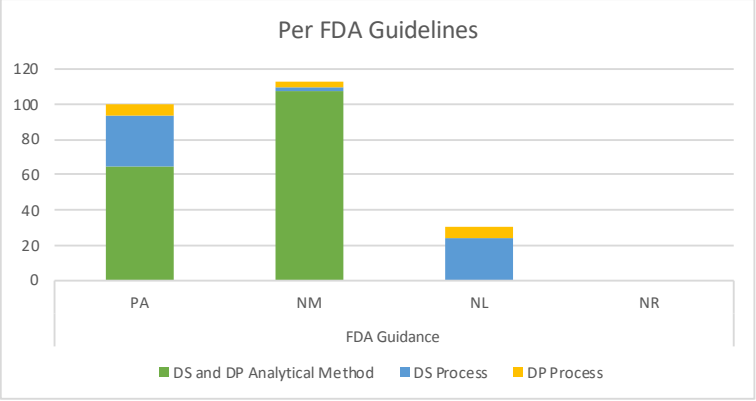
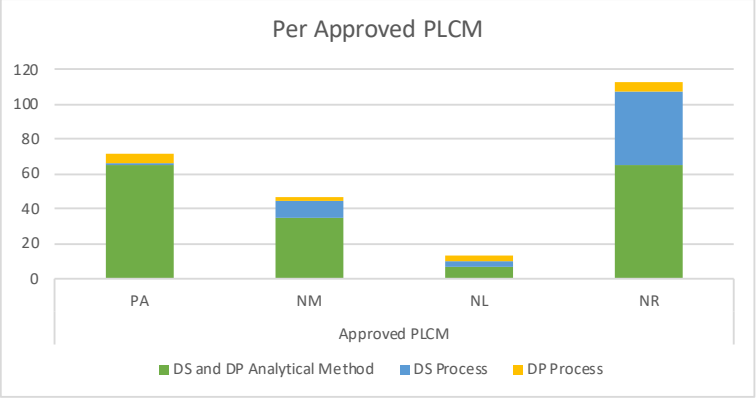


Figure 2: Reporting categories for changes in the drug substance (DS) and drug product (DP) process and analytical methods per approved PLCM based on ICH Q12.



substance (e.g., benzene levels from solvents or palladium levels). If a change to a raw material specification would not impact the quality or safety of the drug substance, the reporting category is lowered to NM.

- A similar safety- and risk-based approach was used to define reporting categories for critical IPCs and intermediate specifications, as shown in row 12 of the Appendix. The reporting category ultimately depends on the impact that change has on the quality of the drug substance. Additionally, if it is understood that the process control limit is not critical for ensuring drug substance quality (it may be referenced as "key"), the reporting mechanism was lowered to NL.
- The quality attributes listed on the drug product specification are identified as critical ECs. There were no specific change categories defined for these attributes because they are aligned with the recommendations in the FDA guidance [8], as shown in row 31 of the Appendix.

Summary of Reporting Categories

The difference in reporting categories according to the FDA guidance [8] versus the approved PLCM is apparent when comparing the graphs in Figures 1 and 2. The largest impact of applying the concepts in ICH Q12 was the ability to manage the 65 individual detailed analytical method operational parameters, 42 drug substance process parameters, and five drug product process parameters within the PQS without reporting. It is clear that the highest degree of regulatory flexibility was achieved for potential changes related to (a) the analytical method parameters, where the number of changes requiring regulatory review and approval (PA and NM) was reduced from 172 to 100, and (b) the drug substance manufacturing process parameters, where the number of changes requiring regulatory review and approval (PA and NM) was reduced from 32 to 11. This operational flexibility should encourage both innovation and continual improvement and improve proactive planning of supply chain adjustments.

The largest impact of applying the concepts in ICH Q12 was the ability to manage the 65 individual detailed analytical method operational parameters, 42 drug substance process parameters, and five drug product process parameters within the PQS without reporting.

CONCLUSION

ICH Q12 [1] provides the regulatory framework to facilitate continual improvement and bridge the technical and regulatory gaps that prevented the postapproval flexibility sought by applying QbD concepts. ECs introduce provisions for reducing the lifecycle management burden and decreasing the time needed to implement some postapproval changes, while at the same time providing quality assurance throughout the product life cycle. The significant reduction in required regulatory reporting for postapproval changes that have low risk to product quality will allow more effective use of resources for both industry and regulatory agencies. In this case study, the approved PLCM does not require regulatory submission for 112 parameters for which postapproval changes would otherwise have been reported, and these parameters represent the largest increase in flexibility gained through the approval of the ECs listed in the PLCM. Strategies with potentially high impacts include (a) the reduction in reporting category from PA to NM for the omission of one of the recrystallization steps in the drug substance process; (b) the ability to manage the 65 individual detailed analytical method operational parameters in the PQS; and (c) the agreement on the safety- and risk-based approach for changes to impurity ECs, which allows impurities in the range of 0.10% to 0.15% to be added to the drug substance specification via NM rather than PA. It should be noted that products developed using minimal or traditional approaches (i.e., not enhanced) may not result in the same level of flexibility through the ICH Q12 [1] framework as those developed through an enhanced approach.

Regulatory approval of ECs by the US FDA permits some future postapproval changes for this product to be managed within the company's PQS without regulatory reporting. Global change implementation planning will be complex as regulatory authorities in other jurisdictions may still require postapproval regulatory submissions. In addition, alignment of local regulatory reporting categories with ICH Q12 [1] is needed; this is especially an issue in regions where changes in the legal framework are required. Global pursuit and acceptance of this endeavor is critical to realize the value of the ICH Q12 vision to harmonize life-cycle management and reduce the postapproval regulatory burden. Postapproval reporting requirements that focus on product quality, safety, and efficacy significantly reduce the number of postapproval submissions and encourage and facilitate continual improvement.

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Appendix: Abridged PLCM from the Full PLCM Approved in the PAS

An appendix presenting an abridged version of the PLCM approved in the PAS is included in the online version of this article, available at ispe.org/sites/default/files/pe/2020-issues/2020-pe-july-aug-appendix-Pfizer-Q12.pdf

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ACHIEVING VERTICAL AND HORIZONTAL INTEGRATION in Pharma 4.0™

By Teresa Minero and Alberto Augeri

This is the third in an ongoing series of articles about Pharma 4.0™. In the Pharma 4.0™ revolution, information is an integral part of the final pharmacological product. A cornerstone for generating this information is the extent, and successful application, of simultaneous, mutual interaction between vertical and horizontal integration.

Recent projects on serialization and track and trace help illustrate the concepts of vertical and horizontal integration. With vertical integration, the unique product identification information (serial number, lot, etc.) used by sensors and printers on the packaging lines is made accessible to the supply chain and regulatory hubs throughout the entire technology stack. With horizontal integration, which employs heterogeneous systems and technologies, a single physical pack of medicines moves through the supply chain accompanied by the correct information about its state and characteristics, right up to delivery to the pharmacist and, ultimately, the patient.

Integration itself is not a novelty. Vertical integration has been connoting industrial system architectures since the 3.0 revolution of the 1970s and 1980s, which was primarily aimed at supporting production and logistic operations and related to automation and IT production. Horizontal integration has also been used for years in the logistic procurement cycle, with dedicated channels between partners as well as business-to-business platforms. Now, in light of the technological, conceptual, and process-related opportunities offered by Pharma 4.0™, the potential of integration in the pharma industry is a promising avenue for investigation.

INTEGRATION'S POTENTIAL IN PHARMA

Let's review aspects of this potential, starting with vertical integration. In its current state, vertical integration makes collecting data from the field simpler (and therefore quicker), less expensive, and more comprehensive than in the past. We can use 3.0 vertical integration methods, such as supporting operations through alarm detection, gaining printouts of process values to be attached to batch reports, and making quick interventions to the machinery. Additionally, we can rely on effective big data collection and treatment to automatically compile batch reports, manage events by exception, join and combine production and quality control results, reduce errors in manual data handling, and assist quality assurance revision and approval processes, ultimately reducing each batch's time to market. To strive even further, with continuous verification toward a well-defined golden batch, we can achieve a deeper understanding of both known and hidden process dynamics, event-based predictive maintenance, and eventual optimization of both operations and investments.

This movement is not just about serialization.

A practical example derives from the increasingly successful application of the concept of digital twins in the equipment control systems in a plant. The entire data and configuration set is replicated by integration in an appropriately configured digital twin. Subsequently, the continuous acquisition of parameters, process values, events, and external actions in all phases of equipment operations, along with intelligent, appropriate elaboration in near-real time, provides a complete set of information that remains available for several different uses, such as overall equipment effectiveness analysis, consumption analysis, product quality review, and the value-added effects described previously. Furthermore, because the initiative engages a wide range of personnel, with a variety of professional skills and potentials, it inherently implements new awareness, participation, and quality in the workplace.

Let's continue with horizontal integration. Full integration between the contract manufacturer and marketing authorization holder is an old dream, unrealized or not fully implemented due to high costs, the need for heavy infrastructure, and concerns about data security, confidentiality, and even validation. Serialization seems to indicate the path to light infrastructure, ensured confidentiality, and security with fully effective information exchanges in the operational cycle, in a validated environment. The old dream seems much closer to becoming reality, along with a wider supply chain visibility, which appears to be increasingly important in mid- to long-term market perspectives. The sooner the dream comes true, the better off all stakeholder in pharma will be.

Should we remark on the effects of the ever-pursued short circuit between the research and development pipeline and punctual information on medicine usage? Or on the feedback made accessible by therapeutic adherence, with its implications in terms of service brought to the patient? Perhaps it is enough to cite the significant movement toward a structural exchange of information that local and global regulations are increasingly developing—this movement is not just about serialization but also, to mention a few other innovations, unique device identification (UDI), eXtended EudraVigilance Medicinal Product Report Message (XEVPRM) and Extended EudraVigilance Medicinal Product Dictionary (XEVMPD) (for drug safety), and identification of medicinal products (IDMP).

CONCLUSION

When conceived in the way proposed in this article, the integration process opens the door to new information robustness and transparency, which are certainly explicit, growing requests by regulators. Additionally, integration in Pharma 4.0™ promises to substantially improve development, production, and logistic operations, with advantages for all stakeholders: the industry in all its components, regulatory authorities, and patients.

About the authors

Teresa Minero is the Founder and the CEO of LifeBee, a business consulting and digital company dedicated to life sciences. For more than 30 years, including more than 25 years in the life sciences, she has managed international consulting and digital innovation projects for production, logistics, quality, regulatory, and R&D, and managed start-ups and business divisions for international consulting groups. She has been a lecturer and chair for many conferences and is the author of several articles on digitalizing life sciences and Pharma 4.0™. Teresa has been an ISPE member since 1996. She is currently the Chair of the ISPE Italian Affiliate and a member of both the ISPE European Leadership Team and the ISPE Steering Committee for Pharma 4.0™ Global Special Interest Group.

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THE UNTAPPED POTENTIAL OF AI AND AUTOMATION in Pharmacovigilance

By Jennifer Markey and Kelly Traverso

Between 2009 and 2019, the number of adverse events (AEs) for drugs and therapeutic biologic products recorded by the US FDA Adverse Event Reporting System (FAERS) increased more than 300%, from 490,032 to 2.19 million cases (as of 31 December 2019) [1]. Given the growth in case volume, the expanding number of sources for potential AEs, and the complexity of new therapies, the pharmaceutical industry is exploring innovative technologies such as artificial intelligence (AI) to improve efficiency and quality in pharmacovigilance.

Safety surveillance needs to go beyond data-mining of spontaneous reporting systems and medical literature. Internal data sources can be supplemented with real-world data from electronic health records (EHRs), insurance claims, social media, and online communities. However, with traditional pharmacovigilance approaches, it is challenging—if not impossible—to incorporate, review, and analyze all these data in a timely manner.

AI can not only automate many manual, repetitive processes and enable greater consistency but also remove human bias and provide valuable insights for data scientists, medical reviewers, and physicians. They can understand their data in a much more comprehensive and extensive way than was previously possible.

By improving data quality, providing real-time data insights during processing, and enabling faster and more proactive signal detection, AI can have a huge impact on pharmacovigilance and patient protection. As drug safety shifts focus from operational tasks to more proactive risk management and greater data transparency among members of the pharma industry, patients, and providers, AI will become more essential. Applying AI in several key areas can help improve the end-to-end pharmacovigilance life cycle. See Figure 1 for an example of a unified solution.

AUTOMATING CASE INTAKE

One of the most frequently discussed areas to apply AI is case intake. With the growing amount of information and numerous data sources containing mostly unstructured content, natural language processing (NLP) can be used to extract information quickly and efficiently. AI can be leveraged to convert content into structured data, autocode the data to dictionaries or code lists, and prioritize case findings based on seriousness, expectedness, and relatedness. Manual confirmations and adjustments to the case are fed back to the AI engine so that the machine learns and adjusts over time, thereby increasing accuracy and consistency.

Other areas where AI can improve case intake include literature monitoring, upfront review and data extraction from legal cases, and, potentially, using voice recognition to automate intake of AEs from call centers.

Literature Monitoring

Many pharmaceutical companies struggle with retrieving and reviewing scientific and medical literature. Challenges include developing a good search strategy, understanding and extracting information from unstructured content, and converting content into AE data for automatic loading into a safety database.

AI can automatically, continuously, and extensively scan literature to find articles mentioning company products and determine whether the mentions involve an AE or multiple AEs. AE data can then be extracted from articles, imported into structured fields, and put directly into the safety database for review.

Figure 1: Example of a unified safety solution.

Legal Case Review

The volume of information received for legal cases can be considerable, and manual review of all source documentation can take days. Similar to medical literature review, AI can be used to efficiently "read and understand" legal case content to extract meaningful information.

Call Center Data Collection

Call centers are important collection points for AE information. Recent advancements in voice recognition technologies are enabling companies to consider using AI to extract AE information from call center recordings and load it into the safety database. Alternatively, AI can be used to quality-check data entered through manual data entry. The advances in technologies and the use of AI will reduce manual data entry, eliminate the need to email AE forms, and ultimately integrate call center systems with a safety database.

STREAMLINING CASE PROCESSING

Many aspects of case processing are still manual, requiring considerable overhead and creating compliance risk. Between 1 April 2014 and 31 March 2015, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) conducted 47 inspections of pharma companies and found 27 critical, 169 major, and 155 minor findings. Of those findings, individual safety case report (ICSR) management was one of the top cited areas, especially for major and minor findings [2]. Leveraging automation and AI can drive greater efficiencies, consistency, and quality in case management, narrative generation, and quality control, and improve future inspections.

Automating Narratives

Challenges with narrative writing include resourcing, consistency, timeliness with high-quality and potentially numerous data sources used as input, and high variability in the templates. In addition, for cases that have multiple follow-ups, the narrative can become disjointed and confusing. Automating narrative writing with natural language generation (NLG) provides greater quality and consistency within the narratives batch and reduces time to develop and finalize the narrative. AI can quickly and efficiently extract all relevant information, generate the narrative, and put it in the desired format or template. Built-in audit trails and version control also ensure that each version of the narrative is automatically tracked and stored for easy accessibility and comparison.

Quality Control

Manually comparing a source document with data entered in a database is a tedious and error-prone task. In addition, ensuring consistency across cases in the safety database is difficult. A "quality bot" can quickly and easily automate the quality review process by comparing the source data with the data in the safety database,

AI is key to moving toward proactive and eventually predictive pharmacovigilance.

looking for accuracy against the data entry guidelines and across the database for consistency with other similar cases—i.e., cases involving the same product, therapeutic area, or AE system organ class. Individual cases reviewed by the quality bot are assigned a quality score, and those that fall outside the threshold are flagged for review by a pharmacovigilance specialist.

With access to better-quality data, medical professionals can better focus their efforts on medical review and deepen their understanding of the safety profile of their products.

PROACTIVE SIGNAL DETECTION AND RISK MANAGEMENT

The goal of signal detection is to identify unknown causal associations between medicines and unexpected events. To achieve this, pharmacovigilance organizations must retrieve and periodically analyze safety data from various sources, including their global safety database, external data sources such as FAERS, VigiBase, and, potentially, real-world evidence sources.

AI can help rapidly analyze data across multiple data sources by many different factors, such as patient demographics, medical history, and medicines, in a fraction of the time comparable analysis using traditional methods would take. With AI, pharmacovigilance teams not only can have more comprehensive, real-time analyses but also gain more time to evaluate potential signals, make the appropriate signal validation decisions, and determine resulting actions to achieve better patient outcomes. After signals are detected and validated, AI can automate and manage the required risk management activities. A risk management plan can be created based on existing templates and related content from internal sources.

With the shift to proactive pharmacovigilance, expanding number of data sources, and technology improvements, it will be insufficient to report when an AE was identified. Regulators will also want to know, "When *should* you have known about the AE?" AI is key to moving toward proactive and eventually predictive pharmacovigilance.

PERFORMING ANALYSIS

In the digital era, more safety data are being collected, and AI is enabling companies to maximize the value of the information beyond interactive analytics. Using different data techniques and machine learning (ML), AI can quickly and efficiently analyze large and varied datasets. It can be used to solve complex problems or identify complex patterns, such as discovering the factors governing the association of a medicinal product and its effects on the population, linking certain compounds to a gene receptor, or flagging possible new indications for a product. Providing better epidemiological understanding of a disease can improve public health as well as patient safety and outcomes.

Analysis is only limited by the available data and one's imagination. AI can analyze data much more extensively and quickly than traditional analytical methods. Stakeholders will have more time to review and validate the analysis and may be able to identify risks earlier.

PREPARING AGGREGATE REPORT CONTENT

Every product, regardless of development stage, has periodic reporting requirements. Pharmacovigilance teams need to submit to regulatory authorities development safety update reports (DSURs), periodic adverse drug experience reports (PADERs), periodic safety update reports (PSURs), or periodic benefit-risk evaluation reports (PBRERs). The exact reporting requirements vary by country, approval status, and stage of development for a medicinal product. The process of scheduling, planning, and preparing these aggregate reports is very time and resource intensive, but it can be made more efficient by AI applications.

Scheduling Line Listings and Tables

Periodic report content can be generated automatically by scheduling an automatic data pull from the safety database based on the product's international birth date (IBD), the report data lock point, and other configurable variables. Once the information is retrieved, it can be placed in the correct template, ready for authoring.

Report Authoring

Using NLG, AI can draft sections of the report such as the worldwide approval status, changes to reference safety information in a PSUR, signal overview for a PBRER, or actions taken for safety reasons since the last report. The most knowledge-intensive steps for aggregate reporting are analysis of the safety data and summarizing it in written form, which requires medical judgment. Eventually, as AI, NLG, and ML become more sophisticated, AI-written draft sections of the report will come to closely approximate the final version, requiring just review and minor adjustments by the human author.

RECONCILIATION AND MASTER DATA MANAGEMENT

Within a pharmaceutical or biotech company, AE information may originate from many areas, including clinical trials, product complaints, medical information call centers, and healthcare provider or patient reports. As the case is processed and more data are

received, all the information sources must stay consistent and harmonious across the organization. When done manually, the data harmonization and cleaning process (i.e., reconciliation) is time consuming and a significant expense for most companies.

The implementation of a cross-development cloud platform with integrated AI processes could significantly reduce the amount of time spent on reconciliation. It could also improve the quality and consistency of the data, reducing risk for the organization.

The same technologies and automation methods can also be applied to data management. Having one source of common data that are used for multiple purposes has historically been difficult to achieve. Using AI to manage data changes and notifications could simplify data management and reduce overhead. For example, AI can help the regulatory team maintain one master company product dictionary that is also used by personnel in safety, clinical, and medical affairs. When the regulatory team changes or updates the master dictionary, other functional consumers automatically receive notifications and updates so there are no discrepancies. AI and automation can also help maintain label information, local licenses, and other types of data.

UNIFIED AI SOLUTIONS

As cases are processed, there are many opportunities for AI to learn from decisions to improve processing of future cases. For example, a person contacts the call center to report they have a throbbing headache after taking a specific medication. The AI engine can process the information and suggest the symptom to be coded as a cluster headache. During medical review of several similar cases, the code is changed to a type of migraine headache. The AI engine can learn from the changes and in the future, for similar symptoms and cases, suggest coding it as a migraine headache.

With a unified pharmacovigilance solution, AI can continually improve, maximizing the value of the safety data and learnings.

Unfortunately, pharmacovigilance systems are typically fragmented, with many tools and technologies from a variety of vendors, and that can limit the AI engine from accessing data to learn and detect patterns. Cloud applications are designed to easily work together. With a unified pharmacovigilance solution supporting seamless, end-to-end processes, AI can continually improve, maximizing the value of the safety data and learnings.

AI CHALLENGES AND RISKS

Though AI has many potential benefits, there are also concerns about the technology, including whether AI can correctly interpret data, how to explain AI-based decisions, and the amount and quality of data needed to train an AI engine.

ML may require large, comprehensive data sets that are difficult to obtain or require significant human effort to create and maintain. In the pharmacovigilance industry, AI solutions can leverage public databases of AE data, such as FAERS, VigiBase, and EudraVigilance Data Analysis System (EVDAS). There are also emerging approaches that can help close data gaps, such as in-stream supervised learning where data are tagged in the course of an activity [3].

To mitigate risks, companies can take a phased approach to adopting AI, such as initially using it to assist in decision-making before automating an entire process. For example, in case intake, AI can provide suggestions on coding and priority that would be reviewed and confirmed by a human. Once companies have confidence in the AI engine, they can enable automatic routing of cases for processing.

CONCLUSION

In recent years, there has been a lot of discussion about how to effectively use AI for pharmacovigilance. Many of these conversations have focused on solving the case intake problem, which is a significant burden and expense for safety organizations. However, the future of AI for pharmacovigilance is much broader as AI can be applied to many other areas.

AI has already made great strides in many other areas of life sciences, propelled forward by cloud technology. For example, it is advancing genomic diagnostics and helps radiologists detect breast cancer in medical images [4, 5]. For pharmacovigilance, cloud technologies, automation, and AI will enable companies to realize the greatest value from their safety data and drive better insights and transparency so that we—as patients and consumers—know that the medications we may need are safe and effective.

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Kelly Traverso

ISPE BRIEFS

ISPE Special Interest Group for Cybersecurity

ISPE has a new special interest group (SIG) to work on IT cybersecurity. The SIG was formed under GAMP®. A conversation with Jason Young of Silver Bullet Security, who heads the new group, provides details about the SIG.

Why has this SIG been formed?

Cybersecurity has become more critical in today's GxP environment. The speed and complexity of growth within information technology that supports business and GxP operations has introduced greater cybersecurity risks. The validation process has to ensure the effective incorporation of important cybersecurity controls and methodologies.

What are the key drivers/objectives of the SIG?

The importance of including key concepts of cybersecurity risk management in GAMP® 5 and Data Integrity models are the key drives and objectives. Cybersecurity requirements should be part of the specification process, included in the risk assessment, and there should be verification that the required controls are operating effectively. We want to educate ISPE members and the industry on these concepts.

> Cybersecurity has become more critical in today's GxP environment.

What regions are represented by SIG members?

The team includes owner companies, consultants, and organizations across the world from the US, Europe, and Asia.

What are the hot topics being addressed?

Topics include identifying relevant regulatory cybersecurity requirements; identifying regulatory expectations; how to manage cybersecurity for infrastructure and GxP regulated systems by using existing good cybersecurity practices; and incorporating cybersecurity into the GAMP® 5 framework of specification, risk assessment process, and verification of appropriate controls.

What are the main challenges with these topics?

The main challenge is creating guidelines that are easy to understand and adopt.

What is the expected output of the SIG, and what is the time frame?

The output will include ISPE education sessions (for example, at the ISPE Annual Meeting & Expo and local ISPE Chapter and Affiliate meetings) and developing ideas and concepts for articles, papers, and presentations. The time frame is late 2020 through early 2021. The SIG is established, and the plan is to define terms, technology boundaries, and an initial set of guidance.

—Anthony Margetts

Welcome *The Bridge*, ISPE Women in Pharma® Newsletter

ISPE Women in Pharma® (WIP) has launched a monthly newsletter devoted to WIP and its many activities and initiatives. *The Bridge* began publishing in March. It was developed to open the lines of communication among ISPE chapter and affiliate WIP leaders, provide news, share ideas and best practices, and ensure WIP leaders are kept informed of helpful information as well as updates in policies and procedures.

The May issue (the most recent issue at *Pharmaceutical Engineering*® press time) featured articles on the "new normal" of life in the pandemic world, a new lead for the WIP Mentor Circle Program, and updates on WIP activities from a number of ISPE WIP Chapters and Affiliates. You can find *The Bridge* on the ISPE website at ispe.org/women-pharma/newsletter

ISPE D/A/CH YPs and Students Face-to-Face Meeting in February

Members of the ISPE D/A/CH Young Professionals and Students at a face-to-face meeting in Cologne, Germany, in February.

Before the onset of the COVID-19 pandemic, the ISPE Germany/Austria/Switzerland (D/A/CH) Affiliate Young Professionals and Students (YP&S) met in Cologne, Germany, in February for a face-to-face meeting. Eleven members discussed strategy and planned events, aligning their strategy with the ISPE Strategic Plan 2020–2022.

The YP&S group plans to focus more on individual development of its members and create a community feeling among the young professionals (YPs) and students in our industry. We want to face the challenges of connecting knowledge between YPs, students, and senior professionals in a more globalized world while questioning the status quo. We like to embrace the paradigm shift in the industry and focus our attention more on the patient and our social responsibilities.

—Leon Clemenz

Share Your SIG, CoP, Chapter or Affiliate News!

We'd like to feature your Chapter, Affiliate, CoP, SIG, or other ISPE group in upcoming ISPE Briefs. Share highlights from training programs, conferences, social events, or other activities in an article of 250 to 400 words. We welcome photos (300 dpi or >1 MB). Email submissions to Susan Sandler, Senior Director, Editorial, at ssandler@ispe.org

LYOPHILIZER INSTRUMENTATION CALIBRATION:

Principles and Practices

By Jason Zagorski, Denise Miller, and Edward H. Trappler

Historically, the pharmaceutical industry's focus has been on the lyophilization process and equipment, but discussion about calibration of process monitoring and control instrumentation has been quite limited. Recently, focused attention has been given to control and monitoring instrumentation for lyophilization.

In 2017, Nail and colleagues published an overview of various process monitoring methods and devices that addresses temperature and pressure measurement [1]. Still, the industry lacks consensus about best practices. A greater understanding of the science and technology of lyophilization drives improvements in calibration, which leads to better process control and increased confidence in achieving product quality.

CALIBRATION REQUIREMENTS

Calibration requirements for the lyophilization process are unique. For example, the process includes a temperature range from extreme cold during freezing to relatively high temperatures during sterilization, as well as multiple pressure ranges. This relatively wide range of conditions poses specific needs that require careful consideration in addressing calibration.

Furthermore, the critical process parameters (CPPs) that directly affect the finished product's critical quality attributes (CQAs) warrant different attention than key process parameters (KPPs), which reflect process conditions and equipment performance. Temperature, pressure control, and time are well recognized as the principal CPPs for lyophilization [2].

Each CPP or KPP requires specific levels of accuracy, precision, and resolution. A thorough knowledge of the instrumentation and an understanding of the process form the foundation for a well-developed calibration program. This is essential to providing a high level of confidence in parameter measurement and process control.

A well-developed calibration program needs to encompass complete and comprehensive procedures, an effective management system, and capabilities to conduct calibration that spans the entire operating range of the equipment with an adequate resolution [3].

Proper calibration of an instrument provides confidence that the reported values accurately reflect the process condition for each measure made. During batch manufacture, well-calibrated instruments are critical to achieve and verify reproducibility of the process for each batch. Adequate accuracy and precision in measurements ultimately establish confidence that the desired level of product quality is continually achieved.

LYOPHILIZATION OVERVIEW

Lyophilization is a drying process for preservation of sensitive pharmaceutical products. This process is conducted over a range of subambient to elevated temperatures and a range of subatmospheric pressures. The three principal parts of the process—freezing, primary drying, and secondary drying—are conducted at different combinations of these temperatures and pressures. Freezing occurs at temperatures as low as –55°C and at or near 1 atmosphere. Primary drying is conducted at both low temperatures and low pressures. Secondary drying is completed at ambient or warmer temperatures and, by convention, low pressures. These varied conditions present unusual challenges in ensuring proper calibration.

In principle, the lyophilization process is driven by the environmental conditions created by the lyophilization equipment. Through the use of a circulating heat-transfer fluid, the product shelves function as heat exchangers, where transfer of heat from the product during freezing and to the product during drying is

accomplished by controlling the shelf temperature. The shelf temperature is measured and monitored using a resistance temperature detector (RTD) in a thermowell immersed in the heat-transfer fluid supplied to the shelves.

The required pressures during the drying phases are achieved by evacuating the atmosphere in the lyophilizer to a relatively low pressure, and controlling the pressure to a specific level by introducing an inert gas, such as sterile filtered nitrogen. The low pressure is measured and monitored using an electronic pressure sensor with the capability to detect pressures at a fraction of 1 atmosphere (760 mm Hg at sea level) and resolving such pressures to at least 1/760,000 of 1 atmosphere (0.001 mm Hg). This electronic pressure sensor is located on the product chamber and condenser vessel. These conditions of shelf (inlet) temperature and chamber pressure are CPPs (i.e., process parameters that directly affect finished product quality). CPPs and KPPs for lyophilization are presented in Table 1 [4].

Table 2 lists the desirable range and resolution for temperature and pressure measurements based on the parameters used for lyophilization. For lyophilizers used in preparation of sterile products and sterilized using saturated steam, the temperature range would increase to 130°C.

Process conditions of temperature are reported in engineering units of degrees Celsius (°C). Typically monitored lyophilizer components are the shelf inlet temperature as a CPP, and the shelf outlet and condenser temperatures as KPPs. Temperatures of other parts of the system (such as subcooled refrigerant into the expansion valve, heat-transfer fluid into and out of the heater unit and each refrigeration unit heat exchanger, and cooling water to and from refrigeration units) are also monitored, primarily to assess performance and for maintenance purposes.

There are generally two scales used for reporting pressure: small fractions of 1 atmosphere, which are reported in hundreds of units, and large fractions of 1 atmosphere, which are reported in tenths. During freezing, and then again during stoppering of vials at the end of secondary drying, chamber pressure may be monitored and controlled to units of pounds per square inch (PSIA) or bars in tenths of 1 atmosphere. During primary and secondary drying, pressures are often measured in tens to hundreds of microns of mercury (µm Hg) or microbars (µbar). The pressure range spans from a few microns or a few microbars to up to 10,000 µm Hg (13,000 µbar).

REFERENCES AND STANDARDS

Standards should be guided by an international or national primary standard from an authority such as the International Bureau of Weights and Measures (BIPM) or the National Institute of Science and Technology (NIST) in the US. These primary standards are used to determine reference (secondary) standards. Calibration labs then use these secondary standards to calibrate the working standards. Working standards are used by individuals to calibrate instruments for controlling and monitoring equipment and processes.

Table 1: Parameters to monitor during lyophilization.

Parameter Type	Definition	Examples
Critical process parameter (CPP)	A condition that may directly affect finished product quality	• Shelf (inlet) temperature • Chamber pressure • Time
Key process parameter (KPP)	A condition that may affect a CPP but does not directly affect finished product quality	• Condenser: temperature sensor attached directly on the condenser surface or at inlet and outlet • Shelf outlet temperature • Heat-transfer fluid temperature (refrigeration unit heat exchangers, outlet from heater) • Condenser pressure • Vacuum pump(s) inlet pressure

Table 2: Engineering units, range, and resolution in temperature and pressure for lyophilization.

Engineering Unit	Range	Resolution
°C	−80.0 to 50.0	0.1
µm Hg	1 to 10,000	0.1
µbar	1 to 10,000	0.1
PSIA	0.0 to 35.0	0.1
mm Hg	1 to 760	1
Bar	0.00 to 1.00	0.01

GUARDBANDING

In conjunction with establishing an acceptable tolerance, an approach called "guardbanding" may be used when clearly defined within the calibration procedure. Guardbanding adjusts tolerance for an instrument to be within a narrower range relative to the allowable instrument tolerance [5]. Guardbanding can mitigate the risk of an out of tolerance (OOT) measurement due to drift in the measurement accuracy or uncertainty.

For example, suppose a unit under test (UUT) has an upper temperature limit or tolerance of 0.5°C and the accuracy of the working standard reference being used to measure the temperature is ±0.1°C. When the UUT is at its limit of 0.5°C, the actual value may be anywhere from 0.4°C to 0.6°C, due to the accuracy of the working standard reference. This means that there is a reasonable possibility that 50% of the time when the UUT is at its tolerance limit of 0.5°C, the UUT may actually be beyond its limit. Depending on the process, exceeding 0.5°C may pose a serious risk. In this case,

Table 3: Uncertainty factors justifying guardbanding for temperature calibration.

Device	Uncertainty
Working standard	0.025°C
Dry block uniformity	0.05°C
Sum of uncertainties	0.075°C
TUR	4
Guardband around target	0.3°C

applying the guardbanding method to set an actual tolerance limit of 0.4°C could reduce the risk that the reference system would result in a false acceptance.

Guardbanding may also be used to prevent drift of an instrument's calibration from causing a future OOT result. For example, suppose a UUT has a calibration tolerance of ±1°C. If the instrument were found during a routine calibration check to be near or at that tolerance limit, it would be appropriate to make a calibration adjustment to bring that unit closer to the temperature indicated by the working reference. Technically, the UUT would be within tolerance and no calibration adjustment would be necessary. However, if the unit's calibration were to drift another 0.1°C before the next routine calibration, that would cause an OOT result. Had the unit been adjusted to within 0.5°C of the reference temperature during the previous calibration, the unit would still be within the acceptable calibration tolerance even after the 0.1°C drift.

Guardbanding can quickly become complicated when a rigorous approach of the principle is applied to a calibration program, particularly when uncertainty calculations are considered. For field-level calibrations, a simple guardbanding practice—such as specifying an adjustment when the value is equal to half a unit's calibration tolerance—may be sufficient. For example, it may be desirable to adjust an instrument when the difference from the working reference instrument approaches 0.3°C. This accommodates any instrument or sensor drift over the interval between calibration checks. Or it may be desirable to select a range at which an adjustment is directed within the procedure to avoid approaching a tolerance limit or even a guardband. Such a pragmatic approach is based on establishing a desired variation from the reference value for making an adjustment, considering the criticality of the temperature or pressure relative to the CPP.

A more rigorous approach is to add the allowable uncertainty for each instrument in the chain of reference standards from the primary standard to the working standard used for calibration. In essence, it is the sum of the errors for each factor that may contribute to a level of uncertainty for the calibration.

Table 3 lists uncertainty levels as sources of error for a calibration. Using these values as an illustration and assuming a reasonable test uncertainty ratio (TUR) based on the sum of the tolerances would provide a total measurement uncertainty. This approach would yield an uncertainty level of 5%, or a confidence level of 95%.

Many resources [6–9] explain the concepts and principles of uncertainty and guardbanding, with official industry requirements outlined in *ANSI/NCSL Z540.3-2006 (R2013): Requirements for Calibration of Measuring and Test Equipment* [10].

CALIBRATION PROGRAM REQUIREMENTS

A well-developed calibration program has three essential aspects: methodology, administration, and the calibration itself.

Methodology

Proper calibration methods inspire confidence that an instrument will render accurate measurements. Establishing a proper and effective methodology requires a thorough understanding of the process in conjunction with basic knowledge of the instrumentation. It is also important to recognize that the entire process operating range is crucial for assurance of the measured parameters.

Calibration frequencies and tolerances should be well defined and reflect the criticality of measurements for different parameters within the lyophilization process. When describing an allowable tolerance, if the desired confidence is to be within one-half of 1°C, the tolerance may be stated as less than ±0.5°C. If a tolerance up to one-half of 1°C is acceptable, the tolerance may be stated as equal to or less than ±0.5°C. For such resolution, the results comparing the reported temperature relative to the working standard should be reported to one-tenth of a degree (0.1°C).

The desired tolerances should be tailored to the process rather than the instrument's capable range. Some temperature measurement and control instrumentation may have an operating range for measuring from –100°C to 400°C (a span of 500°C), while the process range being monitored may be –80°C to 50°C (a span of 130°C). There is potential to experience reduced accuracy and precision with calibrating to the wider instrument span of 500°C rather than to the narrower process span of 130°C. In general, the smaller the range evaluated for calibration is, the greater the accuracy and precision will be. If an instrument cannot be calibrated to the level needed for process control, the instrument is not appropriate for the task.

Through trending, it is possible to provide some flexibility in the requirements for calibration frequency and tolerances and adjust them based on performance. For example, suppose CPPs and KPPs for a process and equipment are monitored by a high-quality stand-alone process recorder for electronic data storage, with the ability to present process data in a trend or alphanumerically. The calibration procedure for such an instrument allows for calibrating a complete range of input channels, all at the same time, to the same reference, and to the same tolerance. It is expected that the calibration of an instrument monitoring shelf inlet temperature (a CPP) will be verified every six months and be within a 0.5°C tolerance. The same instrument may monitor and record the shelf outlet and condenser temperatures (KPPs), and the subcooled refrigerant temperature (a variable of interest for maintenance). Although the calibration expectation for an instrument monitoring these KPPs is an annual verification and a tolerance of

equal to or less than ±1°C, the extra effort to check each sensor semiannually when the shelf inlet is checked and to use the same tolerance for all calibrations is justified by the increased confidence in the monitoring data provided.

Administration

Administrative oversight ensures a proper calibration program is being implemented, and performance of calibration is timely and consistent. Detailed and standardized calibration procedures, a tracking system for all required instrument calibrations, and a thorough review process are vital.

It also may be helpful to implement trending of repeatability and any drift to evaluate instrument suitability and reliability. This trending can demonstrate robustness and may lead to shortening or extending a calibration interval. Considering the ultimate goal of a high level of process control, these components should be tailored to work together in an effective and efficient manner.

The standard operating procedures (SOP) need to be clear, concise, and comprehensive such that any person reasonably trained in instrumentation and electronics would be able to successfully complete a calibration activity. The procedures should be specific to the instrumentation requiring calibration, as well as the criticality of the measurements. The SOP and accompanying data sheets are most useful when important information is included in each section, as outlined in Table 4.

It is imperative to include the rationale for the frequency and allowable tolerance in the SOP. A simple statement such as "This instrument measures and controls a CPP of shelf temperature and is to be calibrated every six months, with an allowable tolerance of equal to or less than ±0.5°C" clearly conveys the importance of the instrument and the relative impact of proper calibration. If a sensor is monitoring a KPP, less-frequent calibration and a wider tolerance may be acceptable.

An effective and efficient management system is essential to ensure adequate and timely calibration activities. A resource planning tool is an easy way to quickly assess the status of any instrumentation and equipment.

The best management system will depend on the company's specific organizational structure. Basic elements of an effective management system include equipment descriptions and unique identifiers, calibration intervals or frequencies, and notifications of overdue calibration in a tracking and scheduling tool. In concert with the calibration management system, the quality management system outlines oversight of the calibration program, approaches to the assessment of results, and impact of OOT results to the process and product.

Performing Calibration

When a calibration is conducted, care and attention to detail promote confidence in the results. For example, adequate time for settling of the calibration condition allows for proper evaluation of stability, particularly for sensors such as a larger immersion-type RTD. This can provide an indication of the potential precision.

Table 4: Sections of a comprehensive calibration SOP.

Section	Content
Objective	• What the procedure is intended to achieve • The accuracy and precision of the measurement
Scope	• Descriptions of the activity, method, and technique, without any room for interpretation • The measurements or instrument to which the calibration applies • The condition or parameter being measured and whether it is a CPP or KPP
General	• Definitions, background, comments, or notes for the parameter, instrument, or procedure • Desired tolerance and range for adjustment, frequency, guardbanding, and any precautions
Safety	• Notice of any safety considerations, such as working at a high temperature or pressure
Procedure	• A logical, sequential series of steps describing the activity or operations required to complete the task, starting with removing the sensor from the lyophilizer (if applicable) through conditions and parameters for calibration and making adjustments to reinstalling the sensor and completing documentation • A description for each step • Descriptions of corrective actions and OOT impact assessment • Instructions for how to address OOT results and take corrective actions
Data sheets	• Used to record the results, both "as found" as well as "as left" • Sufficient space to record information and data to convey a clear understanding • Documentation of the tolerances on the respective data sheets for ease of review by all operations and quality staff • Date for next required calibration

Deviation from the reference reflects the level of accuracy that is achieved for the measurement.

Calibration may evaluate an instrument or sensor alone or assess them together, which is referred to as a "loop check." Whenever possible, performing a loop check is favorable to a stand-alone check of a sensor or instrument.

An instrument's accuracy may be assessed by creating a specific input signal that would be generated by a sensor to represent a condition, such as a voltage or resistance to represent a measured pressure or temperature. A known resistance may be generated and fed as an input to an instrument based on the value from a standard curve, such as the value for a 100-ohm platinum RTD that represents a specific temperature. For example, to check the instrument accuracy at 0°C, an input signal of 100 ohms would be generated. This is a useful technique when there is a question about the results reported by an instrument, as it isolates the cause of measurement error.

The loop check, the most effective calibration approach, includes the actual sensor and instrument as an integral system

Figure 1: Dry block instruments for calibration to 55°C (left) and 75°C (right).

and ensures all associated wiring, cables, and connectors are accommodated, as these may influence the reported measurement. To conduct a loop check, the sensor is exposed to the actual condition for a pressure or temperature, the condition is controlled to be within an acceptable variation to a reference for accuracy, and the measurement is suitably stable to assess precision.

It is best practice that the reference measurement be resolved to at least 1 decade greater resolution to be able to resolve to one additional significant figure than the stated parameter measurement. For pressure, if the instrument calibration is to 1 µm Hg, the resolution of the working standard should be 0.1 µm Hg. If a temperature in process monitoring is calibrated to 0.1°C, the working standard reference should be resolved to 0.01°C.

Approaches to conducting calibration and the working standard used for pressure and temperature instruments have significant influence on reliability and confidence in monitoring and controlling the lyophilization equipment and process.

TEMPERATURE CALIBRATION

Two types of temperature sensors are commonly used on lyophilizers: thermocouples and RTDs. The specific types of sensors used are determined by the temperature ranges normally used for lyophilization. Consideration must be given to the locations of temperature measurement within the lyophilizer.

The shelf heat-transfer fluid temperature is normally measured using a 100-ohm platinum RTD immersed in a relatively large thermowell installed in the heat-transfer fluid piping. For this RTD, a precise measurement location is not required, as when measuring product temperature. Because this sensor measures the CPP of shelf temperature, its reliability and stability are preferred. Product is normally monitored by type T thermocouples, as they provide a precise point or location of the measurement.

An RTD consists of a resistor where the resistance value varies as a function of temperature. A typical RTD sensor consists of a platinum wire wound around a ceramic or glass core encased within a nonconductive protective coating. The sensor is housed within a protective stainless steel sheath. Because the relationship between resistance and temperature is stable and consistent, measuring the resistance across the sensing element at a given temperature allows that temperature to be measured with a high degree of accuracy and repeatability. Two-wire RTDs are commonly used, although a three-wire RTD is preferred, as it compensates for lead-wire resistances, which may introduce a measurement error [11, 12].

Thermocouples operate off the thermoelectric effect, where a voltage is generated when two dissimilar metals meet. This voltage varies as the temperature at that junction changes. Type K (nickel-chromium/nickel-aluminum) and type T (copper/constantan) are the two types used most often for temperature measurements in the range used for lyophilization. Type T has an advantage over type K in low-temperature applications such as freeze-drying, because type T has a narrower temperature range, allowing for slightly better accuracy.

The type and quality of the temperature reference instruments and equipment can significantly affect measurement accuracy and precision. There are two general types of equipment: liquid baths and dry blocks.

Baths use heating and cooling of a solution to achieve a desired temperature. They are composed of a liquid contained within a well-insulated vessel where the liquid is cooled and heated, often by mechanical refrigeration and band heaters surrounding the vessel. The solution may also be circulated or stirred for improved uniformity. The cooling unit is activated with an on/off controller to achieve below-ambient temperatures, and a current proportional controller is used to control the bath at higher temperatures. In general, such units are limited in accuracy and stability, particularly when used below or near ambient temperatures. The location of the reference and sensors under test in the bath may also influence differences from the reference and temperature stability.

A dry block is composed of a well-insulated metal block in which the temperature is controlled by the use of heating and cooling for precise temperature control. Currently available dry well calibrators provide a combination of portability, accuracy, convenience, and stability relative to a liquid bath. Such systems may have the capability of spanning very low to relatively high temperatures, such as –100°C to 400°C. Their portability and ease of use make them ideal for field calibration. A separate temperature sensor, such as a high-accuracy RTD, may be used as a working standard temperature reference. Commercially available dry well heating and cooling blocks, as shown in Figure 1, have multiple wells for holding thermocouples and RTDs, resolve temperature to within 0.01°C, and are temperature stable to within 0.02°C.

PRESSURE CALIBRATION

Pressure within the lyophilizer chamber varies widely during different stages of the process; it may be as high as 35 PSIA during steam sterilization, and as low as 20 µm Hg during primary and secondary drying. Because the pressure ranges are significantly different, specific instruments are needed to monitor and control them.

Low-Pressure Sensors and Calibration

Two types of pressure sensors are commonly used on lyophilizers for the low-pressure ranges during primary and secondary drying: capacitance manometers and thermoconductivity (Pirani) gauges. Of the two, capacitance manometers are the more commonly used, as they provide a direct pressure measurement independent of the gas composition of the environment [13]. In addition, capacitance manometers used on lyophilizers are often heated and controlled at a specific temperature (100°C–200°C) to prevent water vapor from condensing on the sensor. The heated transducer also eliminates temperature influence of the environment on the sensor.

Thermoconductivity gauges use the rate of heat loss of a hot wire to determine pressure and are typically calibrated using nitrogen gas. An error is introduced when the gas composition within the lyophilizer chamber can vary between water vapor, air, and nitrogen, as the vacuum measurement provided by the thermoconductivity gauge may not be an accurate representation of the product chamber's actual pressure. At the same time, using both a capacitance manometer and a thermoconductivity gauge may be beneficial: As the amount of water vapor in the product chamber decreases during drying, the error in the pressure measurement by the thermoconductivity gauge decreases. A comparison between the pressure measured by the capacitance manometer and the pressure measured by the thermoconductivity gauge may help determine the end of primary drying [14].

A high-accuracy capacitance manometer used as a working standard is the preferred instrument for calibration of capacitance manometers and thermoconductivity gauges [15]. The transfer standard is typically incorporated into a bench-top or portable vacuum calibration system, onto which the UUT is installed. These systems consist of the high-accuracy capacitance manometer and its readout, a vacuum pump, a test port to which the sensor being calibrated is connected, manual pressure control valves or a proportional control valve with pressure controller (for automated pressure control), and stainless steel piping connecting them.

An effective procedure to calibrate a capacitance manometer is to remove it from the chamber and install it on the vacuum calibration system, as seen in Figure 2. To verify linearity, as well as accuracy across the range, it is important to perform a check at a minimum of three pressure setpoints: the lowest obtainable pressure (<1 micron), a midpoint (500 microns), and a high pressure (900 microns). Implementing these checks involves comparing the UUT to the standard, making necessary adjustments, and rechecking the calibration at a minimum of three pressure setpoints. Once completed, the sensor can be reinstalled on the lyophilizer chamber.

A thermoconductivity gauge may be calibrated in the same way; however, it is important to remember that the thermoconductivity gauge's measurement is affected by the gas composition of the atmosphere for which it is measuring the pressure. A more rigorous evaluation may be to check the pressure at five different pressures across the instrument range. As an alternative, if there is a difference in any one of the low, midrange, or high pressures for a three-point check and an adjustment is needed, checking the measurement at five points would provide greater confidence in the linearity of the measurement.

Figure 2: A low-pressure, high-resolution test stand for calibration check of an electronic manometer at pressures used for lyophilization, mounted at a target pressure for calibration.

It is possible to calibrate a capacitance manometer in situ by connecting the transfer standard to the lyophilizer chamber as close as possible to the sensor being calibrated and using the lyophilizer's vacuum system to control the pressure at the various test points. The main limitation with this method is the vacuum system on the lyophilizer and the higher potential for leaks make it very difficult to achieve a pressure low enough to zero the UUT. In addition, it may be difficult to install the transfer standard close enough to the UUT to prevent the connection length between the two from affecting the pressure measurement.

Calibrating a thermoconductivity gauge in situ may be a good option on a system that has both an electronic manometer and the

Figure 3: Digital pressure working reference standard and electronic transducer.

thermoconductivity gauge. The steps in this procedure are as follows:

1. Verify calibration of electronic manometer transducer.
2. Ensure the lyophilizer is clean, dry, and empty.
3. Chill the condenser to below –50°C.
4. Evacuate the lyophilizer to the desired pressure for calibration check.
5. Control the chamber pressure to the desired target setpoint by introducing nitrogen.
6. Compare the pressure indicated by the thermoconductivity instrument to the electronic manometer.
7. Adjust the thermoconductivity instrument as needed to match the electronic manometer.

It is important to allow the conditions in the lyophilizer to stabilize at the desired pressure setpoint long enough to ensure the atmosphere within the chamber is dry and predominantly nitrogen. Upon completing calibration, the thermoconductivity gauge can be compared to the lyophilizer's electronic manometer readout to monitor the difference that may reflect the presence of water vapor in the lyophilizer chamber. This procedure may be repeated for any additional calibration pressure setpoints and adjustment to the thermoconductivity gauge can be performed if necessary.

PSIA Sensors and Calibration

At the PSIA range of pressure measurement, two commonly used pressure sensors are the piezoresistive strain gauge pressure transducer and the capacitive pressure transducer [16]. Both translate the movement of a diaphragm during pressure changes to an electrical output (volts or milliamps). There is no clear advantage of one style over the other; however, it is necessary to ensure that the sensor is made from corrosion-resistant material, such as stainless steel or Inconel, and compatible with clean-in-place/sterilization-in-place systems.

A high-accuracy digital pressure gauge displaying pressure measurements in PSIA is the preferred working standard reference instrument for PSIA pressure transducer calibrations. Using a simple hand pump capable of applying both pressure and vacuum along with the high-accuracy digital pressure gauge (Figure 3) is sufficient for quickly and accurately calibrating either style of pressure transducer [16].

To calibrate the pressure transducer, remove it from the chamber and install it on the manifold consisting of an air pump in line with the high-accuracy pressure gauge used as a working standard, ensuring a tight seal between all system components. To verify linearity as well as accuracy across the entire range, it is important to perform a check at a minimum of three pressure setpoints: the lowest obtainable point (e.g., 0.3–1 PSIA), a midpoint at atmospheric pressure (e.g., 14.7 PSIA), and a high pressure (e.g., 35.0 PSIA). Implementing these checks involves comparing the UUT to the working standard reference, making necessary adjustments, and rechecking the calibration at the same three pressure setpoints checked earlier. Once completed, the sensor can then be reinstalled on the lyophilizer chamber.

CONCLUSION

Greater knowledge and understanding of the science and technology of lyophilization have led to improvements in calibration, resulting in enhanced process control. The three essential aspects of a well-developed calibration program—methodology, administration, and the calibration itself—inspire confidence in the instrument's assessment of a measurement's accuracy and precision.

Proper instrument calibration provides confidence that reported values accurately reflect process conditions. This is critical for process control during batch manufacture and helps ensure that the desired level of product quality is achieved.

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Denise Miller, Quality Assurance Associate at Lyophilization Technology, began her career with the company in 2008. In 2014, Denise joined the Quality Assurance Group as a Document Control Specialist and was promoted to Quality Assurance Associate in 2018. She is currently responsible for oversight and administration of Quality Systems for the Development Sciences and Clinical Manufacturing. Denise has published and presented poster presentations at focused industry events. She is a member of the American Society of Quality. Denise's focus is on ensuring clients receive the highest quality and safe lyophilized drug products for their patients.

Edward H. Trappler has over 40 years of industry experience in areas including product development, toxicology and clinical supply manufacturing, and parenteral production. In 1992, he founded Lyophilization Technology as a source of scientific and technical services, with the ambition of expanding the knowledge and understanding of lyophilization throughout the healthcare product industry. Ed has contributed to six books, authored and presented numerous papers and courses, and been a guest speaker domestically and internationally. He is an active member of the Parenteral Drug Association (PDA), serving as Chairperson of the Lyophilization Interest Group, Validation Task Force, and Education Advisory Board. He is a member of and has lectured for the American Association of Pharmaceutical Scientists, International Society of Lyophilization–Freeze-Drying Inc., ISPE, and PDA. Ed has received numerous recognitions, including the Gordon Personeous Award for his contributions to PDA and the PDA James Agalloco Award for Education. Ed has been an ISPE member since 1992.

CONTINUED PROCESS VERIFICATION IN STAGES 1–3:

Multivariate Data Modeling Using Design Space and Monte Carlo

By Zuwei Jin

Continued process verification (CPV) as defined in the US FDA process validation guideline [1] helps bring quality management and compliance in the pharmaceutical industry to the next level, but it has been challenging to implement in practice. This article describes an approach for implementing CPV through the core concept of design space based on online multivariate data analysis (MVDA) and Monte Carlo random simulation.

The approach can use virtually any kind of data source to build the design space, including first-principle dynamical models, design of experiment (DOE) models, clinical trial batches during process performance qualification (PPQ), and historical batches in a production historian. This approach can provide a smooth transition from the research and development (R&D) first-principle model to the permanent CPV program for commercial production throughout the drug development cycle.

The FDA recommends a three-stage approach to process validation. As the US pharmaceutical industry regulator, the FDA has been driving science- and risk-based approaches for almost a decade through documents such as the process validation guidance published in 2011 [1]. The guidance fundamentally affects process development, engineering practice, and commercial production for drug substances and drug products. A new commercial manufacturing process should go through stage 1, process design; stage 2, process qualification; and stage 3, CPV. Whereas stage 2 retains most procedural elements from traditional qualification and validation (such as installation qualification, operational qualification, performance qualification, and process validation), stages 1 and 3 involve many science-, risk-, and statistics-based approaches, such as risk assessment, DOE, statistical process control (SPC), and processing capability (Cpk) evaluation. The FDA now recommends stage 3 for all commercial processes because it provides the ultimate evidence that a process is running under a state of control.

The FDA's process validation guidance [1] also emphasizes statistics. Sponsors are encouraged to identify critical process parameters (CPP) and critical quality attributes (CQA) through risk assessment according to the quality target product profile (QTPP) and evaluate them using statistical approaches such as DOE early in stage 1. The historical standard of three consecutive batches may no longer be sufficient for chemistry, manufacturing, and controls (CMC) submission. The FDA is now considering the entire drug development approach, how much product and process understanding the drug manufacturer has demonstrated, and statistical evidence that the process is running as designed and in a state of control. Including CPV as part of CMC submission is therefore highly recommended.

CPV is now included as part of annual product review. SPC charts and Cpk analysis are the most common tools used in current CPV programs. They are univariate methods and are usually used after batch completion. SPC charts for quality attributes are usually used to evaluate processing capability and may also be used to assess control capability for specific process parameters. Cpk analysis evaluates control system capability by monitoring variation of the process parameters. From a statistics standpoint, far more than three batches will usually be needed to sufficiently analyze process capability of both process parameters and quality attributes. Therefore, a CPV program using univariate tools would usually not be established until phase 3 commercial production.

Because of its complete statistical analysis capability, MVDA is sometimes used to better understand the correlations between the CQAs and CPPs in place of SPC and Cpk. Such analysis would, however, still have to be done after batch completion, and extensive modeling and computation would usually be involved. The

obvious advantage of MVDA is its ability to count the interactions between multiple process parameters that a univariate approach would fail to detect.

In following sections, an online MVDA–based approach is introduced to allow CPV to be planned as early as stage 1; this approach can make CPV an integral part of process validation throughout stages 1, 2, and 3. It provides not only the ability to statistically evaluate the correlation between the CQAs and CPPs but also the ability to detect process fault and predict CQAs in real time.

ONLINE MVDA

Online MVDA is a relatively new data analytics technology that can be used for CPV. Online MVDA is based on the traditional MVDA methodology and a batch simulation scanning concept. Before we discuss the challenges of implementing CPV for the entire drug development cycle, let us briefly review how online MVDA can be achieved.

Batch Simulation Using MVDA

MVDA is a powerful improvement to the current univariate approach in CPV and is recommended by many industrial experts [2]. Primary component analysis (PCA) and projected latent structure (PLS) in MVDA are highly recommended in data analysis. With modern computing power and iterative PCA/PLS algorithms, both enumerative and analytical statistics can now be achieved efficiently online in real time.

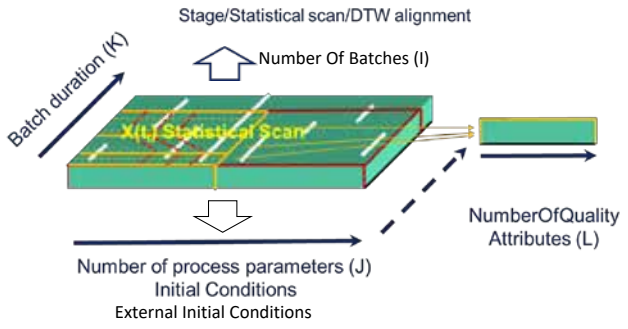
How can MVDA be used for a batch process, which is dynamic and can't be directly analyzed with MVDA?

MVDA is complicated with its high number of dimensions, but batch simulation is complicated in its own way because of its dynamic nature. Batch simulation using MVDA requires an additional concept or data structure. Such a data structure would allow for sufficient description of any batch process in a time-evolving fashion. In practice, MVDA modeling for batch would involve scanning a batch process into many frames over the batch duration (Figure 1). These frames are called statistical scans. The statistical scan averages the process conditions between two nearby frames. A batch process can be represented by many statistical scans that are sometimes separated into several groups called stages [3].

Within the stages, statistical scans may need to be appropriately aligned from batch to batch. One of the challenges of batch simulation is that batches may be of different durations and pauses/holds may occur during them; therefore, the alignment of statistical scans can't be based on time only. A well-accepted approach to addressing this challenge is an algorithm called dynamic time warping (DTW). DTW is an optimization that looks not only at the time but also the physical characteristics—such as process parameters—of a batch process to determine the alignment of the statistical scans [4].

Batch MVDA models contain hundreds of MVDA models that are lined up at different time frames in the scanning structure. The amount of modeling in a batch simulation is a hundred times greater than what would usually be modeled in an R&D project. Batch simulation with MVDA is not be feasible without an automated platform.

Figure 1: Batch simulation using MVDA.



Automating MVDA

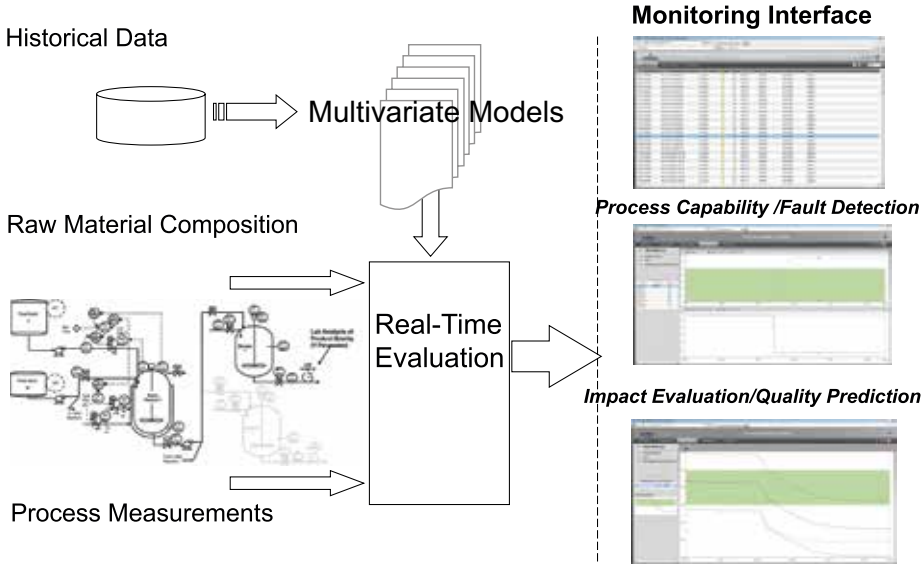
MVDA can be fully automated online to provide real-time analysis thanks to the modern computing power of servers, the standardization of plant models as defined in ANSI/International Society of Automation (ISA) Standard S88 [5], and digitization of almost all process parameters and initial conditions. Algorithms such as NIPALS, which is an iterative decomposition algorithm for matrix data, make PCA/PLS an effective online method for analyzing large amounts of data and building MVDA models.

Another important foundational piece of online MVDA is the algorithm to align statistical scans from batches of different durations. One of the most popular approaches is to use DTW, which takes a certain number of adjacent statistical scans into consideration during alignment. MVDA models can therefore be generated automatically from historical data in manner similar to the way Google performs an internet search.

Online MVDA is an integrated part of many common process control systems, such as distributed control system (DCS). An online MVDA platform positioned on top of historians includes a model builder, an analytics server, and a monitoring server (Figure 2). The model builder builds MVDA models from historical data. The monitoring server uses appropriate MVDA models to evaluate the actual performance of a real-time process and predict batch quality. The online MVDA platform sits on top of a process control system at level 2.5 or 3 in the ISA S95 hierarchy.

Online MVDA incorporates built-in model-building tools such as PCA and PLS as well as a real-time monitoring server based on the ISA S88 structure to provide the capability to detect faults and predict quality in real time. The fault detection and quality prediction windows are essentially the automated form of CPV, continuously measuring real-time process against the design space.

Figure 2: Online MVDA architecture.



Compared to traditional biplots in PCA, normalized T^2 and Q (between 0 and 1) are a more statistically robust method to identify irregularity and ensure a process is running under a state of control. In addition to providing enumerative statistics such as those used in CPV, online MVDA provides real-time monitoring functions such as process fault detection and batch final quality prediction.

In Figure 2, the middle window on the right illustrates how the monitoring service performs statistical tests on process parameters, specifically on T^2 and Q based on PCA. Statistically improbable behavior will be called out. Specific contributions from different process parameters can be further investigated from the same window by clicking the process parameter contribution on the left. The bottom window on the right shows the quality prediction (middle line) for the real-time batch. The top and bottom lines represent the upper and lower limits, respectively, of the prediction, all at 95% confidence level. Operators may be trained with standard operating procedures to use the fault detection and quality prediction tools to intervene in the process when required.

IMPLEMENTATION CHALLENGES

Figure 3 shows the landscape of process simulation and current CPV practice in the pharmaceutical industry. Implementation of a golden (i.e., ideal) batch profile is desirable to comply with industry regulations and achieve operational excellence. The challenge, however, has been the disconnect between the dynamic nature of the R&D first-principle model, the statistical nature of DOE design space, and the actual discrete data from real-time processes. Most of the current control platforms do not allow the manufacturer to set a golden batch profile as the background for batch operations, particularly at process start-up. In the case where a golden batch profile with standard deviation can be provided by the historian, such monitoring is usually univariate and not statistically meaningful enough to detect fault or predict quality.

Design space is the common thread that connects all these pieces together, but there has been no common form for representing it from stage to stage. The pharmaceutical industry generally lacks platforms that can fully integrate R&D, technology transfer, clinical manufacturing, commercial operations, regulatory compliance, and manufacturing intelligence.

The online MVDA model has been successful with production monitoring, but implementing it for CPV throughout the phases is challenging. It takes far more than three actual batches to build an MVDA model through PCA/PLS; therefore, MVDA historically could not be used in early stages because there were not enough batches. Furthermore, the R&D DOE design space and first-principle mechanistic models early in process development can't be directly used for building the MVDA model because such equations can't be included in an MVDA platform. Most MVDA online platforms do not take in loose data or equations for model-building. Thus, CPV in current practice is mostly SPC charting and quality parameter trending at clinical phase 3 and commercial phase 4, and is completely disconnected from earlier stages.

IMPLEMENTING DESIGN SPACE USING MONTE CARLO SIMULATION

An application of Monte Carlo simulation and open data sources for MVDA model-building can bridge the gaps discussed previously. It allows online MVDA to be a solution throughout the entire

Figure 3: Disconnects in current technology transfer practice.

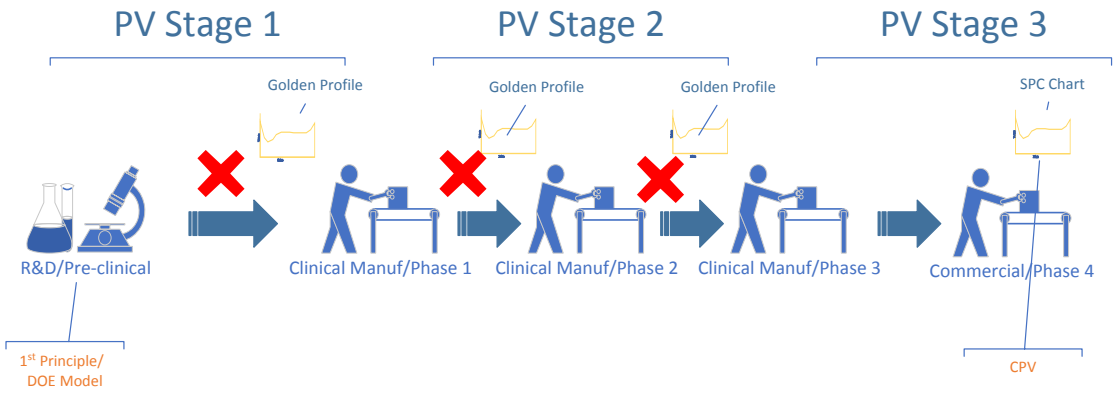
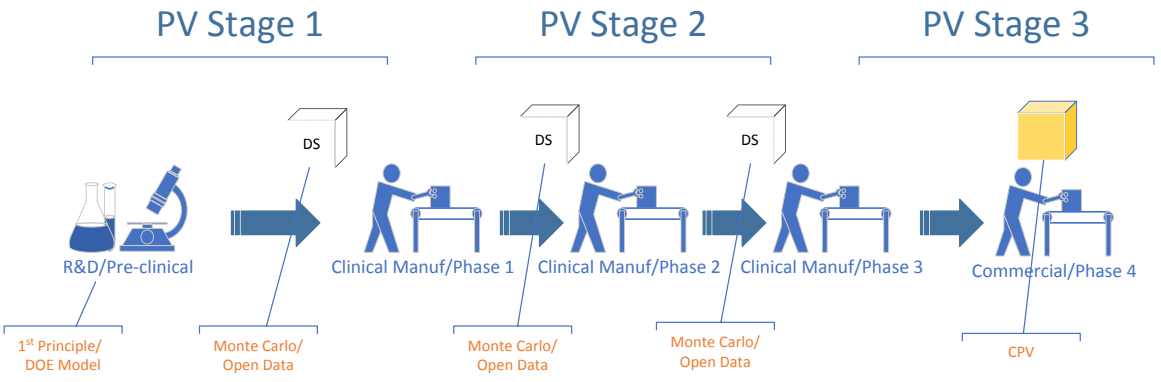


Figure 4: Implementing design space through stages 1, 2, and 3 for CPV.



drug development cycle from process development to commercial production, and that solution is applicable to the entire plant [6].

Although batch history data are highly structured in the historian, they can also be randomly simulated as new batches within the design space. With a Monte Carlo simulation framework, the design space and a reference batch can be used to construct as many batches as desired. The parameters required in the Monte Carlo simulation are the approved parameter range, the parameter control capability, and a reference batch.

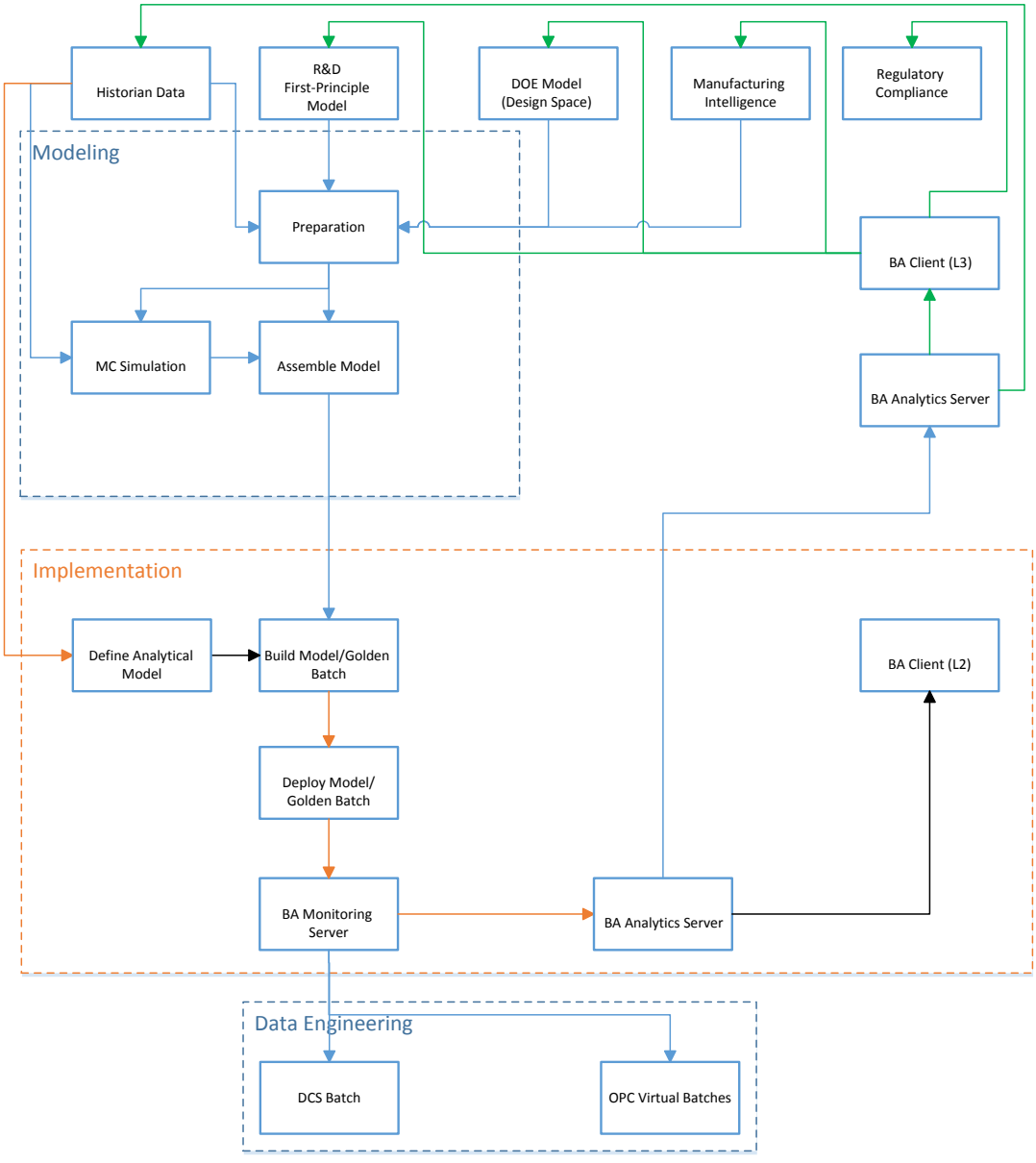
The simulated batches are initially used to build the MVDA model and gradually replaced with real batches from commercial production to rebuild the model. In this way, the MVDA model improves over time. CPV can be achieved when all simulated batches are replaced with real batches.

Allowing the use of open data sources means that the model definition can be defined not only through the batch historian but also through ISA S88 hierarchy exported from a DCS or other control systems, separate batch data files, and batch event files. This means third-party historians and even data from a first-principle mechanistic model can all be used for MVDA model-building on such platforms.

The way to implement a first-principle or DOE model for production is not to take in the equations directly but to take in a sufficient amount of data from the DOE or first-principle equations for the MVDA model to learn. When a process is transferred from one phase to the next, the design space may have to be transferred using Monte Carlo simulation with an open data source because the process will be built anew at a different scale (see Figure 4).

With the Monte Carlo capability and the open interface in building batch context, any golden batch profile or DOE design space—regardless of where it came from—can be implemented as an MVDA model for process monitoring. Figure 5 shows how an MVDA model may be constructed and deployed using the Monte Carlo method and an open data source.

Figure 5: MVDA model-building with Monte Carlo simulation and open data sources.



The MVDA model in this case can be built from the historian, the DOE models, or first-principle models. If simulated batches are needed for model-building, Monte Carlo simulation must be performed to generate such batches before a complete MVDA model can be assembled. Process parameters and quality attributes must then be defined for the batch, and PCA/PLS are run to generate the specific characteristics of the MVDA model, such as eigenvalues, loading, and scores. The MVDA model can then be deployed to the specific control platform for real-time monitoring. This effort must be coordinated with plant automation. As shown in Figure 5, the foundation for MVDA model deployment and model-building is data connectivity within the plant.

IMPLEMENTING ONLINE MVDA FOR THE ENTIRE PLANT

From a business standpoint, implementation of online MVDA involves two challenges: First, the manufacturer wants to find an analytics solution for the entire plant, if not the entire enterprise. Second, the solution should function not only as an operation support tool but also as a manufacturing intelligence tool that supports business decisions.

Thanks to the Open Platform Communications (OPC) connectivity standard, the MVDA online platform can be applied to all control systems in a plant. Most modern control systems have open connectivity, such as OPC, which can allow the control system to have virtual batches in the MVDA online platform; those virtual batches can then be monitored just like regular batches by online MVDA solutions.

MVDA models can be built for a specific product on a specific unit. The MVDA online platform can therefore be used for multiple products on nondesignated equipment.

MVDA can be a powerful tool for both operations and business decisions. MVDA analytics can be used for decision support, manufacturing intelligence, or quality assurance for business improvement. Most MVDA online platforms have the capability to work across different domains and can be configured through network firewalls.

MVDA analytics can be used for decision support, manufacturing intelligence, or quality assurance for business improvement.

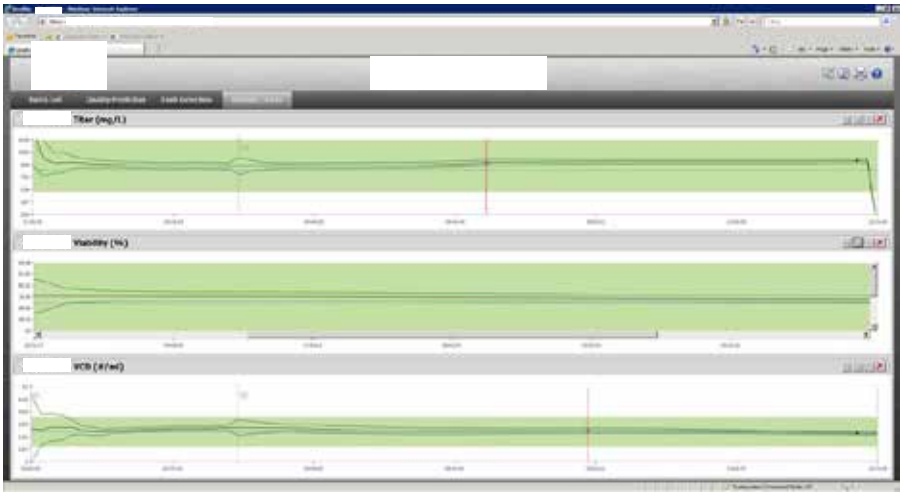
IMPLEMENTATION COST OF ONLINE MVDA

An MVDA online in a production environment is generally assumed to be expensive because of MVDA licensing costs and the complexity of project implementation. Although online MVDA is by far one of the most powerful analytics tools available, the threshold for adopting it is still high.

Implementing MVDA throughout a drug development pipeline requires long-term collaboration among experts in operations, process engineering, automation, statistics, data sciences, and information technology (IT). For example, experts in IT must help with data connectivity, and model-building requires process-modeling and statistics knowledge.

Figure 6: An example of a golden batch profile implementation through MVDA modeling.

Figure 7: Real-time monitoring of the batch process using an MVDA model.



Online MVDA licensing costs may vary significantly from vendor to vendor. Some MVDA online solutions have been highly integrated with a particular control system, which could reduce the implementation threshold for that control platform; however, integration with third-party control systems may be difficult.

CASE STUDY

Figure 6 shows a golden profile/MVDA model built from a reference batch and a design space. This ideal batch profile is an active statistical model simultaneously used for statistical evaluations of the actual running batch based on T^2 and Q, as explained previously. When the running batch is not performing normally, T^2 and Q will signal that issue by showing the values moving out of the green area.

A production process, 5K bioreactor cell culture batch, in a large US pharmaceutical manufacturer's facility was used as a proof of concept for this approach to implementing design space using Monte Carlo simulation. Simulated batches were generated using the Monte Carlo method based on reference historical data from an IP21 historian and a design space available from earlier development work.

The simulated batches were then used to build an MVDA model, which included 26 process parameters as the process input and three quality attributes as output. The model was then successfully deployed for online real-time monitoring in production. The monitoring results are shown in Figure 7.

The MVDA statistical model calculates T^2 and Q on a periodic basis to monitor real-time batch processes. Essentially, the real-time batch is being constantly measured against its design space, which is represented by the MVDA model built through Monte Carlo simulated batches.

The top windows in Figure 7 show T^2 and Q for fault detection of the process conditions. The bottom window shows the conventional univariate golden profile or historical behavior for one of the selected process parameters. T^2 and Q statistics plus the univariate golden profiles are the design space of the process, which can then be used to measure the running batch in real time.

As more batches are completed, the MVDA model is rebuilt with the new batch history data as part of the training or testing batch data set. This rebuilding process continues until all simulated batches are replaced with real batch history data.

CONCLUSION

Online MVDA is emerging as the solution for CPV throughout the drug development cycle, connecting stages 1, 2, and 3 and allowing CPV to be included early in the drug development life cycle.

Design space is the common thread that connects stages 1, 2, and 3 in process validation. MVDA modeling with Monte Carlo simulation and an open data source for model-building is one of the approaches moving the design space of the drug-making process from stage to stage and from phase to phase to achieve CPV, as the FDA recommends in its process validation guidance.

Although equations from first-principle and DOE models can't be used by an MVDA platform, first-principle models and DOE design space can be used to provide the data that the MVDA model builder uses to learn about the design space of the first-principle or DOE model.

The online MVDA solution is particularly suited for handling large amounts and complicated sets of data in plantwide applications, and it can be applied to different control platforms with OPC connectivity. Analytics by online MVDA can support not only operations but also quality assurance, compliance, and manufacturing intelligence.

Online MVDA can be used for CPV throughout the drug development cycle, connecting validation stages 1, 2, and 3. It is arguably the future direction of process monitoring in the pharmaceutical industry.

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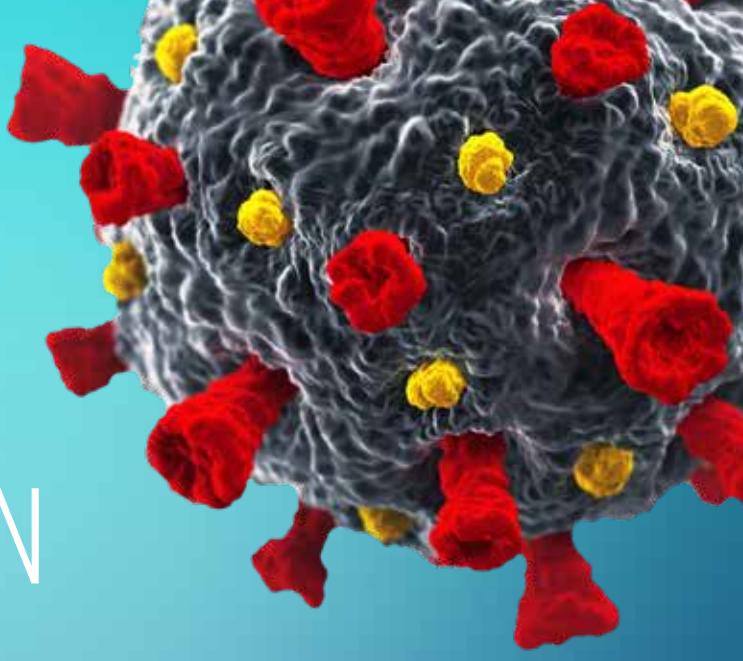

CORONAVIRUS COLLABORATION

Industry interaction is key to understand and cope with the challenges of life during the pandemic. Collaboration (of the social distancing variety) can help manufacturers, consultants, and other members to stay informed and to share information.

ISPE has created a group for members in the ISPE Community Connection to share news, updates, best practices, and professional advice.

Member login is required to participate in the ISPE COVID-19 Discussion forum. To access the forum, visit the ISPE Community Connection page (cop.ispe.org) and click the "Join" button.

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