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The Official Magazine of ISPE
January-February 2021 | Volume 41, Number 1

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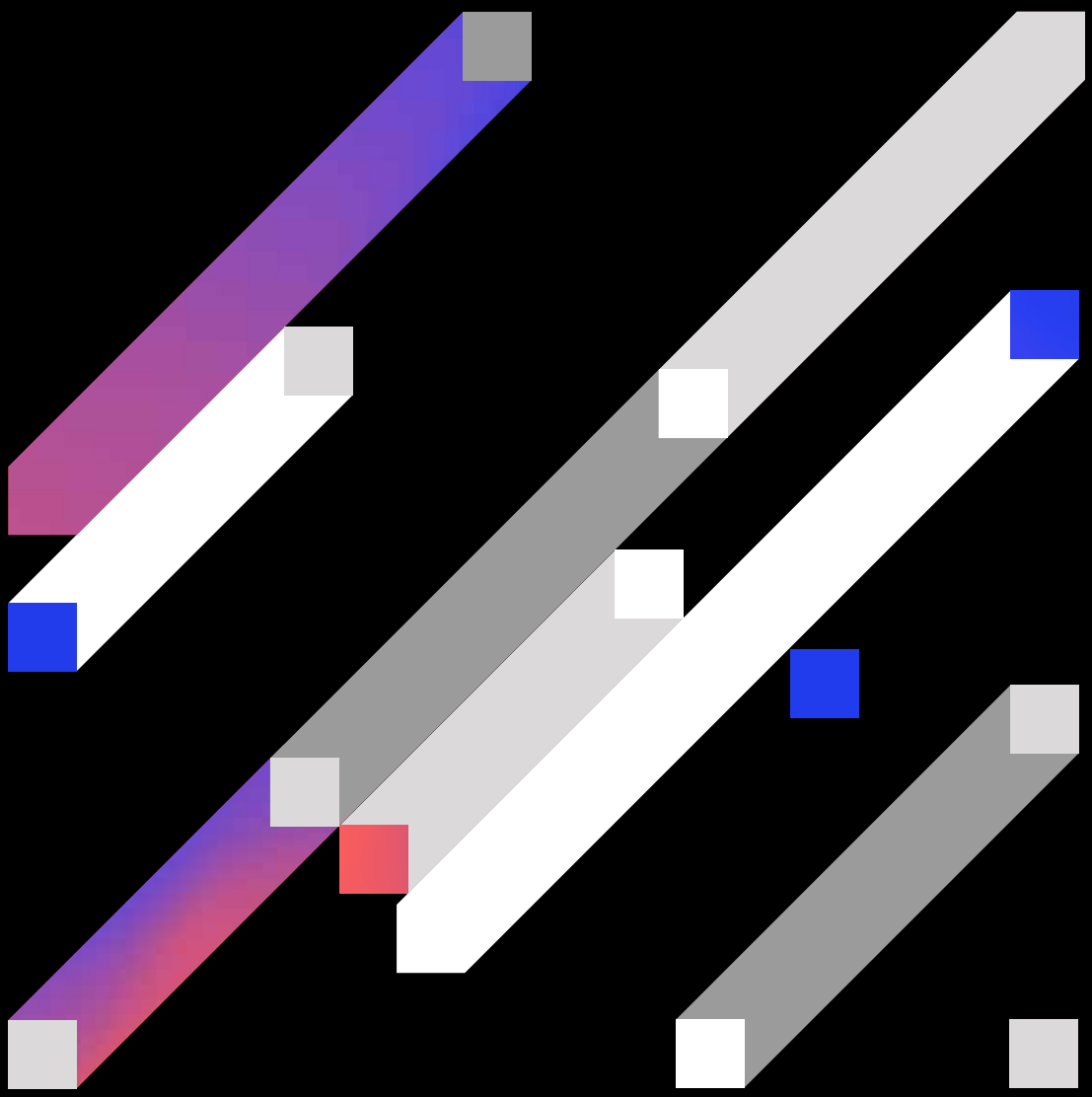

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FEATURES

ON THE COVER The woman on the cover symbolizes the many women who have joined–and will join—the pharmaceutical industry.

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Volume 41, Number 1
Published since 1980

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Stock Photography and Illustration
iStock

Art Direction and Graphic Design
THOR Design, Inc., www.thor.design

Printing
Royle Printing

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Letters must include the writer's full name, address, and organization. Letters may be edited for length and clarity. Send correspondence to ssandler@ispe.org

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ISSN 0273-8139

Pharmaceutical Engineering is published six times a year by ISPE and is online at ISPE.org/Pharmaceutical-Engineering

US Postmaster
Send change of address to:
Pharmaceutical Engineering Magazine
600 N. Westshore Blvd., Suite 900
Tampa, FL 33609 US

Periodicals postage paid at Tampa, Florida, US, and additional post offices

Canada Postmaster
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By Joanne R. Barrick, RPh

Joanne R. Barrick, RPh

Women in Pharma®: A Key Part of ISPE Professional Career Development

I was a skeptic. When the Women in Pharma® (WIP) program started in 2016, I had previously attended several other professional women's programs and usually left disappointed, as these programs did not provide the information I was seeking. The ISPE WIP program is different. The program has an energy and enthusiasm rarely seen in professional groups, as evidenced by the "buzz" at every event and numerous follow-up hallway conversations.

I continue to be astounded (at least up to the time when we had to halt face-to-face meetings) by seeing about 100 to 125 women and men attending the WIP breakfast sessions at most major ISPE conferences. The enthusiasm for the program has also spread to our Chapters and Affiliates with many programs such as the ISPE Brazil Affiliate's support of the homeless impacted by COVID-19 (with backing from the ISPE Foundation), the ISPE UK Affiliate WIP's new webinar series, and numerous other examples cited in Alice Redmond's WIP editorial, "A Year of Mentoring, Education, and Collaboration" in the November-December 2020 issue of *Pharmaceutical Engineering®*. WIP has expanded its Mentor Circle program, exceeding its goal of 20 Mentor Circles in 2020, and there are more than 1,700 WIP Community of Practice members. But why? What is the reason for this dramatic success?

My hypothesis is that the world has changed so much, with so much availability and emphasis on technical information, that we have lost focus on career development, leadership, and soft skills. Professionals are now very hungry for this information. WIP provides an opportunity to hear career success stories, which sometimes include how the speakers overcame significant obstacles and beat the odds to achieve great success. In many cases, WIP program sessions provide valuable fundamentals that can be immediately applied to assist in career progression and success, as well as a forum to discuss application of these fundamentals and exchange learnings. WIP provides connections, and, as Co-chair Vivianne Arencibia says, "sometimes WIP just provides a place to bounce ideas."

MORE ISPE DEVELOPMENT OPPORTUNITIES

ISPE provides additional opportunities to develop leadership skills. As leader of the ISPE Process Validation Team for many years, I had the opportunity to convince numerous emerging leaders and early career professionals to participate in and lead some of our conference sessions and publication efforts. One such individual co-led the effort to develop an ISPE process validation life-cycle implementation discussion paper. He contacted me some time later to thank me because he received a significant promotion, and attributed the opportunity to the confidence he gained in leading the writing team, interacting with industry leaders, and being aware of industry issues, as being significant factors in preparing him for his new role.

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I urge you to assist in raising student and early career professional awareness of the opportunities and career satisfaction that await in the pharma industry.

WORKFORCE OF THE FUTURE

The world is watching our industry, maybe like never before. I am so proud of how we have responded. With new technologies, innovation, and acceleration of bio product development and manufacturing, there may never be a more important time to attract students with an aptitude for engineering and bio science to pharma. We are making exciting and unprecedented progress in addressing previously untreatable diseases.

I urge you to assist in raising student and early career professional awareness of the opportunities and career satisfaction that await in the pharma industry. Involvement in ISPE can introduce the many facets of the pharma industry and shepherd professionals through all phases of their careers, enabling a greater level of success at a faster pace. The WIP program is a great introduction as there are many small groups where initial participation and questions may feel safer, plus all the benefits of the larger ISPE organization.

While our virtual world and working from home have so many drawbacks, information may be more accessible than ever. Traveling to a conference has some benefits that cannot be replicated online, but virtual participation in conferences offers tremendous opportunity to interest students and emerging career leaders for a very small investment. Our work is exciting and fast paced and an opportunity to truly improve life for humankind. Please consider giving back by "passing on" our work and our passion.

Joanne R. Barrick, RPh, is Advisor, Global Validation, Technical Services/Manufacturing Science, at Eli Lilly and Company, and the 2020–2021 Chair of the ISPE International Board of Directors. She has been an ISPE member since 1998.

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 By John Clarke


John Clarke

Celebrate the Emerging NEW YEAR

I think everyone will join me in celebrating the start of 2021! With all the challenges brought by 2020, last year also demonstrated the resilience and innovative thinking of ISPE members. With collaboration and perseverance in mind, I was delighted to begin my tenure as ISPE International Emerging Leaders Chair at the virtual 2020 ISPE Annual Meeting & Expo in November.

As recently announced, the ISPE Young Professionals (YPs) community has been renamed ISPE Emerging Leaders (ELs). This is a very welcome change that better describes the diversity in experience across our more than 1,700 members. Since the establishment of the ISPE Young Professionals community, the membership has evolved from recent graduates into a network of professionals who are developing into leaders through building their respective careers and the industry. The change in name at this point reflects the growth and maturity of the community, and I'm excited to continue this trajectory in 2021.

BUILDING A CAREER IN PHARMA

In 2014, I became involved as an active member of the ISPE Ireland Affiliate Young Professionals Committee, shortly after the YP branch of the Ireland Affiliate was established. I had recently begun working with Pfizer in Grange Castle, Dublin, Ireland.

As I progressed through roles in engineering, validation, and operations disciplines, my involvement with ISPE evolved alongside. Membership in ISPE supported my career progression through attending technical conferences on cutting-edge topics and building leadership skills through holding roles of increasing responsibility on the committee.

ACTIVITIES THIS YEAR

In February, the ISPE Emerging Leaders are holding a major international EL event: a virtual hackathon over two weeks. Over 50 students and EL participants with up to five years of experience will be involved in working on a problem statement provided by our sponsor, Bayer. Members from over 20 Affiliates and Chapters will be represented and will work in teams to prepare proposed solutions. The teams' solutions will be presented to a judging panel of industry experts to determine the winners.

Another goal for the ISPE ELs in 2021 is to build our membership and volunteer network. We want your expertise and your thoughts to continue our development and growth. Whenever I'm asked, "Why should I get involved with the ISPE Emerging Leaders?" my answer is always "the people!" From my years of volunteering with the ISPE Ireland committee to planning events with the ISPE European EL Affiliate leads, I have built contacts and friendships that will remain with me throughout my career. As we continue meeting virtually, a goal of the ISPE ELs will be to maintain the networking and camaraderie we have become known for.

Being a member of ISPE Emerging Leaders has many other benefits, including:

- Joining an established network of industry peers at both the Affiliate/Chapter and international levels
- Access to guidance and best practices for new Affiliates and Chapters for the establishment of Emerging Leader chapters or student groups
- Interfacing with ISPE Communities of Practice to increase EL and student involvement
- Involvement in ISPE initiatives such as Women In Pharma® and special interest groups such as Pharma 4.0™.

JOIN US

By volunteering at a local or international level with an EL professional committee, you get as much benefit out of it as the effort you put in. If you are looking to get involved with the Emerging Leaders committee at your local ISPE EL Affiliate/Chapter or want to set one up, contact me at John.Clarke2@Pfizer.com or post on the Online Community at ISPE.org/membership/young-professionals (the ISPE website will be updated to reflect the new Emerging Leaders name).

John Clarke is an Operations Lead with Pfizer in Dublin, Ireland, and the 2020–2021 ISPE International Emerging Leaders Chair. He has been an ISPE member since 2014.

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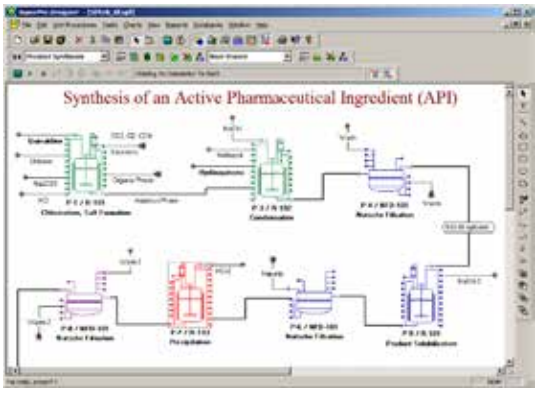

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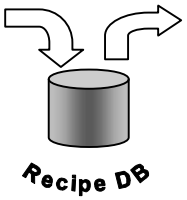

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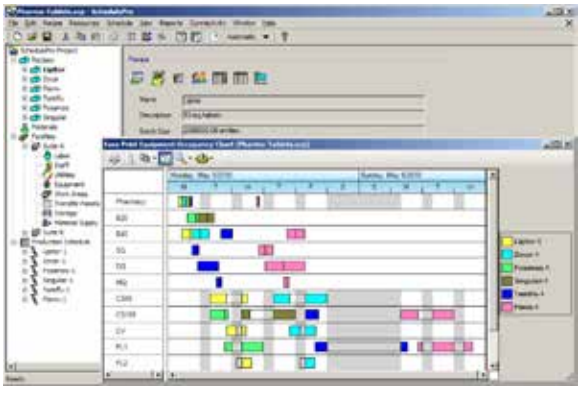

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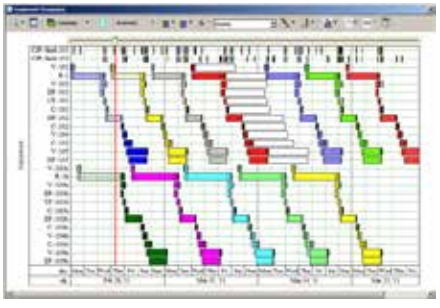

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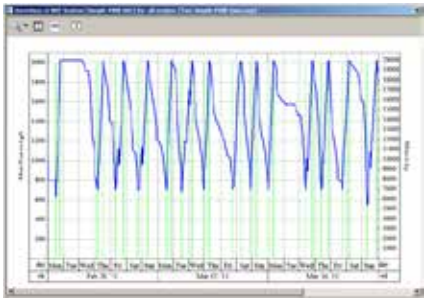

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 By Jennifer Lauria Clark


Jennifer Lauria Clark

LESSONS LEARNED

My parents always told me when I was growing up that I could be anything I wanted to be. They strongly steered me in the direction of engineering at North Carolina State University, so that I would be able to earn a degree that would ensure my future was my own. When I was eight years old, I was introduced to a pharma company my dad worked for and you could say my love of this industry has been in my blood ever since.

I began my biopharma career with the same firm in 2000 as an intern, and since then I have worked with people who have been my champions, my mentors, my sponsors, and my friends. Over the course of my 17-year career in this industry, I have learned many things. As we celebrate Women in Pharma® (WIP) in this issue of *Pharmaceutical Engineering®*, I highlight a few of my most memorable lessons.

ALWAYS STRIVE TO DO YOUR BEST

While an intern, I had the worst desk possible: I sat at a table where all the mailboxes were for the entire floor. There was not enough room for me on the crowded floor, and I was often interrupted. To me, it did not matter. I was working for a top pharma company and learning about quality assurance, building relationships in the workplace, and how to mine data. My work was not sexy, and I did not get a chance to meet the CEO, but what I did learn was patience, and to have a questioning attitude to accomplish my job. I entered batch record data into a spreadsheet line after line for days, and I was an integral part of my manager getting what he needed. The people I worked with remember me as someone always looking to understand the tasks, willing to do anything, and for being kind and respectful. No matter the situation in your personal or professional lives, always strive to do your best.

NEVER GIVE UP

As we have navigated our WIP initiative, we have had challenges along the way, most notably the majority of last year being uncertain because of the global pandemic. Our team met diligently every two weeks to be agile and flexible when it came to providing the content women (and men) were craving during a time of isolation and uncertainty. How can you feel lonely when you are in your house with your family … all the time? Well, I can promise you that as a people person who gains energy from being around others, it happens. I believe wholeheartedly that our WIP initiative kept me going on my toughest days. Knowing that we were working our best to provide an outlet for people to listen to the wisdom of others, learn from our mistakes, and be empowered to never give up on trying to better yourself got me through several tough days.

WISDOM CAN COME FROM ALL AGE GROUPS

I believe you need generational experience to share your wisdom with people when it comes to certain topics. I also believe that the young people of our industry have the potential to be smarter than we ever aspired to be. The next generation are digital natives. They grew up with iPhones, full transparency, and instant access. If they want to understand the difference between a gene therapy and a monoclonal antibody, they pick up their phones and they digest the information much more quickly than I did growing up. Our WIP millennials have been inspirations to me this past year as they teach me the value of listening, creating a culture of diversity, and perseverance through hard times. Take the time to listen to all around you and you may be surprised at the brilliant ideas that can rise to the top through diverse thought and diverse groups of people. Take time for all others in your sphere of influence because wisdom can come from any age group.

CELEBRATE EVERYTHING

I was going to say celebrate the little things, but with the past year we have had, I say celebrate it all! WIP overcame the challenges of flexing into a virtual world to bring together over 400 women and men into 21 mentor groups in 25 countries. We exceeded our goal of raising $25,000 toward WIP programming and the ISPE Foundation. We held meetings, networking events, webinars, confidential conversations, book clubs, and sunrise to sundown events—all for the purposes of bringing people together and allowing them to learn from each other.

These are all things to celebrate. I celebrate not yelling before 7 a.m. daily since I am juggling being a full-time working-from-

> WIP is a safe place where you can be vulnerable, share your dreams and challenges, and have a place to be celebrated.

home mom while monitoring my children's virtual learning five days a week. I celebrate a quick visit with my sister after a full day of work and three hours of grad school class since her home is on my way home from school. I also celebrate taking time for me. So many of us are not making time for ourselves right now as we learn to navigate our new normal. Have some tea, work out for 30 minutes, or call a friend you have not talked to in a while.

We are all in need of some motivation today. None of us are in ideal situations right now, but please know that WIP is a safe place where you can be vulnerable, share your dreams and challenges, and have a place to be celebrated.

WIP is not doing anything new; we are just taking extraordinary measures during these trying times to ensure we are:

- Empowering women as leaders
- Establishing mentorships to improve effectiveness
- Building and leveraging diversity
- Exposing women to opportunities in technology and science

This year, WIP has committed to help increase our membership by 100 people through our programs and to raise $85,000 for our programming. Our programs affect diverse communities all over the world, giving everyone an opportunity to dig deeper into ISPE and our industry.

We are proud that Joanne Barrick, ISPE International Board Chair, and Tom Hartman, President and CEO of ISPE, have given us an opportunity to build upon our success during 2021 that will help change the lives of so many people around the world.

I invite you to join ISPE and our WIP initiative in your individual journey to improve the working world and focus on creating diverse thought and teams within your organizations and at home.

Jennifer Lauria Clark is Executive Director, Strategic Development, for CAI and the ISPE Women in Pharma® 2020–2021 Steering Committee Chair. She has been an ISPE member since 2003.

WOMEN IN PHARMA®: Empowering Women as Industry Leaders

By Scott Fotheringham, PhD

Women in Pharma® is a place where women and men—especially those new to the industry—can access a network of mentors, role models, and educational resources to support their professional success. The widespread global interest and participation in this initiative and its events have shown that women in the pharmaceutical industry are hungry for the connection, mentoring, and education that Women in Pharma offers.

Scuba divers have a rule: never dive alone. This is a rule that Vivianne Arencibia, President and Owner, Arencibia Quality and Compliance Associates, LLC, and Co-chair of the Women in Pharma® (WIP) Steering Committee, follows whenever she scuba dives. Not only is it nice to have company—it's safer. Buddies keep each other in sight, don't stray too far away, and regularly check on each other's oxygen levels. All of their communication is done with signals to let the other know that everything is all right. And if there's an emergency, having a buddy is essential to being able to return to the surface safely.

For Arencibia, who has been in the pharmaceutical industry for 33 years, including 22 years at Novartis, where she held senior leadership positions, this "never dive alone" rule applies just as much to her career as a woman in pharma. As one of five women on the Women in Pharma steering committee, she knows, like so many others in the industry, what it's like to juggle a career and personal responsibilities, which for her include leading a consulting business and being a single mother with four children.

Vivianne Arencibia

"Many of the younger women who I mentor want to do it all and often ask me how I juggle my career and family responsibilities," Arencibia said. "I have to tell them: sometimes really well, sometimes not. But one thing I have learned is to rely on others and not try to do everything myself.

"In spite of the fact that many women have come into the life sciences, it's still a male-dominated field. Many women still struggle with working in such a field, and the ability to reach out to other women—not just professionally—to speak to issues that are unique to women and to lift each other up is very important to us."

MISSION-FOCUSED FORUM

This desire to lift each other up is at the core of the Women in Pharma mission. WIP provides a forum for women and men who are ISPE members to connect and collaborate on topics that impact their technical work and career advancement. WIP also provides the mentors, role models, and educational resources that can help support both women and men throughout their careers. The widespread global interest and participation in WIP and its events has shown that women in the pharmaceutical industry are hungry for the connection, mentoring, and education that the program offers.

"Everyone's so passionate about this because it's such an important initiative," said Jennifer Lauria Clark, Executive Director for Strategic Development, CAI, and Chair of the WIP Steering Committee. "This is a time in history when people are realizing that there's much more diversity out there and that there could be more empowerment for women. Women in Pharma is allowing us to create leadership positions, volunteer opportunities, and exposure for people to get engaged and be visible."

The enthusiasm with which WIP has been met has allowed it to be largely self-sustaining through donations and fundraising. WIP works to raise money and create scholarships for students and Emerging Leaders (formerly Young Professionals), who would not otherwise have access to the WIP and ISPE programs.

"Supporting and expanding Women in Pharma is specifically called out in the ISPE Strategic Plan," said Joanne R. Barrick, RPh, Advisor, Global Validation, Technical Services/Manufacturing Science, at Eli Lilly and Company, and the 2020–2021 ISPE International Board of Directors Chair. "This is an important part of driving member value and ensures inclusion of experiences based on professional areas of interest and demographics."

"The broad interest our members have demonstrated in the WIP program has made it one of the more participatory activities we have in the Society, and it continues to grow," said Thomas Hartman, ISPE President and CEO. There has been so much growth, Hartman said, "that we now have specific line items in our budget to support WIP, reflecting the program's relevance and importance to ISPE's members and our mission, and enabling us to shine a light on the value that women bring to the pharmaceutical industry."

ALL ABOUT WIP

WIP aims to:

- Empower women as leaders in the industry
- Build and leverage diversity to drive operational excellence within the workplace
- Establish mentor/mentee relationships
- Expose as many women as possible to opportunities in technology and science

In addition to these priorities, WIP set itself two specific goals for 2020: (a) to raise $25,000 for the ISPE Foundation to continue programming, operations, and scholarships for WIP and (b) to expand the number of Mentor Circles from six in the US to 20 worldwide by the end of the year.

Jennifer Lauria Clark

Joanne R. Barrick, RPh

WIP has experienced active growth over the past year. Most of the 39 ISPE Chapters (in the US) and Affiliates (globally) have a WIP group leader. Seventy people are either Mentor Circle leaders or WIP Chapter and Affiliate leaders. Hosted webinars are well attended, with as many as 150 participants, including many men. WIP also exceeded its 2020 goal by reaching 21 Mentor Circles globally as of last October, and the number continues to grow.

WIP hosted a Proactive Career Design session at the 2020 ISPE Facilities of the Future Conference in January 2020, as well as "24 Hours with Women in Pharma" on 27–28 October 2020, prior to the 2020 ISPE Annual Meeting & Expo. The virtual 24-hour-long program included 16 sessions throughout the day to accommodate people in different time zones. Following a webinar to kick off the event, sessions were comprised of Mentor Circles, book clubs that discussed Sheryl Sandberg's *Lean In: Women, Work, and the Will to Lead*, and confidential conversations. The latter are small-group, women-only meetings to discuss five difficult topics in a confidential space. These conversations are the only WIP events meant solely for women.

The Bridge is WIP's monthly newsletter for ISPE Chapter and Affiliate WIP leaders that provides news, shares best practices, and ensures all WIP groups are aligned with the policies and procedures of the ISPE Charter. The digital newsletter also contains news highlights, announcements of upcoming events, and messages authored by different members of the ISPE WIP Steering Committee.

Clark sees *The Bridge*, as well as the Women in Pharma® Editorial that began publishing during 2020 in *Pharmaceutical Engineering®*, as occasions to share individual accomplishments and highlight what is important to women in the industry. The editorial in PE is written by different representatives from the steering committee, ensuring a range of distinct perspectives are presented.

FOSTERING DIVERSITY

WIP is having an impact on ISPE and the industry, especially when it comes to enhancing diversity. This diversity isn't just related to

Women in Pharma®: In the Beginning

When Frances Zipp, President and CEO, Lachman Consultant Services, and Past Chair of the ISPE International Board of Directors, was elected to the ISPE Board in 2013, she was asked to get involved with a group that would focus on the personal and career interests of women.

"I was reluctant at first," Zipp said. "I never associated with a group that was just for women and have never played the 'women's card.'"

She helped gather a small group of women and men to brainstorm what such a group could be and what purpose it would serve. They trademarked the name Women in Pharma, liking how it played off "work in progress," a common industry term.

"We intended it to be a group that would be supportive of women in the industry, either as men supporting women or as women mentoring each other about things like career progression and work/life balance," said Zipp, who has worked in the pharma industry for 35 years. "It is a group for women—and men—that has been supported by men in senior positions from its inception."

It was important to Zipp that the focus of the group was not complaining about the way things were. "From my perspective as the first Chair of WIP, as a single mother and raising three children as I developed my career, I don't see this as a diversity initiative." Instead, the focus for her has always been about equality and the value of discovering opportunities, learning how to promote oneself, and sharing these insights with colleagues. The impetus for WIP was that, at the time, there weren't a lot of women senior-level engineers and there was a focus to get more women into the industry.

First Steps

WIP was launched in Atlanta at the 2016 ISPE Annual Meeting, with sessions and breakouts that included a large number of men, including some in senior leadership positions. The inaugural WIP meetings included panel discussions and breakouts. Sessions were attended by women and men, and WIP sold Women in Pharma buttons to raise funds for the initiative, some of which would later provide scholarships.

"We found sponsors and sold buttons at conferences and meetings for $5 for students and $10 for those with jobs," said Zipp. "It really took off. You'd see most of the speakers at these conferences wearing a button."

Frances Zipp

Zipp recalls a colleague, senior in the industry, speaking at a conference and admitting that she knew that she wasn't the most qualified candidate when she was hired for her first job. "But she told us that she really wanted that job, and she got it," Zipp said. "To me, that's the type of message people who are early in their careers needed to hear."

Jennifer Lauria Clark, Executive Director for Strategic Development, CAI, and current Chair of the WIP Steering Committee, also remembers that inaugural meeting. "Even though we thought it was great, we came away from that experience wanting to do more. We didn't want to just put women on the podium. We wanted to inspire women to put themselves on the podium. We wanted to help them feel empowered to submit an abstract because, traditionally, most women weren't submitting abstracts. So we thought it was our role to be champions to help support women to step up in the industry."

Zipp reflected on the sacrifices that women had to make during the time when she was early in her career. "In my day, I couldn't make the choice to go to parent-teacher meetings or a child's soccer or lacrosse game. I couldn't do that if I wanted to succeed in my career." Now, with the COVID-19 pandemic adding pressure on people who were already juggling career and personal responsibilities, Zipp sees that families are having to make tough choices that are best for them. Some may choose to take a less-senior position to focus on family needs. Others will choose to prioritize their careers. "WIP recognizes that women and men make choices and we are completely nonjudgmental about those choices. Instead, if someone wants to change careers or area of focus, WIP can be a safe haven for networking and a place to find a mentor to help with the transition."

Zipp believes WIP has had a tremendous impact on the industry. Women are now working at all levels, side by side with men. She likes that the focus is on mentorship, not just social interactions. "When I first started, I had 20 different women ask for mentoring. It was a full-time job. We had company-sponsored discussion tables, sponsored by both male and female senior leaders.

"I'm thrilled with the direction WIP has taken. WIP is now positioned to provide mentorship, technical support, and social guidance. I'm so proud of the team and all we've accomplished."

—Scott Fotheringham

gender or ethnicity; it is bringing a wider range of cultures and experiences to the table.

"WIP is pushing to expand to minority groups and to bring people from around the globe together to naturally create a more diverse group with different backgrounds and experiences," Hartman said. "The more diversity of race and gender we have in all our ISPE committees and networks, the better we'll be able to truly represent our diverse, global membership."

Leadership is one area where more diversity would be welcome. Although 42% of science professionals are women [1], women fill only one-third of senior leadership positions, and are only 13% of CEOs in the healthcare industry [2]. The numbers are even more discouraging among the top 50 pharmaceutical companies, where only 17% of board members are women [3]. This disparity not only adversely affects the prospects of professional women but also impacts the bottom line of companies. Those companies with the most gender diversity at the executive level are likely to outperform the least gender-diverse companies by 48% [4].

"Women in Pharma is a way to increase diversity in the pharmaceutical industry," said Barrick. She noted that there is an additional benefit of WIP. "There's going to be a shortage of talent, and this is another way to bring that talent into the industry."

WIP is helping change the face of the industry through such events as panel discussions at ISPE conferences that focus on diversity, including a breakfast session at the 2019 ISPE Biopharmaceutical Manufacturing Conference. WIP has held breakfast sessions on many topics at most recent ISPE conferences.

One series of events that highlights the diversity that exists, not just within WIP but in the industry as a whole, are sunrise to sundown conversations. These are scheduled over 24 hours to include participation from every time zone, reflecting the global nature of the industry and ISPE. One of the first was hosted by the Eurasia Economic Union Affiliate's WIP group, which has 200 members.

"It was so good to connect with them," Arencibia said. "The energy comes from forgetting the boundaries and connecting as women in the industry internationally without defining ourselves as American or Russian. It doesn't matter where you reside. Whether you're in India or Brazil, it's about connecting and finding a voice that speaks on behalf of women in the industry."

WORLDWIDE WIP

WIP has active committees in its Asia Pacific Council (APAC) Affiliates in Australasia, India, Indonesia, Japan, Malaysia, the Philippines, Singapore, and Thailand. WIP also has active committees in the European Union and South America, as well as in the US.

The APAC WIP committee, with representatives from each Affiliate, functions to coordinate, collaborate, and share best practices among the region's ISPE Affiliates. The WIP program further strengthens collaboration by holding joint WIP events, such as the ISPE WIP APAC conference held 12 November 2020.

"Asia is culturally diverse, including the way business is done in each country or Affiliate," said Vivien Santillan, Regional Director for Asia, Novatek International, President of the ISPE Philippines Affiliate, Chair of the Asia Pacific Council, and a member of the WIP International Steering Committee. Each country in the region has different concerns or issues, depending in part on whether they are more technologically advanced (e.g., Australia, Singapore, and Japan) or belong to the emerging markets category (e.g., India, Indonesia, the Philippines, and Thailand).


Vivien Santillan

The demographics of the industry in the Asia-Pacific region are also quite different from those in North America and Europe. "There is greater involvement of women in the region, and the industry is predominantly led by women here. Most of the ISPE APAC leadership are women," said Santillan.

In APAC, where the WIP program is relatively new and rapidly expanding, organizers are hoping to continue the momentum by providing opportunities for members to build on their technical knowledge and career development. WIP also became the forum for APAC Affiliates to provide appropriate guidance to students and Emerging Leaders (formerly Young Professionals), through Mentor Circles, including on technical topics in quality assurance, quality control, and manufacturing, as well as soft-skills development like boosting confidence, effective communication, and improving productivity. Santillan is excited to see how WIP has helped the mentees who joined a Mentor Circle in their career advancement.

Each APAC Affiliate has its own activities. For example, the Philippines Affiliate has a 10-month mentor program that emphasizes technical and soft skills, whereas Mentor Circles were initiated in the Japan and Singapore Affiliates in 2020. Santillan sees tremendous room for growth in places like India.

"The concerns of work/life balance for working women that exist globally also exist in Asia," Santillan said. "Asia has a patriarchal culture, in which women are expected to manage the household. This makes it quite a challenge to maintain that balance."

As in other regions, APAC WIP provides opportunities to engage in conversations with a less-technical focus, something Santillan feels is needed even more during the pandemic.

"Discussions on social skills and other nontechnical topics gives members the opportunity to share with like-minded individuals on how their everyday life is outside their usual work routine," she said. "Women in Pharma gives the members a balance and some form of sanity in these trying times."

WIP AND MEN

While the mission of WIP is to help women enhance their careers and give them resources, tools, and education to improve in their professional and personal lives, men are welcome


Tanya Sharma

A Look into Mentor Circles

A Women in Pharma® Mentor Circle is a group of diverse professionals that engages on topics that are relevant in the industry, including maintaining a work/life balance and ways to develop a personal brand. Some Mentor Circles are situated within ISPE Chapters and Affiliates, while others have been started at pharmaceutical companies.

The Mentor Circles function as a connection to facilitate interactions for and between ISPE members to discuss personal and professional topics of interest. The program allows mentors and mentees, each with a different and diverse experience, to learn from each other, and includes a Mentor of the Month program that helps to introduce leaders to other countries and expands network opportunities.

"Early in the pandemic, I was in the Netherlands, and I was talking to a WIP leader in Singapore about the challenges of maintaining work/life balance during lockdown," said Tanya Sharma, Principal Consultant, Assurea LLC, and International Mentor Circle Leader for WIP. The conversations inspired the growth of the Mentor Circles initiative. "It was a breath of fresh air to me and inspired me to consider how others might be dealing with these challenges."

Sharma moved into the Mentor Circle leadership position after Jeannine Hillmer, Key Account Manager, USA, W.L. Gore Associates, Inc. Hillmer was instrumental in forming the program in 2019. The growth of Mentor Circles has been robust, rapidly exceeding the steering committee's goals to increase the number of groups from six to 20 by the end of 2020. There are now 21 Mentor Circles (and counting) in 19 countries, including the US (over 10), the UK, Russia, Brazil, Ireland, Indonesia, Japan, India, and Singapore.

"The level of engagement has been phenomenal," Sharma said. "We didn't think it would be picked up like it has been all over the world."

—Scott Fotheringham

to participate—and many already benefit from these good ideas.


Thomas Hartman

"It's so important for men to be involved," said Clark. "Men will get a better understanding and empathy for what others are going through in their lives and careers." She sees this as especially helpful during the COVID-19 pandemic. "Working dads and husbands know that their partners who are working from home are currently more stressed out than normal. It is different for the parent who has now become a caregiver, teacher, laundress, and referee. Sharing those pains and creating a space where working professionals can understand what their partner is going through can create a positive outcome for our members. When men participate in WIP events, they're gaining a lot of education about women in general, and they're getting to see the vulnerable side and hear the types of conversations that are typically not happening in the workplace."

Hartman, who retired from GSK last year, is a strong advocate for the role of women in the life sciences and has been an ardent supporter of WIP since it started.

"Men who join a WIP event should do so to learn other perspectives on life, the work/life balance, and some of the challenges women have in the workplace," Hartman said. "Learning these things would make men far more effective as colleagues, managers, and in other leadership roles where supporting their staff or being able to communicate with their colleagues brings value more effectively to their own careers."

Clark estimated that about 10%–15% of attendees at many WIP events are men. She would like to see more, and she believes that the male attendees are the men who are going to be the champions and who will help their female colleagues advance.

Arencibia agrees, noting that it is important to not underestimate the power of giving women a forum to speak. "Women in Pharma has taken some effort to launch and find its identity, but it really started to take off when it became evident that ensuring the success of women in pharma requires much more than women—it requires our male colleagues."

After WIP invited male industry leaders to discuss how they have supported their female colleagues in their careers, interest in the program really expanded, Arencibia said. "From there, we connected to the Young Professionals and had table breakouts—and all of a sudden, it just took off. I chaired a session and had the thrill of thinking, 'Oh my God, this is it. It's just not going to be like it was before.'"

PANDEMIC IMPACT

The COVID-19 pandemic turned expectations upside down in 2020 and continues to disrupt businesses, careers, and personal lives. In

fact, one in four women working for US corporations is considering downshifting her career due to the pressures that have been exacerbated by COVID-19 [5].

"It's heartbreaking for me to hear that women want to downsize their careers because we have worked so hard to get where we are," said Clark. "I haven't heard any of my male colleagues say that they're going to downsize their career to be able to maintain their households. But I have heard my female colleagues and friends say they're going to have to take a sabbatical from work or quit their jobs because of circumstances created by the pandemic pertaining to childcare and educating their children remotely."

Like many, Clark admits to finding it more challenging to balance working from home with parenting while her children need to be homeschooled. She is grateful that WIP is providing a forum for women to support each other and share their thoughts about these struggles, as Arencibia did in her editorial, "Pandemic Coping Strategies," in the September/October 2020 issue of this magazine. "By writing about it and talking about it, we're saying to each other, 'You are not alone in this situation, and we're going to get through this together,'" Clark said.

WIP has adapted to the pandemic by going virtual. Perhaps counterintuitively, COVID-19 has given the WIP Steering Committee the opportunity to initiate programs sooner than anticipated. This includes virtual book clubs, a webinar hosted in May 2020—and attended by 150—that was meant as a pilot to test whether a full-blown women's conference would be possible, the 24 Hours with Women in Pharma event held before the 2020 ISPE Annual Meeting, and sunrise to sundown meetings.

"The sunrise to sundown events are a good example of how we've adapted to the pandemic," said Clark. "I attended a really good one. There were people from all over the world on the call, with all of us socializing, discussing books, and even playing a trivia game. I wasn't sure how the heck we were going to play trivia with 25 women on the phone, but it was awesome. You got to know people through the chat box. We figured out how to have a social time and feel connected, laughing and sharing stories in a virtual environment."

Once all of their meetings and events needed to be virtual, WIP groups were challenged to find a consistent way to host activities. When using free Zoom accounts, hosts found that meetings might end prematurely after 45 minutes and were limited to a certain number of participants.

Three corporate sponsors—Pharmatech Associates, IPS, and PQE Group—provided generous sponsorships to allow WIP initiatives around the world to have access to host their virtual events.

"In some ways, COVID-19 has actually helped WIP grow the way it has," said Tanya Sharma, Principal Consultant, Assurea LLC, and

ISPE® FOUNDATION | WOMEN IN PHARMA

WIP is here to foster an environment where women can excel in the pharma industry. This means more women at the podium, more women at the table, and more women on the board. We want to inspire women to take risks, be assertive, enhance their knowledge and education, and adhere to professional standards in the workplace.

28% women engineers in research and development

17% women hold Board seats on the top 50 pharmaceutical companies

22% women comprise tech roles in the US and other mature economies

International Mentor Circle Leader for WIP. "The focus on hosting virtual events allows us to have regional events that blend the experiences of members from different countries."

For example, WIP held virtual meetings in Latin America, APAC, and Europe last fall. All three had a theme of inspiring women in leadership positions and creating a support network to navigate difficult obstacles, like working from home during the pandemic.

MORE GROWTH AHEAD

When WIP leaders were asked what is next for WIP, the overwhelming response was unsurprising. The steering committee wants to grow its base, have more webinars, increase the number of Mentor Circles, and continue to offer opportunities to educate, support, and provide resources to people worldwide.

"I want to see Women in Pharma recognized as a significant value proposition for joining ISPE," said Arencibia. "I'd like to see more access to leaders in the industry, and to see more leaders contribute their time and mentoring. I'm passionate about seeing mentoring evolve from the group settings of Mentor Circles to allow women to connect directly with one-on-one mentoring."

Barrick believes there is an untapped opportunity to publicize WIP outside of ISPE, where it is not yet broadly recognized. "The members of Women in Pharma find WIP very attractive and helpful," Barrick said. "Women who are considering joining ISPE may not be aware that the group exists, and letting them know presents a great opportunity for us going forward. I'd like to see it evolve into a selling point to becoming an ISPE member."

Some novel initiatives in the works include a merchandise store, a podcast series, a webinar series and more stand-alone webinars, WIP conferences, and more fundraising for student travel grants in the US and other developed countries as well as emerging markets.

Clark hopes to encourage members to build stronger relationships within their own companies, and Santillan believes ISPE APAC WIP groups will continue to strengthen their network and relationships, sharing technical resources and best practices, especially for students and Emerging Leaders (formerly Young Professionals), in keeping with Workforce of the Future, a key area in ISPE's Strategic Plan.

"I have worked with many talented, bright, and ambitious women throughout my career," Hartman said. "From both a personal and professional perspective, I understand why ISPE Women in Pharma is growing rapidly, and why such interest and engagement is occurring within it. I'm delighted to see this, and ISPE is behind the WIP initiative's continued growth and success."

"Women in Pharma, thanks to the ISPE Foundation, has created a strong movement to help make a difference in the industry," said Clark. She has a colleague who was recently tapped to start a women's initiative at her employer, a large pharma biotech company. "She asked me all about WIP. How did we start? What is our charter?

"I told her it's just like anything else: We're a bunch of engineers who set goals for the year. Then we just started attacking those goals. I told her we're a positive group of enthusiastic people trying to empower others. And that we have proven that enthusiasm is contagious."

For more information

Visit the WIP webpage on the ISPE website at ISPE.org/women-pharma

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About the Author

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Creating Effective STANDARD OPERATING PROCEDURES

By Tom O'Leary

Personnel management is the most challenging variable in maintaining current Good Manufacturing Practice (cGMP) across the life cycle of drug manufacture, safety, and supply. A standard operating procedure (SOP) outlines agreed-upon instructions for personnel training and instructions for maintaining systems, machines, documents, and records in a qualified state to produce safe products. This article explores the role of SOPs, as well as their structure and components.

The need for succinct, well-written, and focused SOPs is best illustrated by examples. The following are gleaned from our experience, from design to compliance, helping companies respond to adverse regulatory findings by the US FDA, EMA, and others.

In one case, a lengthy and unclear SOP was ignored and the "best operator" was "training" others in vial capping procedures. The spring pressures applied to dies on a vial capping machine were observed to be variable and the dies mismatched. The operator compensated for this mismatch with trial-and-error adjustments, and the trainees learned unqualified methods.

In cases where such practices survive regulatory inspections, this may enshrine the belief that they are compliant with regulations. However, when inspectors issue their reports, their lists are not comprehensive and may include only the most egregious issues found. Even though the inspectors may not have listed concerns about the vial capping procedures, the procedures were not cGMP compliant and increased patient risk.

A developing trend is for corporations to generate corporate SOPs for use as site SOPs. An often-stated justification for the practice is that it limits the number of SOPs, which is supposed to make the SOP update process easier. However, the practice may blur the distinction between corporate documents and site-specific SOPs and lead companies to stray from cGMP.

For example, when a company included as many dependent procedures as possible in an SOP, the result was an unwieldly, inefficient calibration SOP. The SOP encompassed multiple analytical and nonanalytical subsystems, and some types of calibration were understood by personnel to be the domain of certain departments, even though this was not stated in the SOP. Because many departments and systems were included in a single SOP, those tasked with performing specific activities had the unnecessary responsibility of remembering the SOP's nuances and exceptions. Regulators looking at these kinds of SOPs may rightfully question the efficacy of training, especially when the duration of training is too short to plausibly learn the documented procedures.

SOP BUILDING BLOCKS

To be most effective, SOPs should be succinct, intuitive, easy to navigate, traceable, and regularly approved. Concise SOPs greatly help users and provide assurance to regulators that procedures are controlled and compliant.

To ensure compliance and traceability to a qualified state are achieved, companies should make approved SOPs traceable and confirm they have an audit trail. Appointing a single individual as owner of approved SOPs further strengthens control over them. When this does not happen, original approved documents may be lost or untraceable.

Revisions should be made only when changes occur to the process or the procedural steps, or when a review is compulsory. Nonprocedural changes—such as inconsequential typographical errors and logo changes—should be noted by the SOP owner and only added to SOPs during subsequent revisions.

SOPs should be hard copies or noneditable files that are controlled and archived in a secure location. Although editable files such as Microsoft Word documents may be used and circulated prior to approval, they are not suitable media for approved documents.

To generate an SOP or revise a legacy SOP to be as effective as possible, the authors of the SOP should use clear wording, break down content into parent and child documents as needed, use detailed work instructions when necessary, include engineering references and images for clarity, and follow a defined, easy-to-use structure.

Clear Wording

The apparent simplicity of high-quality SOPs belies the effort and cost of producing and editing them. When companies spend insufficient time editing and producing SOPs, wordy and confusing documents are a likely result. For instance, SOPs may include awkward, repetitive text because they were hastily completed in an effort to close corrective and preventive actions (CAPAs) and authors inserted partial transcription related to regulatory (FDA, EMA, etc.) observations. During follow-up visits, inspectors may be impressed by seeing the exact CAPA wording in the SOP, but the insertions can be counterintuitive or ineffective for those who are expected to adhere to the procedures. Staff training can suffer as a result, leaving personnel dependent on heuristic learning from the "best operator." Consequently, operations can resemble trade practice instead of qualified procedural methods.

Parent and Child SOPs

To prevent SOPs from becoming bloated, one solution is to adopt independent parent SOPs, child SOPs, and annexures. For instance, a preventive maintenance SOP can be broken down into child SOPs for consumables, equipment, buildings, and so on, or a calibration SOP can have child SOPs or other types of attachments for calibration masters, analytical subsystems, nonanalytical subsystems, etc.

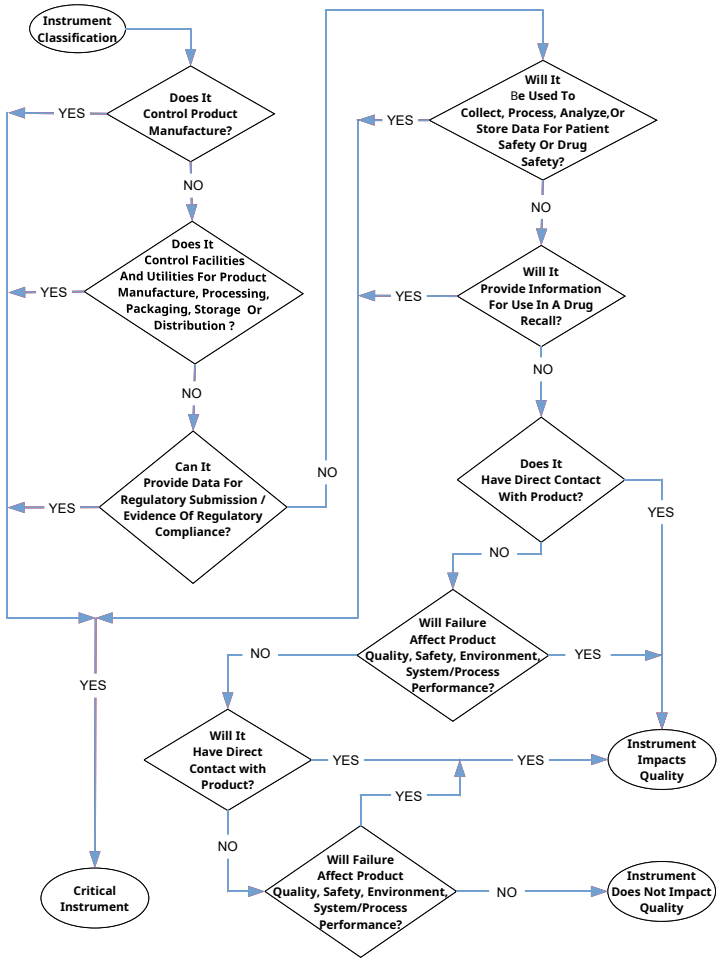
The advantage of using a parent document and child documents is that when subcategories change or need to be revised, the focus is limited to discrete SOPs or attachments. Consequently, retraining cost is lower because it is specific to the subcategory rather than the SOP in general. As SOPs become more succinct, they become easier for staff, auditors, and regulatory inspectors to understand and explain.

Work Instructions

Using work instructions to provide detailed step-by-step instructions to operators on a separate document, instead of in the SOP proper, can be effective. The SOP can provide general information, and the respective work instructions can address the details.

This approach is especially useful when the language of the SOP and its associated documents is not in the native language of operators. Although only one version of the work instructions can be regarded as the master file, multiple language translations can be of great benefit. To prevent confusion caused by mistranslation of the master, a note in the translated document should state it is a translation of the official work instructions, and the original document should hold precedence. Revision numbers of the official work instructions and their translated versions must remain the same. Unfortunately, we have seen cases of multiple versions of documents in more than one language, with different instructions.

Figure 1: Example of a flowchart to classify instruments.



Engineering References

Another cause of vague SOPs may be the lack of master drawings, such as process and instrumentation drawings and process flow diagrams. In our work, we have found multiple drawings for the same process, computer-aided design files presented as "master drawings," and different drawings from different departments.

Without a reliable engineering reference, companies may have multiple unrelated drawing revisions indicating different configurations and instrument identifiers, SOPs can become vague, and traceability suffers. To prevent these problems, master drawings should be the responsibility of a designated owner within a department, not, as has been observed, an entire department.

Images

When judiciously used in SOPs, flowcharts, photographs, and diagrams can help personnel understand a process, especially when the SOP user's first language is not the same as that of the SOP. However, overuse and

Table 1: Example of provenance details in an SOP header.

Site details	Document description		SOP no.	Rev.
Title:				
Supersedes SOP no.:	Issue date:	Review date:	Effective date:	Page X of Y

Table 2: Example of an SOP footer.

Form number–revision	**Page X of Y**

When judiciously used in standard operating procedures, images can help personnel understand a process.

haphazard insertion can lead to fragmentation of text. Images should be annotated to prevent ambiguity.

Flowcharts can provide useful overviews of processes. They aid training, and staff can use them as quick reference guides. For instance, a flowchart such as Figure 1 can illustrate the classification of instruments, which has often been a source of confusion in many plants.

SOP flowcharts must be carefully edited and reviewed. They can be deceptively difficult to align with the written procedure. It is essential that approved SOPs do not include flowcharts that introduce ambiguity (i.e., the text describes one course of action, but the flowchart indicates another).

SOP CONTENTS AND STRUCTURE

An SOP generally includes an introduction, background, ownership, instructions, and traceability, all outlined in an agreed-upon format and complete with references, appendixes, and annexures. Although the presentation may differ from the order described here, it must comply with Good Document Practice (GDP). The following SOP sections are included for completeness; their inclusion in a specific SOP is a decision for site management.

Provenance

An SOP's provenance (its history of ownership and origin) should be included in the header—this will assure users of its validity. At a minimum, the header should include the site details, title, document number, version number, and revision date (see Table 1).

- *Site details* may include the site or corporation's logo or printed details.
- *Document description* can be "Standard Operating Procedure" or "SOP Appendix."
- The *SOP number* must be unique and comply with a documented numbering system.
- *Title* is the subject of the procedure. (Note: there is no value in restating the description.)
- *Superseded SOP number* is included for traceability. This information is especially helpful when a numbering system changes or the contents of an SOP change radically.
- *Issue date* is recorded because SOPs may be issued in advance of the effective date, which is preferable because it allows for an orderly transition and time for training.
- *Review date* is noted to ensure that a review takes place before an SOP is no longer valid.
- *Effective date* is the first day on which an SOP is valid.
- Every page should show the unique page number and the total number of pages contained in the SOP (i.e., Page X of Y). This might be included the header, the footer, or both places.

In addition to the page number, the footer may contain the form number (see Table 2). Form number–revision refers to the form identifier used for the SOP, usually with the revision identifier as a suffix. The footer may also contain provision for signatures of approvers if required (not shown in Table 2).

Purpose, Objective, and Scope

The SOP's purpose, objective, and scope of systems, equipment, facilities, and/or process are best described in the introductory sections of the document.

- *Purpose* outlines the qualified processes, equipment, or systems activity used in maintaining cGMP for which the SOP was developed. It should indicate the user and any customer requirements, and identify the site owner.
- *Scope* identifies the target department (or departments) of the SOP, their locations, and the personnel to whom the SOP applies. For clarity and to exclude ambiguity, a description of items not within the scope should be included.
- *Objective* describes the tasks required for each goal of the SOP and specifies the target process, equipment, utility, or facility. This section should also support the company's mission statement (and is sometimes called "mission statement") with respect to the activity for which the SOP was developed.

Some sites combine the purpose or scope with the objective. However, this format is only recommended when the combined section improves clarity and conforms to an agreed-upon layout.

Approval Signatures

SOPs must include an approvals section or page where owners can append their signatures and the date of their signing. Some companies require the author, reviewers, and approvers to sign every page, even when the SOPs are lengthy. As a result, some SOPs that we reviewed had more than 200 signature/date insertions. Signing every page is generally unnecessary. Instead, consider using only initials on individual pages, or provide signature sections in the front and back sections of SOPs to bracket their contents.

Table of Contents

A table of contents helps users locate relevant sections, which is particularly useful during an inspection or audit. Most writing software can automatically generate the table of contents.

Definitions and Abbreviations

A definitions section clarifies any unfamiliar terms or jargon for the reader. It is especially useful when auditors and regulatory inspectors review procedures.

All acronyms or abbreviations should be defined. This may be done in a list or by enclosing the acronym or abbreviation in brackets and displaying it immediately after the spelled-out term is presented in the text.

Roles and Responsibilities

A roles and responsibilities section identifies the duties of the author, owner, reviewer, technicians, operators, management staff, and quality assurance. For situations in which technicians or operators are not staff, reference to the relevant SOP for contractors should be given.

Procedure

The procedure section should outline the process and enumerate the steps necessary to accomplish tasks. As noted previously, if there are many steps in a procedure, consider including only the main content of the procedure and reserving details and specifics for child SOPs and other addenda.

Revision History

A history of SOP revisions must be included for traceability. Such a history is easily maintained if the parts of the SOP (sections, paragraphs, subparagraphs, etc.) are comprehensively enumerated for easy identification. Only the history of the most recent revisions, usually the prior three or four, must be shown, provided all other revisions have been archived and are easily retrievable. The company's approach to tracking SOP revisions may be noted in its SOP for SOPs or in the revision history section itself.

References and Related Documents

Relevant references to other documents should be listed in a separate section, as this reinforces the SOP's authority. Unfortunately, some SOP writers will copy references from other documents without assessing their relevance. Unnecessary references should be avoided.

Appendixes and Attachments

Most SOPs have forms, appendixes, addenda, or annexures containing samples of documents or records to be used when executing procedures. These should be used for illustration purposes only and not copied for use as cGMP documents because control over documents would be negated.

CONCLUSION

Although generating and maintaining SOPs can seem time-consuming, the best SOPs adapt to contingencies without major modifications. The value of producing SOPs that are clear, concise, and intuitive is usually evident when things go wrong, at which time the cost of any corrective action may be greatly magnified.

To avoid SOP-related problems, companies should consider instituting a program of SOP revitalization, especially for legacy SOPs. This activity can be conducted by a dedicated team from within the organization, or it may involve the use of consultants. Team members should be experts in an activity covered in the SOP who are capable of writing in a clear, concise, and intuitive way. Most important, they should write SOPs with the target audience in mind (not only peers or superiors), and peer reviews should be used for technical content.

About the author

Tom O'Leary is a compliance professional (facilities, utilities, equipment, packaging, and validation) with over 30 years of experience in EMA and FDA biologics, parenteral, OSD, and sterile and nonsterile API-regulated industries worldwide. He has conducted cGMP audits; responded to FDA Form 483s, major findings, warning letters, consent decrees, conducted remediations, due diligence, and mock audits; and troubleshot systems, processes, and equipment. He has been an ISPE member since 2014.

MODEL-INFORMED DRUG DEVELOPMENT

Addresses COVID-19 Challenges

By Patrick Smith and Karen Rowland-Yeo, PhD

Drug developers know that the odds of any one compound demonstrating safety and efficacy for a disease and its affected populations are low. How can drug developers improve these odds and increase the efficiency and effectiveness of drug development? One useful tool is model-informed drug development (MIDD), which uses computer models to inform the design of clinical trials or to run simulations when human or animal trials are not feasible. By ensuring that appropriate drugs are advanced and the clinical trial design is optimized, MIDD helps drug companies develop therapies for emerging diseases like COVID-19.

MIDD, also called modeling and simulation (M&S), is the application of in silico quantitative models in drug development to facilitate decision-making. MIDD is centered on knowledge and inferences generated from integrated mathematical models of the physicochemical characteristics of a molecule, its disposition in the body, and its mechanism of action, and how the drug might affect a disease from both an efficacy and a safety perspective. MIDD informs, reduces, and sometimes can eliminate the need for clinical trials, guiding decision-making on dose regimen optimization, safety, and toxicology, as well as clinical trial design and supportive evidence for efficacy.

REGULATORY FRAMEWORK

Encouraged by global regulators, MIDD is used in virtually all novel drug development programs. Specifically, the US FDA has MIDD provisions under the Prescription Drug User Fee Act (PDUFA) VI [1]. One provision includes the MIDD Paired Meeting Pilot Program, where drug developers can meet with the FDA and receive input on their proposed MIDD application in specific programs [2]. MIDD has become integrated as part of new drug applications (NDAs) and biologics license applications (BLAs) at the FDA (Figure 1) [3]. It is also accepted in applications to the European Medicines Agency and the Pharmaceuticals and Medical Devices Agency in Japan [1, 4].

Work is ongoing to create international guidelines to standardize the validation and verification of MIDD models for use in regulatory filings. Two concerns in guideline development are (a) the reliability of models is only as good as the data used to generate them [1, 4], and (b) authorities do not want to limit sponsor creativity and innovation by making guidelines too restrictive.

APPLICATIONS

MIDD has many applications (Figure 2). It is used to determine product development go/no-go decisions, moving the most promising candidates forward and stopping development of prospects that are unlikely to be effective. MIDD is also employed to translate data from in vitro to in vivo research, animals to humans, smaller to larger/more diverse populations, adults to pediatric patients, and so on. Additionally, it can be used to model drug performance in different organs, evaluate drug-drug interactions (DDIs), and analyze optimal drug combinations.

Overall, MIDD helps drug developers answer key questions (Table 1). By leveraging expertise in clinical pharmacology, accelerated regulatory pathways, and M&S, companies focusing on drug development can partner those with specific expertise in MIDD protocol development, thereby expediting trial enrollment.

PBPK AND POPPK MODELING

MIDD encompasses a range of techniques to inform drug development. Physiologically based pharmacokinetic (PBPK) and population pharmacokinetic (PopPK) modeling are two broadly used

Figure 1: Adoption of MIDD by the US FDA. Key: CTS, clinical trial simulation; DDI, drug-drug interaction; D/R, dose response; E/R, exposure response; IVIVC, in vitro/in vivo correlation; PBPK, physiologically based pharmacokinetic; PK/PD, pharmacokinetic/pharmacodynamic; PopPK, population pharmacokinetic; QSP, quantitative systems pharmacology. (Adapted with permission from reference 3.)

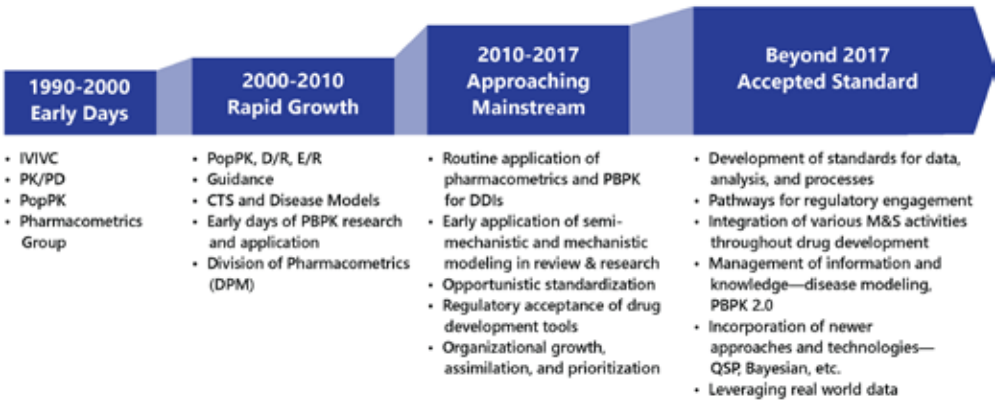


Figure 2: MIDD applications.

Table 1: Key drug development questions that MIDD can address.

Topic	Questions
Selection of optimal drug candidates	What is the best target and modality for pharmacological intervention to treat the disease? Can drug candidates be compared for safety, efficacy, and potential for regulatory and payer approval? Can the effectiveness of an existing drug be improved through combination therapy?
Trial optimization	What is the most efficient, targeted, and safest trial design? How can the number of animals required for toxicity testing or the number of subjects required for clinical trials be reduced? What biomarkers are available to demonstrate efficacy?
Safety and toxicity	How can safety-related drug attrition be reduced? Can we accelerate the pace of reducing risk associated with developing drug candidates? Can DDIs and food-drug interactions be identified and evaluated without conducting trials? How can drug exposure for specific organs, such as the heart or lungs, be determined to predict potential side effects?
Dose selection, special populations, and formulation	What are the optimal, final-dose, and dosing regimens? How is the most appropriate drug dose determined for unstudied populations, such as pediatric patients, and high-risk patients, such as pregnant women? Are there alternative drug formulations?
Regulatory and commercial success	How can the comparative effectiveness and commercial potential of the target compound be validated? What is the shortest path to regulatory approval? Are there enough data to support bridging into new indications? Can existing drugs be repurposed for new indications?

MIDD is being used to aid in triaging COVID-19 drug candidates according to their likelihood of demonstrating safety and efficacy.

MIDD approaches. The former is a mechanistic, "bottom up" technique, and the latter is an empirical, "top down" technique.

PBPK M&S links in vitro data to in vivo absorption, distribution, metabolism, and excretion, as well as pharmacokinetic/pharmacodynamic (PK/PD) outcomes, to explore potential clinical complexities prior to human studies and support decision-making in drug development. Each individual subject has a set of PK/PD parameters based on their individual characteristics, drug concentration, and drug effect information. Thus, in individual model fitting, a full PK/PD profile is required to generate the PK/PD parameters of interest.

Population PK/PD M&S expands upon individual PK/PD analysis by (a) relating individual PK/PD parameters to a set of theoretical "typical" PK/PD parameters, and (b) quantifying the impact of known information (e.g., age, sex, weight, phenotype) on the variability in the individual PK/PD parameters.

DEVELOPMENT OF COVID-19 THERAPEUTICS

Several lines of investigation are open for COVID-19 drug development, and multifaceted modeling approaches are required to handle the different scenarios. MIDD is being used to aid in triaging COVID-19 drug candidates according to their likelihood of demonstrating safety and efficacy. Simulations are being performed to fill critical data gaps and determine in silico the impact of both new and existing therapies.

Determining Therapeutic Dosages

It is critical to optimize the dose for any therapy intended to treat COVID-19. If the dose is too low, it may be falsely concluded that the drug is ineffective. On the other hand, if a dose is too high, the drug may cause toxicity. Recent M&S work has predicted that certain drugs under consideration for COVID-19 treatment, ivermectin and lopinavir/ritonavir (LPV/r), are not efficacious at the doses studied.

Ivermectin

Ivermectin, an antiparasitic drug, is also approved for head lice and scabies. Researchers in Australia recently announced that a single dose of ivermectin could kill SARS-CoV2 in vitro within 24 hours [5]. PBPK modeling was used to assess whether clinically relevant doses of ivermectin were able to attain the concentrations evaluated in vitro for treatment of patients with COVID-19 [6]. The simulations showed that ivermectin is unlikely to be effective. Even at a high-dose ivermectin regimen of 600 μg/kg daily for three days used in a previous clinical trial [7], with the most generous assumptions for clinical translation, the in vitro half-maximal inhibitory concentration (IC50) is more than 9-fold higher than the day 3 plasma-simulated maximum plasma concentration (C_{max}), and more than 21-fold higher than the day 3 lung tissue–simulated C_{max}. This dose scenario exceeds the highest regulatory-approved dose of ivermectin, a 200 μg/kg single dose for the treatment of strongyloidiasis (roundworm infection) [8].

If the developers of ivermectin create a potentially effective way of administering a higher dose of the drug, such as a nasal spray or inhaled drug, PBPK modeling could be applied to determine whether ivermectin in this form could effectively reduce viral counts. However, if the higher dose of ivermectin is limited because of safety concerns, it is unlikely that this candidate will move forward.

LPV/r

The limited viral kinetic data available for COVID-19 suggest that the duration of viral shedding (i.e., the process of the virus being released into the environment after it has replicated inside the body) is longer than that for influenza, and longer treatment may be necessary to continue to fight the virus. Investigators are interested in LPV/r, an approved HIV treatment, as a potential COVID-19 therapy because it decreases HIV levels in blood and theoretically may have similar effects on SARS-COV-2 [9].

In vitro data on the effects of LPV/r against coronaviruses indicate that the drug combination may be significantly less active against SARS-COV-2 compared to HIV-1 [9]. This suggests that the HIV dose for LPV/r would be unlikely to be successful against SARS-COV-2, where it is much less potent.

A collaborative research team used PopPK models and tested a range of potential PK/PD relationships to simulate LPV/r plasma and lung exposures in adults [10]. The analysis indicates that standard LPV/r doses are at high risk of COVID-19 treatment failure, especially without a loading dose. The standard LPV/r dose takes 36–48 hours to reach full plasma concentration, which would lead to a loss of valuable time in the SARS-COV-2 treatment window. Given that the dose regimen for COVID-19 needs to reach therapeutic concentrations quickly, the models indicate that a standard HIV dosing regimen is unlikely to be effective against SARS-COV-2 [10].

Additional modeling with a loading dose could be performed to determine whether reaching higher plasma LPV/r concentrations in a shorter time can alter the COVID-19 disease course (e.g., whether the patient requires hospitalization and a ventilator).

Viral Kinetic Modeling

Another approach for advancing treatments for COVID-19 involves viral kinetic models that use mathematical equations to describe

how viral load changes with time in an infected patient [10]. Originally used for HIV-1, these models can provide important information about the cell infection rate, viral production, and clearance rates. They are also used to predict disease course and treatment outcomes. With SARS-COV-2, there is a wide range of potential disease courses, from asymptomatic cases to patients requiring hospitalization and a ventilator [11]. Therefore, COVID-19 models may include additional variables to account for disease course variability and complexity.

Research teams are combining viral kinetic modeling with PK/PD modeling to quantify drug effects based on their mechanism of action and evaluate in silico the efficacy of specific drug combinations in treating COVID-19 and other viral diseases [12]. These models can help link the antiviral drug of interest to its impact on a patient's viral load, which is an important driver of the duration and severity of disease. Patients who shed virus are infectious, and such viral kinetic models have been coupled to epidemiological models to assess the effectiveness of drug treatment strategies on reducing the number of infections in a population (i.e., "flattening the curve").

Lung Exposure Modeling

Another MIDD approach relevant to COVID-19 involves modeling the lung exposure of drugs. To combat the tuberculosis (TB) epidemic, a research team in collaboration with several leading global health institutions developed a multicompartment permeability-limited lung model. This newly developed PBPK model helps drug developers leverage in vitro and in silico data to understand drug disposition and penetration in plasma, lung tissue, epithelial lining fluid, and TB granulomas. In addition, these tools allow researchers to simulate a range of variables—drug dose, disease state, and concomitant medications—and thus support designing more-effective drug regimens [13]. This model has been used to evaluate drugs that can treat COVID-19 [14].

CONCLUSION

The global community of scientists is working 24/7 to identify, study, and test potential treatments and cures for many diseases, including COVID-19. In the current pandemic, there is a compelling need to speed progress, evaluate opportunities to shift regulatory paradigms, and efficiently make go/no-go decisions. It is time for researchers to open the MIDD toolbox and leverage it. Together, using multiple advanced modeling tools, collaboration, and expertise, the scientific community will prevail in finding appropriate treatments and preventive measures for COVID-19.

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Acknowledgment

The authors thank Mia DeFino, MS, ELS, for medical writing support.

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Karen Rowland-Yeo, PhD, is Senior Vice President, Client and Regulatory Strategy, at Certara UK Limited's Simcyp Division. Prior to this, she was the Head of PBPK Consultancy Services at Simcyp, where she led a team of scientists engaged in consultancy projects relating to the application of PBPK modeling in drug development. She has worked directly with global regulators to gain acceptance of PBPK models, increasingly raising the bar in innovation and quality. She received her BSc Honours degree in physics at the University of Natal in South Africa in 1989 and her PhD in drug metabolism from the University of Sheffield in 1995. Prior to joining Simcyp in 2002, Karen held a five-year lectureship in clinical pharmacology and therapeutics at the University of Sheffield. Karen has authored more than 100 peer-reviewed articles In the field of in vitro–in vivo extrapolation and PBPK modeling.

ISPE'S APQ PROGRAM AND GUIDES

Advance Pharmaceutical Quality

By Christopher J. Potter

ISPE has announced the launch of its Advancing Pharmaceutical Quality (APQ) Program with the publication of the ISPE *APQ Guide: Corrective Action and Preventive Action (CAPA) System*, a guide dedicated to the topic of CAPA. This article describes how the APQ Program has been built and summarizes the content covered in the Advancing Pharmaceutical Quality Guide series, using the CAPA guide as an example.

The CAPA guide provides guidance, recommended tools, and suggested key performance indicators (KPIs) to assess, aspire, act on, and advance a CAPA system. To provide quantitative business context, ISPE has partnered with the University of St.Gallen in Switzerland to include in the APQ Program an optional operational excellence (OPEX) benchmarking exercise, which offers objective evidence of performance improvement to support ongoing investment of time and resources. The CAPA guide is the first of a series aligned with ICH Q10, Pharmaceutical Quality System (PQS), elements and principles [1], with other APQ guides likely to publish in the near future.

BUILDING ISPE'S APQ PROGRAM

For more than a decade, ISPE has actively supported industry efforts to understand, implement, and comment on several high-profile, often global, regulatory initiatives. Since 2018, these initiatives have been focused under the Regulatory Steering Council (RSC) [2]; examples of RSC efforts include:

- Product Quality Lifecycle Implementation (PQLI)®: Through PQLI, ISPE assists industry and regulators in advancing manufacturing sciences across the product life cycle to achieve excellence in drug development and pharmaceutical production.
- The Drug Shortages Initiative: This initiative is facilitating communication and creating tools to help improve industry's capability to mitigate and prevent drug shortages.
- The APQ Initiative: This initiative is building industry-for-industry tools and programs to help companies assess and improve their quality operations.

In 2018, the RSC provided strong support and guidance when the Quality Metrics Core Team proposed that the Quality Metrics Initiative evolve into the APQ Program, with the concept being beta tested by developing assessment criteria, development tools, and KPIs for evaluating the maturity of a CAPA system. This proposal was based on ICH Q10 and described with supporting background and justifications in an article published in *Pharmaceutical Engineering*® in September/October 2018 [3]. Figure 1 summarizes the initial proposed APQ concept.

A preliminary quality assessment (PQA) would allow determination of the potential value of and need for a "deep dive" (i.e., thorough) examination of an assess-and-aspire series of activities. The assess-and-aspire component would be used to assess a company's own quality maturity and decide, based on this assessment, how much the organization aspires to improve. Should the organization decide that they wish to improve, the program would point

Figure 1: Initial proposed APQ framework.

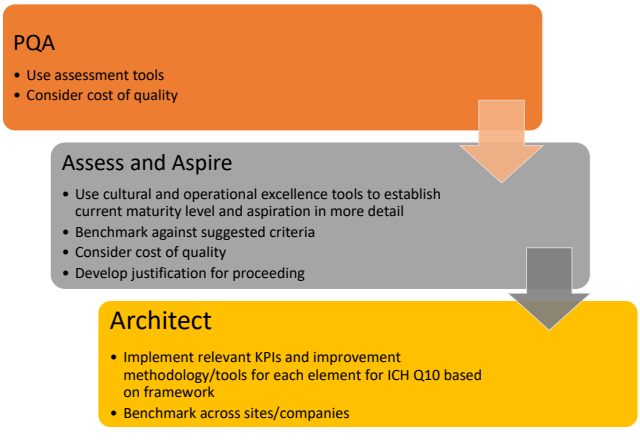


Table 1: APQ program benefits.

Beneficiaries	Benefits
Industry	Access to an ICH Q10–based quality maturity framework that can be used in full by an organization to understand the impact of their quality maturity assessment, KPI application, and improvement actions to the overall performance of the organization Support and incentives for sustained, continual improvement of a firm's PQS Benchmarking and best-practice sharing to accelerate progress
Patients and consumers	Increased reliability of supply of quality product
Health agencies	Better insight into the industry's focus and current expectations regarding critical quality areas for advancing pharma quality
ISPE	Source of educational and training materials and ongoing publications Building an APQ good practice community for knowledge sharing and support

to tools and KPIs that would be the architects of improvement. Tools and KPIs to conduct these activities, along with those to assess, benchmark, and improve quality maturity, would be identified from those that are already available to the company. Where tools and KPIs do not exist, ISPE teams would propose new or alternative options.

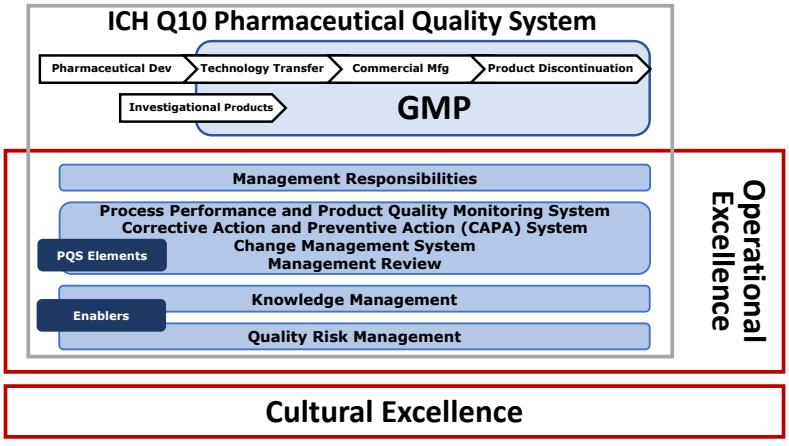
The goals, benefits, and principles set out in 2018 have remained unchanged, with the overarching goals of the APQ Program being to:

- Integrate quality management maturity, cultural and operational excellence principles, tools, and approaches.
- Foster industry ownership of quality beyond compliance.
- Promote effective and efficient use of resources.
- Support and incentivize continual improvement.
- Encourage self-improvement and supplier improvement.
- Enable structured benchmarking, knowledge sharing, and learning among companies.
- Increase the reliability of supply for quality products.
- Offer routes for delivering a sustainable competitive advantage.

Benefits were identified for industry, patients/consumers, health agencies, and ISPE (Table 1), and the following guiding principles for the program were established:

- Maintain simplicity.
- Be applicable across all sectors of the pharmaceutical industry.
- Deliver value and benefits for industry.
- Use "as-is" company data and site procedures as much as possible.
- Minimize additional work.
- Be "by industry, for industry."

Figure 2: APQ program links to the ICH Q10 PQS model.

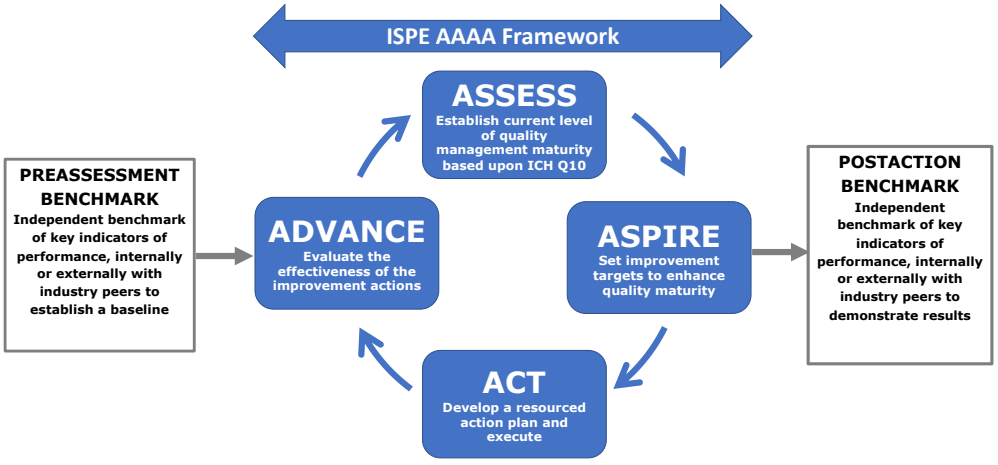


- Leverage existing benchmarking and performance management/OPEX methodologies and principles where relevant.
- Build on the ICH Q10 framework, with enhancements to include operational excellence and quality culture (Figure 2).
- Be complementary, where possible, to current regulatory initiatives promoting quality excellence, such as PIC/S data integrity guidance, the US FDA's New Inspection Protocol Project (NIPP), and the MHRA data integrity guideline.

The initial APQ proposal has been refined and enhanced as a result of the following:

- A pilot exercise run by an ISPE subteam using the ICH Q10 element CAPA as an indicator of company health. An effective CAPA system demonstrates whether issues are acknowledged, tracked, and, ultimately, remedied in an effective and permanent manner. Feedback led to refinement of maturity assessment descriptors, how KPIs are presented, and how improvement tools are aligned to maturity level.
- Continued collaboration with the University of St.Gallen leading to a formal memorandum of understanding whereby ISPE can use in the APQ Program, as an option, the OPEX benchmarking and quality maturity assessment tool, both of which were developed by St.Gallen.
- Increased FDA interest in quality management maturity.

Figure 3: The APQ Program containing the ISPE AAAA framework.



Overall, these enhancements and refinements led to the program being renamed the Advancing Pharmaceutical Quality Program. Furthermore, the goals are being realized with publication of the CAPA guide as the first guide in ISPE's APQ Guide series.

AAAA FRAMEWORK AND BENCHMARKING

The APQ Program has been designed with an assess, aspire, act, and advance (AAAA) framework as a core to provide formal continual improvement (CI) opportunities: Assessment allows a baseline to be established and opportunities for potential CI to be identified; aspire involves selecting and prioritizing the improvements to act upon; act requires a detailed, resourced action plan to be developed with targeted improvement outcomes; and, advance evaluates and confirms the required outcomes have been achieved.

The APQ AAAA framework is:

- A self-assessment process
- Composed of four distinct but interconnected stages
- Based on a five-step maturity model
- Intended as an iterative CI process
- A detailed quantitative and qualitative exercise with criteria to evaluate the current state of quality, diagnose gaps, and identify improvement opportunities

To provide a quantitative baseline, the University of St.Gallen OPEX benchmarking and quality maturity assessment tool is included as a pre- and post-benchmarking exercise for the APQ AAAA framework, as shown in Figure 3. This benchmarking could be performed optionally by St.Gallen or by self-application using tools provided by St.Gallen in the APQ Guide.

To assist practitioners performing the ISPE APQ AAAA process, each APQ guide will address:

- Background, overview, and structure of the APQ Program
- How to conduct the quantitative pre- and postassessments either in the St.Gallen benchmarking program or through internal use of methodology provided by St.Gallen
- How to conduct and score a deep-dive assess-and-aspire exercise for each ICH Q10 element
- How to set up an act-and-advance improvement program
- A case example to assist practitioners

The APQ Guide series is based on ICH Q10 and hence will cover the following elements: the CAPA system; management responsibilities and review; the change management system; and process performance and product quality monitoring system. Because management responsibilities and management review are strongly linked, one guide is being created for those two elements.

Notably and as shown in Figure 2, the concepts, principles, and tools given in ISPE's cultural excellence work—for example, *The Cultural Excellence Report* [4] and the ISPE/Parenteral Drug Association article on root cause analysis [5]—are embedded into the APQ AAAA framework.

In addition, there are ISPE publications and resources that support the guide series and specific guides, such as:

- The Knowledge Management Good Practice Guide, which is in development
- ISPE resources such as training programs on quality risk management
- *PQLI® Guide, Part 3: Change Management System as a Key Element of a Pharmaceutical Quality System* [6]
- *PQLI® Guide, Part 4: Process Performance and Product Quality Monitoring System* [7]

APQ CAPA GUIDE STAGES

Stage 1: Preassessment Benchmarking (Optional)

At the outset of the CAPA process, it is useful to establish a baseline

The APQ Program has been successfully developed, tested for practicalities and value, and refined and enhanced.

of current performance by formally documenting selected KPIs and organizational enablers. This preassessment benchmark may be completed using the companion tool provided by the St.Gallen OPEX team, designed specifically for use with the APQ program as a low-resource, simple-to-complete exercise. This step is optional but recommended. In total, the benchmarking involves providing values for 13 KPIs in four dimensions, answering 18 maturity questions, and providing information for some contextual factors (e.g., site type and size).

The St.Gallen APQ benchmarking tool can be used for self-evaluation conducted internally by a company, or in a benchmarking process evaluated by the St.Gallen OPEX team with results provided in a formal analysis report highlighting potential areas for improvement. (Note: This APQ preassessment performance analysis report can also be provided by participation in a full St.Gallen OPEX benchmarking study.)

The preassessment may also inform the prioritization of where a company should focus its resources to apply the deeper diagnostic APQ quality management maturity self-assessment in stage 2. Ultimately, the results can act as an important comparator or baseline against which future advancement results can be evaluated using the postaction benchmark.

The core of the ISPE APQ Program, the APQ AAAA framework is outlined in stages 2 and 3.

Stage 2: Assess and Aspire

In this stage, using the APQ self-assessment tools detailed in the guide, a cross-functional assessment team will perform a deep evaluation of the organization's quality management maturity. The APQ assessment process is a guided process providing objective quantitative and qualitative criteria to assess business process capabilities and performance, leadership and workforce competencies, and associated behaviors of a selected quality system element. The self-assessment process enables a proactive and honest review of current practices and outcomes to determine the current level of quality management maturity. When the APQ self-assessment is conducted, any underlying gaps or issues and opportunities for improvement are formally identified and documented.

A matrix has been created with five levels of maturity common to all elements/APQ guides and an appropriate number of subelements/areas relevant to each ICH Q10 element. For each subelement assessed using the APQ assess tool, the assessment team will observe, review, and provide demonstrated evidence of current policy and practice compared with specific criteria set out across the five-level maturity model. From this detailed review and as explained in the guide, a maturity level is assigned.

The next step is to complete the APQ aspire process, where an analysis of the results of the self-assessment process is undertaken to review the improvement opportunities identified and to determine where and by how much the company aspires to improve. This analysis will confirm the overall maturity score for the element under consideration and prioritize the specific improvement opportunities based on current performance or business needs. The output of the APQ aspire process forms the basis for the improvement action plan.

Stage 3: Act and Advance

The next step is the APQ act process. Its purpose is to develop an improvement action plan that is appropriately resourced and defines the necessary actions to enhance maturity to the next level. The APQ guide contains a catalog of improvement tools and KPIs and has been developed to provide further recommendations on available supporting resources and useful KPIs worthy of consideration by the team responsible for the improvement action plan.

The APQ advance step involves the careful design and evaluation of the effectiveness criteria necessary to demonstrate achievement of the improvement goals.

Stage 4: Postaction Benchmarking (Optional)

At an appropriate duration after completion of the APQ AAAA process, it is recommended that a postaction benchmarking exercise be conducted using the same St.Gallen APQ benchmarking tool used in stage 1. This postaction benchmarking is intended to evaluate the impact of the improvements on the overall company performance.

It is hoped that in time, as the APQ knowledge-sharing forum develops, case studies quantifying the benefits gained will become available to share with others. These cases will serve to provide incentives for broader adoption within the industry by demonstrating the value to the business of adopting such a formal program.

INFLUENCES ON THE INITIAL APQ PROPOSAL

As summarized earlier, major influences on development of the APQ AAAA framework were the ISPE CAPA pilot; St.Gallen research (which included research funded by the FDA); and evolving FDA publications on assessing the state of pharmaceutical manufacturing quality.

ISPE CAPA Pilot

The CAPA maturity pilot was described in a *Pharmaceutical Engineering* special report (September-October 2018) [8] and a presentation at the 2018 ISPE Annual Meeting & Expo in Philadelphia [9].

Table 2: Lessons from the CAPA maturity pilot.

Topic	Lessons
Maturity assessment	Detailed descriptors helpful in clarifying how the concepts and principles are to be applied. Consider making level 5 more transformational; make sure the tool does not convey an overly prescriptive approach. There is a preference for an overall score based on a weighted approach, but looking at individual scores is also seen as valuable.
KPIs	The definition of "what good looks like" varies across companies and may vary based on whether a company is benchmarking against other companies or current performance. Trend versus target.
Tool catalog	A catalog of tools is helpful and has benefit. Tools should be aligned according to the different maturity levels so that you know what tools are appropriate for a given level of maturity.

The objectives of the pilot, which involved nine companies, were validating the concept and understanding its value to the industry. Feedback particularly focused on questions related to the following:

- Maturity level descriptors and how participants conducted assessment
- How and from where KPI data were obtained
- The value and appropriateness of KPIs
- Whether the catalog of tools is helpful

Key insights from the pilot (Table 2) were then incorporated into the final design of the CAPA framework and guide.

St.Gallen Research

Figure 4 presents the timeline and major milestones of the Quality Metrics Initiative. This graphic illustrates the origins of the St.Gallen research that informed the creation of the ISPE APQ framework, and which may also have influenced the evolution of the FDA's thinking on evaluation of the state of quality in the pharmaceutical industry.

ISPE has conducted two pilot research studies into quality metrics to provide data-driven responses and comments about FDA quality metrics guidances. ISPE has also organized several workshops involving participants in the pilot studies as well as representatives of the FDA and the University of St.Gallen. These workshops were designed to provide input for ISPE positions and responses to quality metrics guidances and to broaden thinking as ISPE focus evolved from quality metrics to the more expansive and challenging task of assessing the state of quality in the pharmaceutical industry.

In response to a request in 2015 for academic research into the application of quality metrics in the pharmaceutical industry, the University of St.Gallen was awarded a research grant, which was subsequently extended. This research by St.Gallen has been published in three reports [10–12] and influenced the FDA in their efforts to assess the state of quality in the pharmaceutical industry.

An outcome of this St.Gallen research and the original St.Gallen OPEX benchmarking program was a concise, user-friendly benchmarking module. In this module, all selected performance indicators and enablers are meaningful for understanding overall plant stability and performance. Developing this set of measures required extensive research, primarily using St.Gallen's databases containing operational performance data from more than 380 manufacturing sites and around 100 quality control labs. These databases were built over the last 15 years and contain the outcomes of the full St.Gallen OPEX benchmarking programs. Based on the available data sets, statistical exploration—such as correlation and regression analyses or *t*-tests—led to the selection of a subset of 13 metrics surrogating overall performance. Additional validation comprising the direct comparison of the new abbreviated overall performance score calculated based on the chosen measures only, and comparison with the full performance score used in the legacy benchmarking, provides confidence from a system perspective.

The ISPE collaboration with St.Gallen provides a platform for the university to advance their OPEX benchmarking database work and research within the industry.

FDA Publications on Quality

In 2018 and 2019, the FDA drew from St.Gallen research as the agency started to discuss the concept of quality maturity in public presentations [13], leading to an extensive discussion on quality management maturity in the FDA report "Drug Shortages: Root Causes and Potential Solutions" [14]. The report concludes that "economic forces are the root causes of drug shortages" and further identifies one of three major root causes to be that the "market does not recognize and reward manufacturers for mature quality management systems."

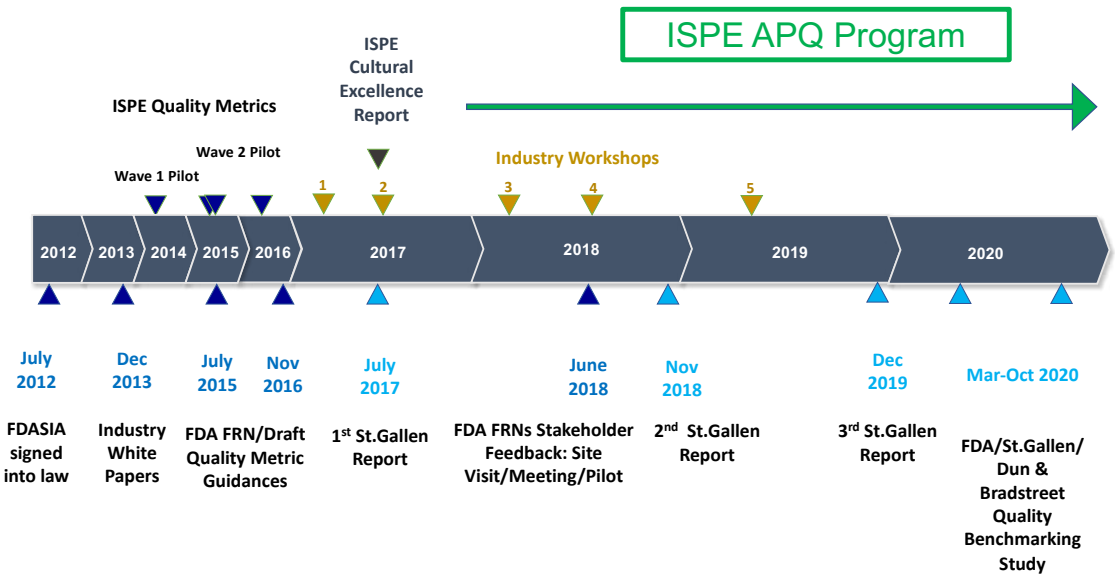
The report also contains a substantial discussion of quality management maturity in Appendix B and has a section on the challenges in assessing quality management maturity. It states:

> *A quality management system is a collection of business processes focused on consistently meeting expectations, expressed as the organizational goals and aspirations, policies, processes, documented information and resources needed to implement and maintain quality. Quality management maturity is a measure of the consistency and reliability of business processes related to an organization's goals.*

ISPE asserts that the APQ AAAA framework should assist with the challenge of assessing quality management maturity.

In March 2020, the FDA funded a global quality benchmarking 2020 study (also referred to as Pharmastudy) as a collaboration between the University of St.Gallen and Dun & Bradstreet [15]. The

Figure 4: The ISPE Quality Metrics Initiative/APQ timeline. Key: FDASIA, Food and Drug Safety and Innovation Act; FRN, *Federal Register* notice.



study will produce a globally representative baseline data set that characterizes quality management maturity among human drug manufacturers. It strives to analyze quality management maturity and operational data from approximately 2,000 manufacturing establishments in 52 countries. This benchmarking study has used the same ICH Q10 quality maturity benchmarking module as that used in the APQ Program.

In parallel, the FDA has continued its investigations into the potential for a quality metrics program. In June 2018, the FDA published two *Federal Register* notices (FRNs) announcing new voluntary efforts to gather stakeholder feedback on the use of quality metrics.

The first FRN described a quality metrics feedback program with efforts that include Type C formal meeting requests and pre-abbreviated new drug application (pre-ANDA) meeting requests, as well as a pilot study to gain feedback from establishments [16]. The second FRN announced a 2018 CDER and CBER staff experiential learning site-visit program to provide learning opportunities for FDA staff involved in the agency's quality metrics program and to give stakeholders an opportunity to explain the advantages and challenges associated with a robust quality metrics program [17]. Some companies with members on the Advancing Pharmaceutical Quality Core Team have participated in these programs, and ISPE has facilitated interactions between company members relating to preparation for and feedback from participation in these feedback efforts.

CONCLUSION AND NEXT STEPS

The APQ Program has been successfully developed, tested for practicalities and value, and refined and enhanced based on feedback and collaboration with the University of St.Gallen. The first APQ guide, on the ICH Q10 CAPA element, is available, and other guides in the series are planned: The management responsibilities/review guide criteria, tools, and KPIs are developed and being tested. Criteria, tools, and KPIs for the change management guide have also been developed. Work to develop the matrices for the process performance and product quality monitoring guide has commenced.

ISPE considers the APQ Program as applied using the APQ guide series to be a major tool that the industry can use to assess and advance the state of quality management maturity.

To purchase the APQ guides, go to ISPE.org/publications/guidance-documents

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Acknowledgments

Thank you to the APQ CAPA subteam members: Lori Chelemedos, Pac-Side LLC; Andrew Denny, Bristol-Myers Squibb; Ketan Gujarathi, Bristol-Myers Squibb; Kira L. Ford, Eli Lilly and Company; Tami Frederick, Perrigo; and Blain Spangler, Baxter.

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A NEW PHARMACEUTICAL EQUIPMENT EXPOSURE MEASUREMENT DATABASE

By Takahide Hashizume, Yuko Tanaka, and Haruka Futamura

This article describes the Pharmaceutical Equipment Exposure Measurement Database (PEEM-DB), which was launched in July 2019 by the ISPE Japan Affiliate for its members. PEEM-DB is offered as a tool for rationally advancing optimal containment equipment settings by collecting exposure measurement results for pharmaceutical product manufacturing equipment and statistically analyzing the data.

The March 2015 revision of cross-contamination prevention requirements in the EU GMP guidelines [1, 2] states that manufacturers must identify, assess, and control cross-contamination risks in buildings and equipment for manufacturing pharmaceutical products; these efforts are essential to optimize equipment and facility design and ensure product safety. In the manufacture of high-potency active pharmaceutical ingredients (APIs) in particular, companies must adopt appropriate containment equipment for the specific manufacturing process. However, unless the containment performance expected from the proposed equipment is quantitatively defined, equipment selection is difficult.

As stated in the ISPE *Baseline Guide: Risk-Based Manufacturer of Pharmaceutical Products* [3], four exposure routes can trigger cross contamination in the manufacture of pharmaceutical products: mix-up, retention of parts that come into contact with products in shared equipment, mechanical transfer, and airborne transfer. Containment equipment for airborne transfer and mechanical transfer should be adopted in pharmaceutical product manufacturing lines. To analyze and evaluate the cross-contamination risks caused by airborne transfer and mechanical transfer, the basic principle is to evaluate the containment performance of the containment equipment. To quantitatively implement such evaluation, the exposure measurement data for the containment equipment must be statistically organized.

Exposure measurements for containment equipment have frequently been conducted by the methods described in the second edition of the ISPE *Good Practice Guide: Assessing the Particulate Containment Performance of Pharmaceutical Equipment* [4]. Presenters at the ISPE Japan Affiliate Annual Meeting have reported cases in which pharmaceutical companies have organized the measurement results and applied them to configure settings in containment equipment. However, because the measurement results are limited and companies' measurement approaches vary, such methods have not been adequate for sharing information across the industry.

In response to these circumstances, the PEEM-DB working team in the ISPE Japan Affiliate's Containment Community of Practice (CoP) has developed a platform for widely collecting and analyzing exposure measurement data from pharmaceutical product manufacturers, equipment manufacturers, engineering companies, and other companies related to the manufacture of pharmaceutical products. The platform thus enables implementation of quantitative methods to assess risk of airborne transfer.

Moreover, during the prototype development stage, the CoP surveyed ISPE Japan Affiliate members' companies to determine what the companies require from this platform. We distributed a questionnaire to participants in the Containment COP workshop

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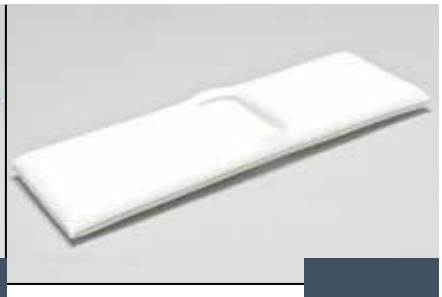

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organized at the 2017 ISPE Japan Affiliate Annual Meeting [5]. About 50% of the 70 respondents expressed the desire to use this platform, and a similar percentage requested that it be shared online for direct access by users. Also, nearly 90% of respondents expressed interest in the platform's future development.

As a result of these efforts, PEEM-DB was created. The ISPE Japan Containment CoP administers the PEEM-DB.

DATA SET

PEEM-DB is a database of the results of airborne transfer exposure measurements in containment equipment. It contains measurement data of airborne concentrations (μg/m³) of substances using lactose and other surrogate materials in manufacturing processes for drug substances and products.

For containment equipment, these data mainly target the glove box/isolator (GB), flexible glove box (FGB), fume hood/draft chamber (FH), and localized exhaust (LE) stand-alone products and assemblies. Details such as environmental conditions during equipment operation, work processes, types of powder, handled amounts, and airborne measurement locations are added to support the data analysis.

The data stored in PEEM-DB include test data results from containment performance evaluations implemented by ISPE Japan Affiliate members' companies, mainly based on the ISPE *Good Practice Guide: Assessing the Particulate Containment Performance of Pharmaceutical Equipment* [4]. Furthermore, the database contains results from trial exposure measurements. In total, PEEM-DB currently makes approximately 300 data items available to ISPE Japan Affiliate members.

The ISPE Japan Affiliate and the Containment COP receive permission for use from the companies that own the data. To encourage companies to share their data, detailed data are disclosed to ISPE Japan Affiliate members only.

For data reliability, the PEEM-DB working team checks and confirms data before inputting, and the ISPE Japan Affiliate currently manages the database by linking companies, data providers, and the PEEM-DB working team. This system efficiently brings together users and participants, while maintaining security and protecting data from unrestricted modification.

DATABASE FORMAT

PEEM-DB uses general spreadsheet software (Microsoft Excel), and users can download the database from the Japan Affiliate website. Excel was chosen because the system is reliable and easy to use. During the selection of registered items, convenience for users and comprehensiveness of data were emphasized. Items in PEEM-DB are divided into four categories (Tables 1–4).

DATA USES

As already mentioned, PEEM-DB is compiled in Microsoft Excel. The filtering feature in this software allows users to extract only required information, and the results of analysis can be visualized as graphs (see Figure 1 for examples).

Table 1: Containment equipment category.

Item	Data Type
Data registration date	Date
Containment equipment	Notation of equipment name: GB, FH, LE, RTP (rapid transport port), SC (safety cabinet), other
Detailed equipment specifications	Notation of equipment name: TM (tableting machine), FC (film-coating machine), ML (mill), GL (granulator), other Combination notations
Differential pressure set (negative pressure or positive pressure, kPa)	Numerical value
Air velocities at point of use (meters per second)	Numerical value

Table 2: Process category.

Item	Data Type
Handling form	Text: Powder, liquid, tablet, etc.
Product process	Text: Tableting, grinding, screening, other

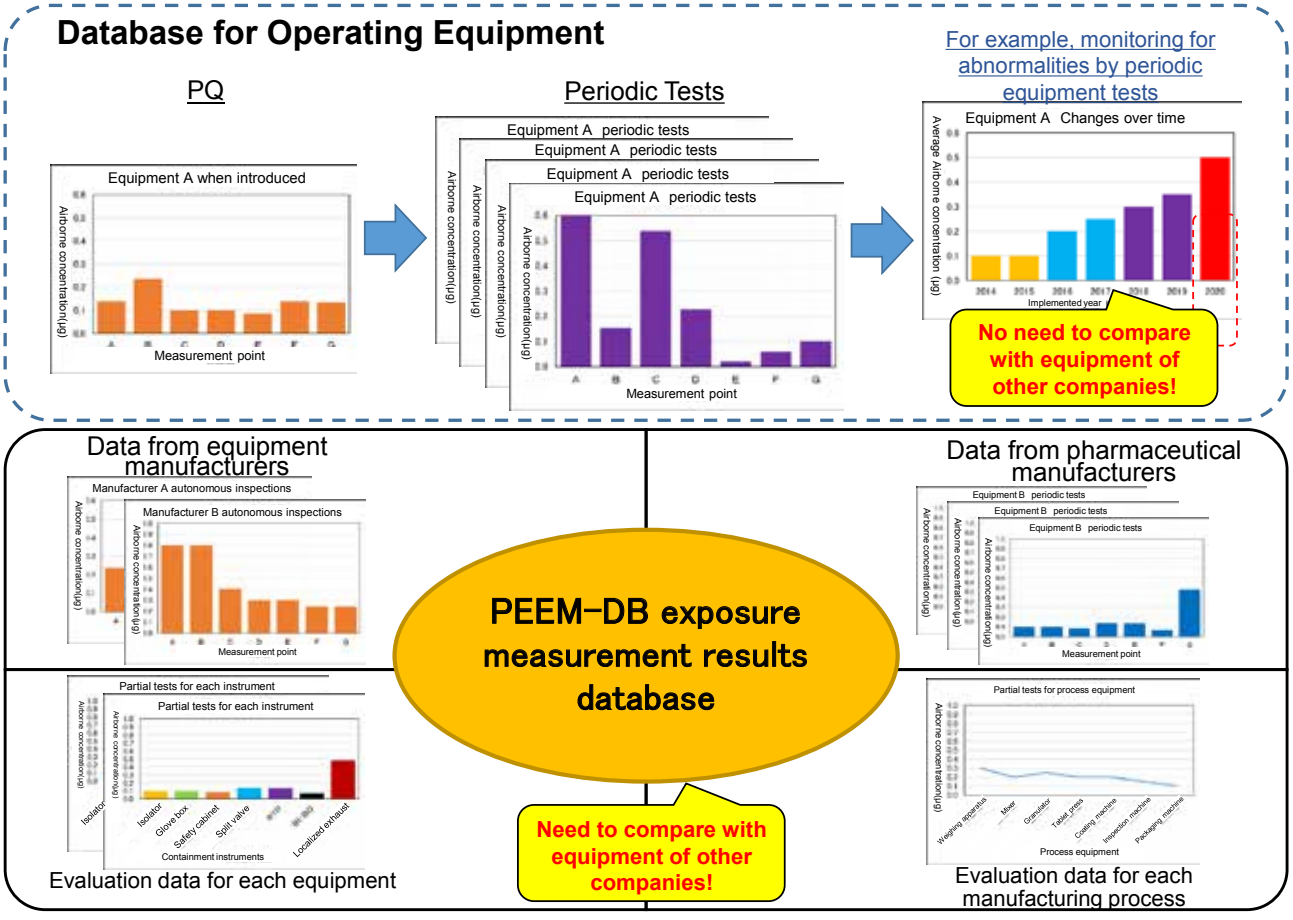
Table 3: Pharmaceutical category.

Item	Data Type
Evaluation powder	Text: Lactose, acetaminophen, API, other
Pharmaceutical ratio (%)	Numerical value
Handled amount (kg)	Numerical value

Table 4: Monitoring category.

Item	Data Type
Data source	Text: Equipment manufacturer, pharmaceutical company, engineering company
Work process	Text: Equipment operation, insertion, removal, washing, other
Airborne measurement location	Text: Worker, window, port, other
Measurement time (min)	Numerical value
Suction pump flow (L/min)	Numerical value
Air suction flow (L)	Numerical value
Airborne measurement actual value (μg)	Numerical value
Airborne concentration at measurement (μg/m³)	Numerical value
Baseline (background) airborne measurement actual value (μg)	Numerical value
Baseline (background) airborne concentration at measurement (μg/m³)	Numerical value

Figure 1: Examples of graphs generated from PEEM-DB.



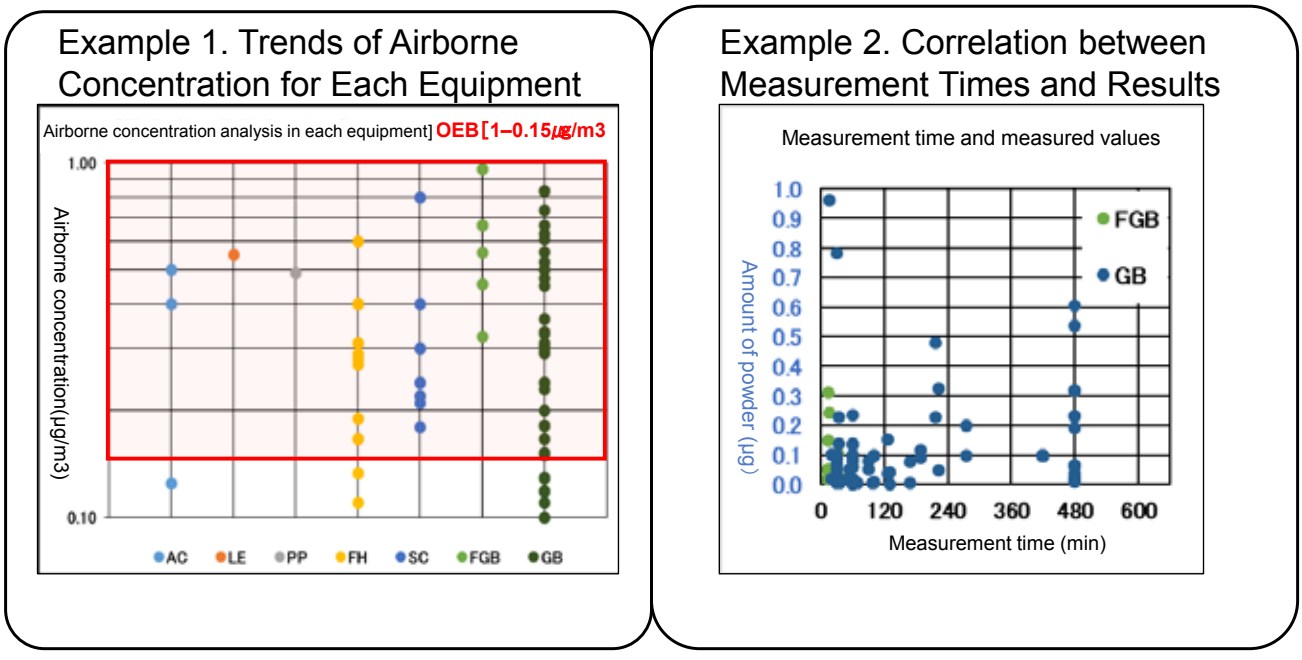
The goal is to collect a large amount of widespread data from differing measurement conditions so that PEEM-DB can be treated as "big data."

A general database can be used for managing equipment-related data. For example, appropriate maintenance time can be checked and confirmed on the basis of the trend of changes over time at the same measurement point (Figure 1, top). Because measurement conditions vary from company to company, it is difficult to compare such performance data between companies.

Despite the differences in company data, there is still considerable value to be obtained from conducting verification. Therefore, PEEM-DB actively stores various data from many companies, such as the private data held by equipment manufacturers, comparative data for equipment (Figure 1, bottom left), operating data and process-based measurement data from pharmaceutical manufacturers (Figure 1, bottom right), and other data.

Figure 2 shows examples of actual analyses implemented using PEEM-DB. Example 1 shows an airborne concentration plot for each type of equipment. It can be seen that airborne concentration from FH, SC, FGB, and GB is largely distributed within the specific occupational exposure band (OEB). Moreover, by focusing on a field with the target OEB, it can readily be seen which equipment satisfies the target. Further, an understanding of airborne concentration distribution zones containing numerous plots

Figure 2: Case examples of PEEM-DB data analysis.



provides a guide for determining the appropriateness of equipment for the design OEB. Example 2 shows whether there is a correlation between measurement time and amount of recovered powder. It is confirmed that extending the measurement times does not always lead to an increase in the amount of powder.

In addition to these analyses, we have attempted to conduct statistical risk evaluation through application of the process capability index (Cpk) method. Cpk is a standard indicator in the quality control field used to quantitatively evaluate the process capability of manufacturing processes. In PEEM-DB, when focusing on any equipment type, Cpk is used to quantitatively evaluate the performance stability simulated for the target OEB. For example, when Cpk is 1.00 or less, the probability of deviation is 0.3% or more, and it is assumed that the target OEB is unlikely to be met. If Cpk is 1.67 or higher, it means that the deviation occurrence rate is equal to or less than 1/1,000,000. It is also possible to reverse-calculate the extent that performance can be forecast, based on the deviation occurrence rate. Even if the target data count is small, trends can be evaluated by this method.

By filtering data for each equipment and measurement point, localized airborne concentration trends in certain equipment can also be forecast. For example, it is possible to ascertain the size and variance of airborne concentrations on the external door of the pass box, glove port, bug-out port, or other parts of the glove box.

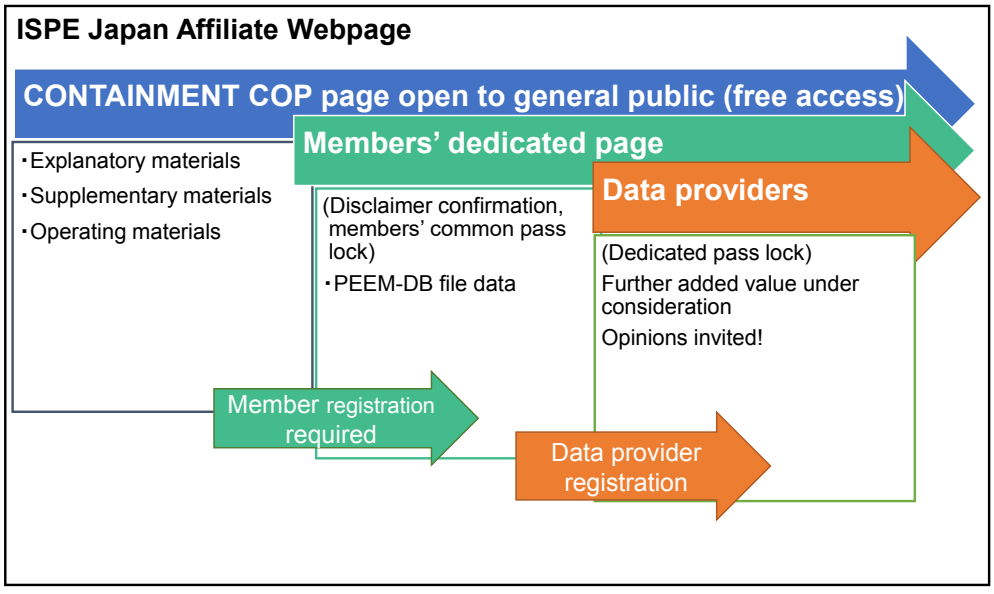
As mentioned, because the test data stored in PEEM-DB are not based on unified conditions (e.g., target performance, purpose of use, operating method, operating time), numerical values cannot be compared. PEEM-DB is simply a collection of test data that can be used to analyze trends and generate suggestions for risk assessment and equipment design choices. It does not guarantee the performance of individual devices, nor does it provide data relevant to compliance with legal or regulatory requirements. Users must be aware at all times of patient safety, product quality, and data integrity when drawing on PEEM-DB as a resource. However, such analysis does make it possible to see trends in certain evaluation items for the equipment.

The goal is to collect a large amount of widespread data from differing measurement conditions so that PEEM-DB can be treated as "big data." By integrating large quantities of diverse data, the analysis results obtained through statistical processing provide more accurate values, making it possible to also conduct quantitative analysis. Thus, it is expected that PEEM-DB can be used in various ways. One example is to provide base values in risk assessment.

ACCESS

The ISPE Japan Affiliate Containment CoP has published a webpage (ispe.gr.jp/ISPE/04_cop/04_14.htm) that offers general information about PEEM-DB, and Affiliate members can download the database

Figure 3: Levels of access to PEEM-DB.



through the dedicated members-only page. Figure 3 shows the scope of disclosure by layer. Overviews that can be freely viewed by anyone are distinguished from detailed data that are disclosed only to Affiliate members.

CONCLUSION

PEEM-DB was only very recently released and is still a limited database. From a risk assessment perspective, we believe PEEM-DB will be useful as a database of measurement values that can be qualitatively or quantitatively analyzed to help with containment equipment and system selection and the setting of control values. However, many issues cannot be evaluated using airborne transfer–related data alone. Therefore, it will be necessary to add data from mechanical transfer exposure measurements in the future.

The working team members are convinced that a fully developed PEEM-DB can be effectively and flexibly used. We are actively acquiring measurement test data to expand the database. Our aim is to include case studies of analysis and evaluation on the website and at the ISPE Japan Affiliate Annual Meeting, with a view to promoting and sharing PEEM-DB with ISPE members and others.

We will continue to discuss methods for acquiring and analyzing data for the effective use of PEEM-DB. Our wish is to include the participation and opinions of many from our industry in our activities.

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ISPE BRIEFS

New Guidance Document Available on Data Integrity by Design

Data Integrity by Design is the concept that data integrity must be incorporated from the initial planning of a business process through to the implementation, operation, and retirement of computerized systems supporting that business process.

"It promotes the application of critical thinking to identify how data flows through the business process, and to proactively assess and mitigate risks across both the system and data life cycles. It emphasizes data integrity as foundational to protecting patient safety and product quality," said Lorrie Vuolo-Schuessler, Senior Director Computer Systems Quality and Data Integrity, Syneos Health, and Guide Co-Lead.

The ISPE *GAMP® RDI Good Practice Guide: Data Integrity by Design* supports organizations as they embrace and implement a holistic approach by leveraging data governance and knowledge management activities to drive continual improvement in data integrity. The guide promotes a patient-centric mindset, focusing resources and management attention on quality best practices that inherently facilitate meeting regulatory compliance requirements. It also provides a bridge between the system life-cycle approach defined in ISPE *GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems* and the data life-cycle approach in the ISPE *GAMP® Guide: Records and Data Integrity*. Data integrity can only be achieved when both life-cycle approaches are adopted, understood, and actively managed.

Several new areas are covered in this Guide's appendices, including knowledge management and instrument devices, and there is an appendix on Computer Software Assurance (CSA) that details CSA key concepts and provides illustrative case studies. "Computer Software Assurance was born from US FDA CDRH's Case for Quality, which treats compliance attainment as the baseline and promotes the inclusion of critical-to-quality practices that result in improved quality outcomes," said Charlie Wakeham, APAC GxP Compliance Manager, Waters Corporation and Guide Co-Lead. "An industry team was formed and work begun on the development of an FDA draft guidance to apply this paradigm to Computerized System Validation (CSV)." Jim Henderson, Business/Computer System QA, Eli Lilly and Company, and Guide Co-Lead added, "In an industry first, members of this CSA team have collaborated closely with GAMP subject matter experts to create an appendix detailing the key concepts of CSA and providing illustrative case study examples of its application."

Several new areas are covered in this guide's appendices, including knowledge management, instrument devices, and Computer Software Assurance.

More information about this and other guides is available at ISPE.org/Publications/Guidance-Documents

—Marcy Sanford, ISPE Editorial Assistant

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ISPE Introduces Quarterly E-Newsletter on Regulatory and Quality Activities

ISPE has launched a new quarterly e-newsletter, *The Regulatory Digest,* about activities by ISPE's regulatory- and quality-focused volunteers on behalf of the Society. The e-newsletter will keep you informed about the important work these members are doing to build productive relationships with global health authorities and position ISPE to be their organization of choice for scientific and technical consultations.

The first issue was released on 30 September 2020 and emailed to more than 20,000 ISPE global members, industry professionals, and regulators. It included accounts of recent ISPE activity related to mitigating and preventing drug shortages, considerations for pandemic-related supply chains, and ISPE member input to significant draft consultations such as Annex 1 and the PIC/S GMP Guide Annexes on ATMPs and Biologics.

ISPE is committed to fostering communications and interactions to advance common interests among the pharmaceutical industry and regulatory agencies, and to supporting convergence of global regulatory and quality expectations for the benefit of the patients we all serve. To view past issues of *The Regulatory Digest* or to subscribe, visit ISPE.org/initiatives/regulatory/newsletter

—Carol Winfield, ISPE Senior Director, Regulatory Operations

MEET THE ISPE STAFF

CARRIE MARINA MCMANUS

In each issue of *Pharmaceutical Engineering®*, we introduce a member of the ISPE staff who provides ISPE members with key information and services. Meet Carrie Marina McManus, Manager, Volunteer Engagement and Development, Member Services Department.

Tell us about your role at ISPE: what do you do each day?

I manage the volunteer program and oversee ISPE Affiliate/Chapter relations. This encompasses a wide range of activities around developing the volunteer program, including processes for recruitment, vetting, placement, training, and recognition. I also coordinate with the regional councils APAC (Asia Pacific Advisory Council), EAC (Europe Advisory Council), and NASAAC (North America South America Affiliate Advisory Council) to develop process improvement and coordination between our Affiliates/Chapters and ISPE headquarters to best meet the needs of all members.

What do you love about your job?

I love connecting with ISPE members from around the world. I can have a morning meeting with our Asia Pacific leaders, an afternoon chat with members from Europe, and attend an evening webinar featuring Women in Pharma® from Latin America. I get insights into all their lives and cultures. I love getting to work with multiple departments within ISPE and have forged excellent working relationships and friendships with my peers. I truly miss working in our office where we could interact in person.

What do you like to do when you are not at work?

I enjoy travelling, DIY projects, and community service. I love spending time with my family, going on walks with my pup, listening to audio books, working out, and watching anything Marvel-related. I have been learning how to cook healthier versions of my favorite foods and incorporating vegetarian and vegan recipes.

QUALITY RISK MANAGEMENT
to Address Product Impurities

By Muhammad Naeem

Recently, recalls of angiotensin receptor antagonists, particularly valsartan, and warning alerts about N-nitrosodimethylamine (NDMA) impurities in drug substances such as ranitidine and metformin have demonstrated the urgent need for manufacturers and regulators to control impurities throughout the product life cycle to ensure patient safety [1–5]. In this article, all plausible pathways related to the formation of NDMA impurities in pharmaceutical products and a possible control strategy using quality risk management (QRM) as a tool are discussed.

Based on analytical lab test results, NDMA may be classified as a carcinogenic substance for humans. NDMA, a known contaminant found in water and foods (meats, dairy products, and vegetables), is also found in drugs as an impurity [6]. Generation of impurities like NDMA in drug products has raised questions about manufacturing process controls. No matter how impurities are formed, the mechanism of their formation should be known and controlled.

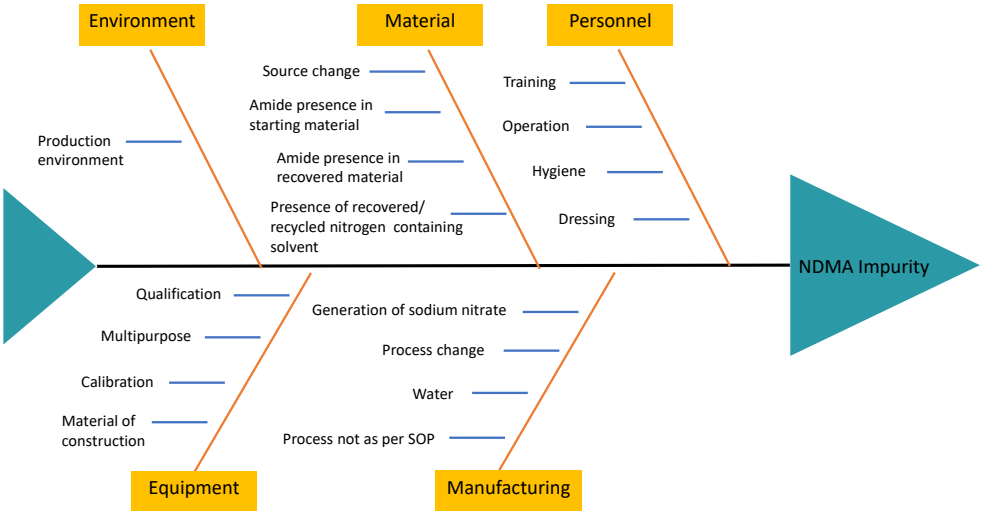
Manufacturers adopt various strategies to ensure impurities are quantified and well within the desired limit. One of the best and more proactive strategies uses QRM as a tool to assess the risk for and control of impurities such as NDMA. This approach requires a thorough knowledge of the product, its manufacturing process, the impurity, the product's and the impurity's chemical structures, situations ideal for the formation of the impurity, and the controls adopted.

RISK MANAGEMENT

To assess the risk of impurities, a company should form a cross-functional team with personnel from research and development, quality, manufacturing, regulatory, and other relevant departments. This team acts as a unit to determine all possible or probable causes of the generation of impurities and to then identify the adequacy of current controls used to bring these impurities within the desired limit. During QRM, the following steps are carried out:

- Risk assessment
- Risk control (reduction or acceptance)
- Risk review
- Risk communication

Figure 1: Example of fishbone analysis as a tool for risk identification.



RISK ASSESSMENT

The risk assessment steps may be considered the most important aspects of an overall QRM process. If the risks are not identified, analyzed, and evaluated properly, decisions about how to control risk cannot be made efficiently.

Part of the risk assessment process is to consider whether there are any possible pathways that might realistically give rise to formation of impurities. At the conclusion of the risk assessment, risk should be expressed in quantitative or qualitative terms, depending on the data available from the three steps of the risk assessment [7]: risk identification, risk analysis, and risk evaluation.

Risk Identification

Risk identification, which starts with qualitative hazard identification, is the process by which existing hazards are identified, initially without assigning magnitude. All available data should be reviewed to address the question "What could go wrong?"

This first step in the risk assessment process also identifies possible consequences. It serves as a prelude to the later steps of risk analysis and risk evaluation that ultimately lead to the appropriate control and management of risk.

There are various tools to identify risk, such as fishbone diagrams, process mapping, and process breakdowns. To identify the risks of NDMA in the manufacturing process of a pharmaceutical product, one must understand the complete chemistry of NDMA—its chemical structure, chemical and physical properties, possible pathways by which it can be formed—as well as complete process mapping, complete details of ingredients used in manufacturing, interactions between different ingredients and environmental factors, and so on. Figure 1 presents a fishbone analysis identifying risk factors that may lead to the formation of impurities.

Risk Analysis and Evaluation

In these risk assessment steps, identified risks are analyzed and evaluated either qualitatively or quantitatively. Various tools are used worldwide to analyze and evaluate risk. Among these tools, failure mode effective analysis (FMEA), failure mode, effects, and criticality analysis (FMECA), fault tree analysis (FTA), process mapping, and hazard analysis and critical control point (HACCP) are used primarily in pharmaceutical sector [7–13].

Selecting the appropriate tool for risk assessment is of prime importance. For the purposes of NDMA risk assessment, FMEA is used here. It is a widely used tool for risk management of processes and can be useful to proactively identify failure modes, evaluate their impact, and determine process steps that must be changed [8].

FMEA includes a review of the following process steps [7]:

- Failure modes (What could go wrong?)
- Failure causes (Why would the failure happen?)
- Failure effects (What would be the consequences of each failure?)

In FMEA, risk is scored on the basis of failure severity, probability, and detectability (see Tables 1–3) [9, 10]. Eventually, the FMEA conclusion is drawn on the basis of a risk priority number (RPN), which is a composite of scores for the three factors.

Table 1: Example FMEA severity criteria.

Value	Description	Criteria
1	Negligible	No impact to product quality and process robustness
2	Marginal	No impact to product quality
3	Moderate	Noticeable impact to product quality, but can be recovered by reprocessing
4	Critical	Definite impact to product quality and patient safety
5	Catastrophic	Batch failure; not recoverable by rework; serious concern for patient safety

Table 2: FMEA probability of failure mode criteria.

Value	Description	Criteria
1	Rare	Failure every 10–30 years
2	Unlikely	Failure every 5–10 years
3	Possible	Failure every 1–5 years
4	Likely	Failure more than once a year
5	Almost certain	Failure several times a year

Table 3: FMEA detectability of failure mode criteria.

Value	Description	Criteria
1	High degree of detectability	Validated automatic detection system that is a direct measure of failure, direct or indirect indication of failure (e.g., control range and in process control)
2	Likely to detect	Nonvalidated (manual or automated) detection (e.g., visual level check, visual inspection of vessels)
3	Low or no detectability	No ability to detect the failure

The probability criteria assess the frequency (rate of occurrence) of a given failure mode [9, 10]. Table 2 applies a linear scoring scale to the probability of occurrence of failure modes associated with the manufacturing process.

In FMEA, detectability criteria are used to assess the likelihood that failure modes or their impact will be detected [10]. Table 3 shows a linear scoring method used for these criteria in a manufacturing process of pharmaceutical product.

As noted previously, conclusions drawn from the FMEA are based on the RPN, composite score of the three failure mode criteria, which is calculated as follows:

$$RPN = (S \times P \times D)$$

where S is the severity criteria score; P, the probability of occurrence criteria score; and D, the detectability of occurrence criteria score.

Table 4: FMEA assessment of NDMA formation risk for one pharmaceutical product.

Item	Factor	Failure Mode	Existing Control	Severity (S)	Probability (P)	Detectability (D)	RPN = (P x S x D)	Recommended Action for Risk Mitigation	Probability (P2)	Severity (S2)	Detectability (D2)	RPN2=(P2xS2xD2)
Human	Operation	Operation does not follow standard operating procedure (SOP), which may lead to generation of impurities	Every operator involved in manufacturing is trained; second person is available to review critical operation	2	1	2	2					
	Hygiene	Personnel involved in production are unhygienic, which may lead to cross contamination	All personnel involved in manufacturing are trained and maintain good hygiene	5	1	1	5					
	Gowning	Dirty/used clothing may lead to cross contamination	As per SOP, operators are given fresh pair of coveralls at start of shift	5	1	1	5					
Machine	Equipment qualification	Nonqualified equipment or failure in qualification status	Equipment is qualified initially and requalified on defined intervals per the validation master plan	2	1	1	2					
	Material	Material of construction is not of required pharmaceutical grade, which may lead to cross contamination	Material of construction for all equipment is of required pharmaceutical grade	5	1	1	5					
Material	Amide or amine	Presence in any starting material	Amide or amine is not present in any starting material	5	1	1	5					
		Presence in intermediates	Because amide or amine is not present in any starting material, there is no possibility of generation in recovered substance	5	1	1	5					
	Source	Change of material source	Supplier qualification process in place prohibits any material to be the part of process until its qualification is done	5	1	1	5					
	Water	Presence of impurities in water	Water is tested for NDMA using a validated method	5	1	1	5					
Method	Change in manufacturing process	Change in process may trigger NDMA impurity	When change occurs, all methods and steps adopted for manufacturing are validated	5	1	1	5					
	Manufacturing process	In the manufacturing process, dimethylamine and nitrite may generate nitrosamine	Because no starting materials or intermediates involved in the manufacturing process can generate dimethylamine and nitrites, nitrosamine impurities cannot be generated in manufacturing process	5	1	1	5					
Environment	Production environment pollution	Cross contamination on the production floor may generate nitrosamine impurity	All possible pathways of cross contamination are controlled; e.g., dust generation is controlled via a closed process	5	1	1	5					

The RPN scores categorize risk in three levels:

- Low: 1–10
- Medium: 11–20
- High: 21–75

NDMA Case Study

A risk assessment study is conducted identify and devise a recommended corrective action to minimize risk of NDMA impurity. For this purpose, the failure modes most likely to cause the generation of NDMA impurities are identified and their risks given the current controls in the existing manufacturing process are assessed. Table 4 is an example of FMEA risk assessment after initial risk identification, which can subsequently be extended after recommended risk mitigation is implemented.

RISK CONTROL

Risk control is a decision-making activity to either accept or reduce risk. Effort put forth to control the risk should be proportional to the risk's significance and its outputs. During risk control, the following are addressed [6]:

- Is the risk above or below the acceptable level?
- What will be done to reduce or eliminate the risk?
- What is the appropriate balance of benefits, risks, and resources?

Before evaluating the probability that a hazard could occur, or assessing the ability to detect whether the fault can be found before the harm occurs, existing controls should be identified. This helps assess the current situation with respect to risk severity. This step can also identify the level of effort required to eliminate or mitigate that risk.

RISK REVIEW AND COMMUNICATION

Risk review and communication are an ongoing part of a quality management system. Participants in risk management should review outputs and results while taking into account new knowledge and experience. Once the risk management process is initiated, risk review will be an ongoing process to consider events affected by the earlier decisions made during the QRM process. Risk review includes reconsidering earlier risk acceptance decisions.

The risk analysis presented in Table 4 did not identify any risk in the process that may have led to the formation of NDMA impurities in one product. However, companies should take a comprehensive approach to risk assessment to ensure that there is no risk of impurity being generated in other pharmaceutical products. It is necessary for every pharmaceutical manufacturer to conduct a thorough risk assessment study related to the generation of impurities and put controls in place to ensure the patient safety.

CONCLUSION

Unwanted impurities are among the biggest challenges facing pharmaceutical manufacturers and regulators. These impurities can pose a serious threat to the health of patients. The recent NDMA alerts for angiotensin receptor antagonists (valsartan, ranitidine, and metformin) have fueled the issue. In response, pharmaceutical manufacturers have taken various steps, such as product recalls and alerts, stringent supplier qualification programs, and routine batch testing for NDMA. Still, these efforts pale in comparison to the seriousness of issue.

In this regard, the strategy presented in this article to assess the control of impurities in the manufacturing process of pharmaceutical products via QRM may be crucial. When we apply QRM holistically to the manufacturing process, it will help us identify and devise control strategies for potential failure modes or gaps that could lead to the formation of impurities in product.

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About the author

Muhammad Naeem has more than 20 years of diversified experience in quality operations, regulatory affairs, research and development, and operational excellence. Currently, he is Chief Operating Officer (Technical and Innovation) at Indus Pharma. Muhammad has RAC-Global certification from Regulatory Affairs Professionals Society (RAPS) and is an active member of ISPE, the Parenteral Drug Association, and RAPS, USA. He has extensive working knowledge of global pharmaceutical regulations and has led investigational/developmental and technical/analytical projects at contract manufacturing organizations in the US, Europe, and Pakistan. Muhammad has presented on QRM, data integrity, pharmacovigilance, QMS elements, validation, and cGMP guidelines at national and international conferences. He has been an ISPE member since 2015.

CLEANING VALIDATION PROGRAM MAINTENANCE

in a Process Life-Cycle Model

By Elizabeth Rivera

The process life-cycle model, as discussed in the US FDA guidance on process validation, is a significant change in how we view validation [1]. The three-stage product life-cycle approach—design, performance qualification, and continued process verification—emphasizes that scientifically sound decisions are required in all process stages. Overall, the process life-cycle model provides a higher level of understanding, which ensures a more robust, complete process. This article discusses how to maintain validated cleaning procedures as part of a process life-cycle approach.

Over the past few decades, various cleaning validation guidance documents have provided the industry with insight on how to comply with individual country regulations [2–4]. These guidance documents primarily focus on general validation aspects (see Figure 1). Although the prevalidation design phase and postvalidation monitoring stages were factored into the process, they are not explicitly indicated or emphasized in the regulatory guides. Today, this guidance is referred to as the "traditional cleaning validation approach."

By building robust scientific knowledge before validation, the design phase is the base that supports the decisions made in the process. As presented in the 2011 US FDA process validation guidance [1], the design phase calls for up-front work and use of modern tools such as risk evaluation (e.g., design of experiments, risk ranking), bench- or pilot-scale experiments, and novel equipment and instrument technology [5]. In contrast, many validated cleaning validation programs under the traditional approach have minimal documented work to fully support, for example, the best selection of critical parameters or methods to determine the impact of those parameters on cleanability.

For GMP manufacturing processes where new cleaning procedures (or improved ones) are being considered, applying a three-stage process life-cycle validation approach is more feasible and justifiable than the traditional approach. GMP manufacturers must ensure that the site is equipped with the necessary resources and technology early in the development of the new cleaning procedure. This enables the manufacturer to successfully complete the design phase, which helps streamline the qualification and, subsequently, the monitoring stage of the product life-cycle model [6].

However, there remains an underlying question about current manufacturing processes with cleaning procedures validated under the "traditional" approach (e.g., legacy drug products): Must companies revalidate cleaning procedures starting from scratch to perfectly comply with the three-stage process life-cycle model?

Figure 1: Traditional cleaning validation approach emphasizes validating the cleaning process.

For now, systems must be in place to supplement any validated cleaning program regardless of the extent of prevalidation work. GMP manufacturers must at least assess the risk of the current cleaning procedure and provide assurance that it performs as validated and remains in a state of control for the life of the product(s) being manufactured. Failure to establish an adequate ongoing monitoring program, or at least a periodic revalidation program, is likely to result in sanctions from health authorities [7]. Only time will tell whether the local and global regulatory expectations will change in the future.

The system to evaluate the current cleaning process's performance may include, for example, a collective assessment of cleaning-related data to detect undesired variability. This evaluation is equivalent to stage 3, continued process verification (or ongoing process verification, as it is called in the European Union) [8].

Figure 2 presents recommended elements to maintain validated cleaning procedures as part of a process life-cycle approach. Any number of these elements may be taken into consideration for different cleaning scenarios, and the selected elements must be established in a procedure, protocol, or master plan.

PRODUCT GROUPING

Product grouping is a popular cleaning validation strategy used in multiproduct facilities. Products manufactured on the same equipment can be grouped together if the cleaning procedure is proven effective for cleaning the hardest-to-clean product in the group down to the acceptable residual limits of the most toxic product in the group. Other approaches include selecting a worst-case representative product based on a point risk-ranking system. Grouping is generally based on three aspects:

- Solubility of the active ingredient
- Cleanability of the process residue
- Toxicity of the active ingredient

In some cleaning procedures that were validated years ago, selection of the worst-case product is based solely on solubility data or solubility data combined with anecdotal evidence. This approach may trigger questions during an agency inspection about the validity of the worst-case selection.

A simple example can be used to illustrate the issue with using solubility data alone. One teaspoon of sugar poured into a cup of water at ambient temperature with mild stirring takes a few seconds to dissolve completely. However, if one teaspoon of sugar is poured onto a hot stainless steel coupon, melts, and then cools down, dipping the coupon in water at ambient temperature for a few seconds is unlikely to remove the sugar residue. In other words, the basic solubility information about sugar in water is insufficient to assess cleanability. Cleanability also takes into consideration the surface-residue interaction (such as residue conditions and the surface type) and how cleaning agents or cleaning mechanisms break that interaction [9]. Solubility is often limited to the active ingredient and may not be representative of the entire process soil, especially if cleaning is performed using a cleaning agent other than water. For these reasons, grouping strategies lacking scientific data to support cleanability must be reassessed to provide better justifications in the selection of worst-case soils.

Cleanability of the process soils can be based on documented pilot plant or laboratory coupon testing. In addition to supporting the current worst-case selection, testing data are also important when introducing a new product into the same manufacturing train. Coupon studies can compare cleanability between the validated worst-case soil with new soil(s), along with an evaluation of the new soil's toxicity. As shown in Figure 3, coupon testing can include coating a stainless steel coupon, or representative substrate, with the new soil and conditioning the coupon for a specified time and temperature [10]. Once the coupon is conditioned, it can be cleaned using the same cleaning method applied for the current worse case.

Figure 2: Summary of stage 3: continued cleaning process verification.

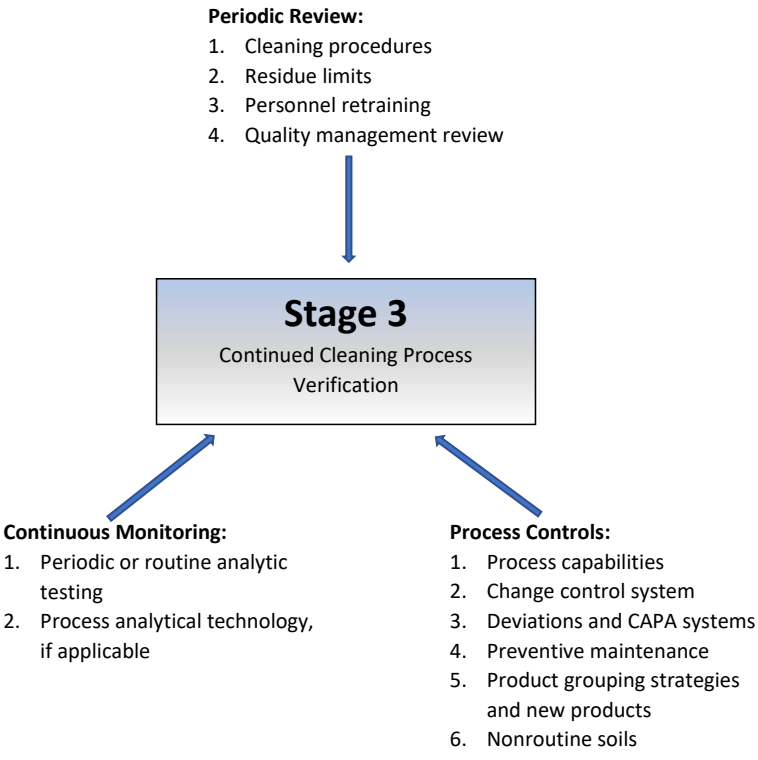


Figure 3: Laboratory studies for cleaning evaluation.

Stainless steel coupons are spiked with sample soils.

Soil conditions are emulated to the actual manufacturing process.

Coupons are exposed to multiple cleaning parameters depending on objectives.

Coupons are evaluated: Visually clean? Water-break free? Weight change?

Coupon studies can help confirm that the current cleaning process is effective for the new residue or determine that the new residue may be considered a new worst case. For example, when combined with a toxicological risk assessment, a residue acceptance limit greater than the currently validated limits may be used to show that the new residue is less toxic and to justify that a new cleaning validation is not required at the time. Alternatively, if the new residue's acceptance limit is lower than the currently validated limits, a new cleaning validation may be necessary.

REVIEW OF ACCEPTABLE RESIDUE LIMITS

Defining acceptance criteria remains perhaps the most challenging aspect of a cleaning validation program.

- How "clean" is the surface considered clean?
- How can an acceptable carryover limit from one product to another be established?
- How can surface cleanliness be demonstrated?

Historically, the commonly used method for determining residue limits is based on the Fourman and Mullen approach, also known as therapeutic dose–based calculation [11]. In addition to a visually clean surface, this approach uses the more stringent of the following two criteria:

- Any active ingredient is less than 10 parts per million (ppm) in any subsequent product.
- Any active ingredient in a subsequent product is less than 1/1,000 of the minimum daily dose of the active ingredient in the maximum daily dose of the subsequent product.

Several articles have described procedures and reported average visual residual limits based on residues, surfaces, and other factors [12, 13].

Many pharmaceutical companies continue to support the dose-based calculation. However, recent industry publications and regulatory changes affecting primarily European countries are leading the way to a different approach, known as the health-based calculation [14, 15]. Manufacturers may wish to evaluate and compare different approaches to residue limits calculation to determine which best fits cGMP requirements, corporate policies, and site objectives. Reviewing residue limits periodically to assess conformance with industry trends helps companies ensure that the validated limits are well within the market requirements where the drugs products are sold.

CLEANING DATA MONITORING AND TRENDING

As suggested in the FDA process validation guidance, to accomplish continuous assurance, the manufacturer must have a system (or systems) to detect unplanned departures from the validated process [1]. An ongoing program to collect and analyze product and process data that relate to cleaning acceptance criteria must be established. The data should be statistically trended and reviewed by a statistician or cleaning subject matter expert.

Routine or periodic sampling must be specified in the cleaning procedure and recorded. The type of sampling, number of samples, sampling frequency, and analytical tests may vary per cleaning method. The routine or periodic sampling plan has a smaller number of sampling points than the validation sampling plan based on the results of the validation study and risk assessment. Routine sampling must be easily collected and tested after each cleaning execution. Technologies such as conductivity probes employed in automated clean-in-place systems are suitable for routine sampling. Periodic sampling may be considered for manual cleaning applications at some defined yearly frequency.

The routine or periodic sampling plan must allow the manufacturer to monitor critical cleaning attributes while minimally affecting the cleaning turnaround time. For example, specific analytical methods such as high-performance liquid chromatography (HPLC) are preferred for validation purposes, whereas nonspecific methods such as conductivity, titration, or total organic carbon (TOC) may be more suitable for routine use due to their fast response times. Similarly, rinse sampling may be selected over swab sampling for routine or periodic analysis because the swab sampling is the more invasive and time-consuming approach.

Process capability compares the output of a process to the specification limits by using capability indices. The comparison is made by forming the ratio of the spread between process specifications and the spread of process values, as measured by three or six times the process standard deviation units [16]. The capability index (Cpk) is a value between 1.25 and 2.00 that represents the ultimate potential for a process to produce an output within specification. More information on process capability can be found elsewhere [16]. In the case of cleaning validation, one-sided only, upper specification limit (USL) is often used to calculate Cpk as follows:

$$\text{Cpk} = \frac{\text{USL} - \mu}{3\sigma}$$

where μ is the average of the measurements and σ is the standard deviation of the measurements.

PREVENTIVE MAINTENANCE

Equipment and instruments employed in the cleaning procedure must undergo preventive maintenance on a regular schedule, which should be set up in advance for all critical equipment and instruments. A combination of equipment manufacturer recommendations, mechanical experience, usage characteristics, and substrate compatibility with cleaning agents can be used to assess the equipment's risk of failure or deterioration and determine the frequency of maintenance. Preventive maintenance should include a calibration procedure for measurement devices such as weight scales, thermometers, flow cells, conductivity and pH probes, and other testing equipment used in the cleaning process.

Preventive maintenance in the cleaning program must address potential risk factors such as surface abnormalities. Discolored or damaged surfaces should be noted during routine visual inspection and scheduled surface inspections. Procedures should be in place to rate the severity of the abnormality and determine the corrective action, if needed. Periodic checks for worn gaskets, O-rings, dead leg orientation, sampling ports, and valves are also recommended to mitigate the risk of substrate deterioration that may result in batch contamination. Table 1 lists several preventive maintenance issues to consider in cleaning validation.

Table 1: Preventive maintenance issues to consider in cleaning validation.

Items	Aspect to consider
Valves and sampling ports	• Proper orientation • Periodic gasket inspection and replacement per manufacturer recommendations • Visual inspection of nonsanitary designs
Dead legs	• Proper orientation and length-to-diameter ratio
Spray devices	• Periodic inspection to verify holes are not clogged • Periodic spray device requalification
Piping and vessels	• Periodic stainless steel passivation • Repair of welding imperfections per sanitary standards • Periodic inspection and replacement of worn gaskets per manufacturer recommendations
Pumps	• Repair of welding imperfections per sanitary standards • Periodic inspection and replacement of worn gaskets per manufacturer recommendations
Flexible hoses	• Periodic inspection and replacement of worn hoses • Proper orientation for drainability and storage
Automatic valves, flow meters and other measuring devices, field test instruments (e.g., passivation test kit)	• Periodic calibration and parts replacement per manufacturer recommendations
Water and gaseous utilities	• Filter integrity testing • Periodic filter replacement • Periodic ultraviolet lamp replacement per manufacturer recommendations

CLEANING NONROUTINE SOILS

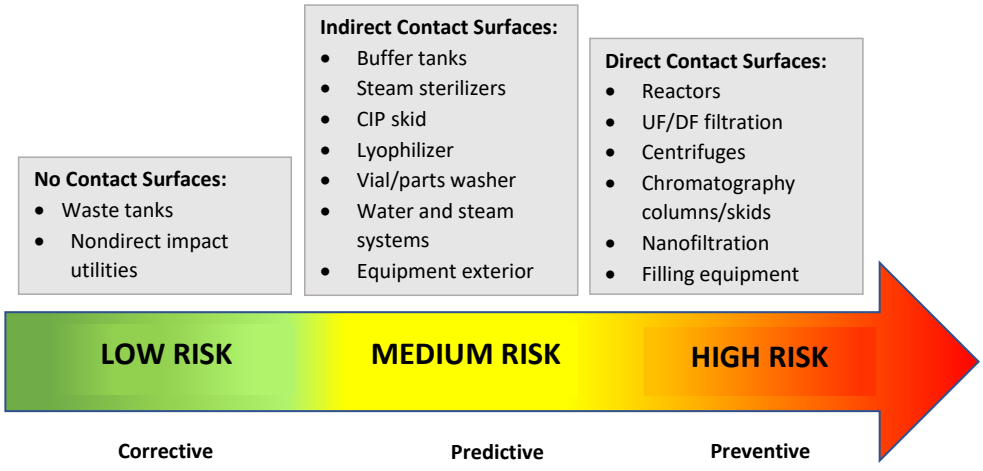
The following are some examples of soils that are not routinely considered in a cleaning validation study because they generally occur in specific circumstances and are often not fully understood until they are investigated. In recent years, various industries have reported having issues of this nature. Nonroutine soils should be investigated, assessed, and remediated to mitigate their impact on the current validated procedure and, hence, product quality.

Rouge

Rouging can occur when stainless steel water generation systems, process tanks, and pipeline systems are routinely exposed to corrosive solutions. The US FDA has stated in at least one warning letter that corrosion is unacceptable in direct-contact pharmaceutical systems [17]. Rouge on product contact surfaces creates an environment for process residues and microbes to tenaciously adhere to the rouged area, causing it to become more difficult to clean and disinfect [18, 19].

Some manufacturers use treatments to prevent rouge from happening in the first place. Other companies wait until rouge has been detected or has affected production to take corrective action.

Figure 4: Example of a rouge risk assessment.



If a process or surface condition is known to cause corrosion that will at some point affect direct product contact surfaces, the manufacturer should try to prevent that corrosion from occurring. Figure 4 illustrates a risk assessment for rouge. When choosing the best strategy to address this risk, it is important to review the potential impact on patients, products, personnel, and equipment [20].

An effective procedure for maintaining stainless steel surfaces in a passivated state and preventing corrosion requires a careful balance of several factors, including:

- Ability to remove any exogenous particles, including rouge
- Equipment and system constraints (e.g., temperatures, substrate compatibility, flow rates)
- Minimal or no surface damage caused by aggressive chemistries
- Personnel safety and disposal concerns
- Adherence to industry standards (e.g., ASTM A967 [21], ASME BPE [22])
- Concerns related to the use of chemicals that are not part of the validated cleaning process

Biofilms

A standard practice in cleaning validation studies is to consider intrinsic sources of bioburden, such as those introduced by raw materials. Cleaning procedures must be designed to be effective against both chemical and intrinsic microbial residues.

Cleaning procedures must also address extrinsic sources of microbial contamination in batches and/or equipment. Extrinsic contaminants can enter a system via air, liquid, or surface contact. Examples are gram-positive bacterial contamination resulting from poor gowning practices, fungal spore contamination from open process containers, gram-negative bacteria from process water, or spore-forming microbes from contaminated raw materials [23].

Biofilms are associated mostly with gram-negative bacteria in process systems or utilities, but they can also involve other harmful microorganisms. Gram-negative microbes contain endotoxins, primarily in the cell membrane, which can build up on equipment surfaces and eventually lead to product failure. Biofilms are also more resistant to destruction than vegetative organisms. For these reasons, biofilm contamination is a serious concern for medical implant, parenteral, ophthalmic, and other GMP products.

When biofilms or endotoxins are present, the strategy required to remove the residue effectively may differ from the validated cleaning procedure. At times, this strategy is more aggressive than the validated cleaning procedure and must be combined with a thorough inspection of the equipment's sanitary design to reduce the risk of microbial contamination reoccurrence. Published studies evaluated the inactivation of *Bacillus cereus* biofilm and recommended using a disinfectant with and without precleaning with a formulated alkaline cleaning agent [24, 25].

Air-Liquid Interface Residue

Common buffers used in pharmaceutical and biopharmaceutical manufacturing processes are generally cleaned with water only, a strategy based on solubility data. However, trace levels of substances present in raw materials such as slip agents and particles from incompatible plastics and elastomers used in gaskets and tubing can migrate to blending and storage tanks walls. These trace substances are hydrophobic and can adhere tenaciously to the sidewalls, causing an air-liquid interface (ALI) buildup (or ring) over time.

Identifying the ALI ring components is the first step in determining the ring's origin. Laboratory studies have shown to be effective as a starting point for choosing the optimal course of action [26], which might involve any of the following:

- Proving that a maintenance cleaning procedure cleans the equipment and either prevents the ring from forming or removes the ring once it is visible
- Modifying a cleaning procedure to clean the ALI residue before the residue is visible

Table 2: Examples of the impact of proposed changes on cleaning validation.

Changes to	May Impact	Actions to Consider
Detergent components	Ability to clean soils, residue limits for the cleaning agent, cleaning agent rinsability	Coupon testing, toxicity reevaluation
Cleaning parameters (time, action, chemicals, and temperature)	Ability to clean soils	Coupon testing
Analytical method	Detectability and quantification of residue(s)	Analytical method validation (e.g., limit of detection, limit of quantitation)
Equipment design	Surface coverage, drainability, change over time, substrate compatibility	Spray device qualification, coupon testing
Personnel	Training and necessary level of experience	Classroom and on-the-job training
Dirty hold time	Ability to clean soils, levels of bioburden	Coupon testing, microbial tests
Cleaning hold time	Extraneous matter, bioburden	Microbial tests
Length of campaign	Ability to clean soils	Coupon testing, full-scale qualification run
New product in the same train	Grouping strategy	Coupon testing, toxicity reevaluation
Manufacturing steps or operational parameters	Soil condition and cleanability	Coupon testing, full-scale qualification run
Batch components or raw material sources	Cleanability, bioburden	Coupon testing, toxicity reevaluation, microbial tests

- Identifying the source of the trace material and trying to eliminate it from the raw material through a corrective and preventive action (CAPA) plan

Common cleaning approaches include using a formulated alkaline cleaning agent at elevated temperatures, often with a detergent additive to increase the surfactant level with or without hydrogen peroxide.

PERSONNEL RETRAINING

It is a standard practice, and a regulatory requirement in some countries, for pharmaceutical companies to periodically review their procedures on a preestablished basis according to company policies—usually every two to three years. The review may involve editorial changes to improve the clarity of operator instructions, but these changes must not significantly alter or change the current validated procedure. A personnel retraining session should be part of the periodic procedure review when procedures are changed. Even when procedural changes are not made, personnel should be periodically retrained in cleaning. As a rule, the more reliant the procedure is on human intervention, the greater the frequency of training should be. Most companies conduct retraining every 3 to 12 months for manual cleaning applications, which have inherent operator-to-operator variability, and schedule retraining for fully automated training every two to three years.

CHANGE CONTROL PROCEDURES AND DEVIATIONS

When manufacturers need to propose planned or unplanned changes to routine operations, these proposed actions may have an impact on the cleaning process. There are cases in which evaluating the impact of the change on cleaning may include laboratory coupon testing, as previously discussed. Therefore, validated cleaning procedures must be included in the change control management system, which ensures that any proposed changes are evaluated fully for their impact on the validated state of the procedure.

Change control systems may affect all or part of the cleaning process in multiple ways, as illustrated in Table 2. This table is not an all-inclusive list but provides examples of changes and their potential impact on cleaning procedures. The company's change control procedure must include a section for the evaluation of the impact of cleaning validation by a designated subject matter expert (SME) within the organization.

The cleaning SME should approve changes before they are implemented. For major proposed changes, the change control management system should coordinate an assessment of the changes and determine whether new validation is required. When new validation is determined to be necessary, the three-stage life-cycle validation model should be implemented.

Manufacturers should fully investigate out-of-specification (OOS) cleaning results (e.g., from visual inspection or analytical data) and deviations from a validated cleaning procedure, per local procedures, and address the issues appropriately. The cleaning SME should provide the initial assessment and also determine the next course of CAPAs when the investigation is completed. In the case of an OOS event, the equipment should not be used for the next product until the equipment has been cleaned, met all cleanliness acceptance criteria, and been released by the quality unit.

CAPAs for a cleaning issue should be based on the results of a risk assessment. The cleaning SME should be responsible for ensuring that the root cause analysis and proposed corrections are appropriate to address the cleaning issue. Sources leading to

initiation of a CAPA related to cleaning may include (but are not limited to):

- Quality management review
- Product contamination incidents
- Audit inspections
- Data trending from monitoring
- Customer complaints

A formal review of the cleaning program should be conducted at least annually and may be conducted as part of the required product annual review. The quality unit should document the formal review. At a minimum, the annual review should include a collective summary of cleaning-related deviations, CAPAs, periodic monitoring, and change controls that have an impact on cleaning validation.

CONCLUSION

The traditional cleaning validation approach has been used for over 30 years to validate cleaning within cGMP manufacturing. The three-stage life-cycle approach adds emphasis from validation to design and monitoring of the cleaning process. Companies should consider establishing a monitoring stage in a cleaning program to be feasible and necessary regardless of the validation approach taken. Systems must be in place to supplement any validated cleaning program regardless of the extent of prevalidation work. Failure to establish an adequate ongoing monitoring program is likely to result in sanctions from health authorities.

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GMP Implementation of ONLINE WATER BIOBURDEN ANALYZERS

By Jesper Hjorth, Peter Annel, Peter Noverini, and Scott Hooper

Online water bioburden analyzers (OWBAs) are analytical instruments providing real-time or near-real-time measurement of bioburden in purified water systems [1–3]. A standardized approach to the application, validation, and regulatory documentation of OWBAs would greatly facilitate the uptake of this promising monitoring technology in the pharmaceutical industry. This article provides points to consider for OWBA implementation and a suggested framework for OWBA technology qualification, validation, and use to support in-process monitoring of a GMP water system.

OWBAs predominantly use laser-based fluorescence to detect and enumerate microorganisms in a flowing column of water [4, 5]. In the pharmaceutical industry, this technology could have value in operations that require high-purity water of a specific microbiological quality. However, implementation of OWBAs into GMP service has been relatively slow due to concerns about using the instruments in a GMP-compliant manner. If OWBAs can be introduced into a GMP environment, there is the possibility of at least reducing the need for grab samples, which are currently used to ensure ongoing acceptability of water. An ultimate aspirational goal is for OWBAs to function in conjunction with online conductivity/total organic carbon (TOC) meters to allow continuous monitoring and real-time release of high-purity waters for GMP use.

CURRENT TECHNOLOGY

A few technologies are currently being used as a basis for online water bioburden detection and enumeration (Table 1). Of these, the technology with the broadest commercial availability is laser-induced autofluorescence. These instruments rely on the intrinsic fluorescence of certain biomolecules inherent in microorganisms. Laser diodes emitting at a specified wavelength of light are used to illuminate a slipstream of water. Microorganisms present in the water absorb this light and release the energy as fluorescent light at a less-energetic wavelength. This light is detected and quantified in autofluorescence units (AFUs). One advantage of laser-induced autofluorescence instruments is that the assay is nondestructive, which means the detected bioburden can be captured and grown for identification.

As noted in Table 1, non-laser-induced autofluorescence-based analysis technologies are commercially available or in development. The approach to installation, validation, and approval as described in this article also applies to them.

AFU VERSUS CFU COUNTS

In all fluorescent dye and laser-based systems, there is a natural difference between AFU counts and counts of colony-forming units (CFUs) by traditional plate count methods. In addition to CFUs, AFUs can also include viable but nonculturable (VBNC) cells, debilitated and recently deceased microorganisms, and extraneous bits of materials that also fluoresce at the monitoring wavelength(s). The fluoropolymers in products such as Teflon and Viton and other polymers can fluoresce at these same wavelengths. These materials and microorganisms have historically been present in water samples, but they were not previously

Table 1: Commercial online water bioburden enumeration technologies for pharmaceutical grade water systems.

Technology*	Detection/Analysis Method
Laser-induced autofluorescence	Flow-through continuous measurement
Dye-based flow cytometry	Sample-based measurements
Lab on a chip (currently in precommercial development)	OWBA

*Technologies used for rapid microbial identification are outside the scope of this article.

quantified, either because they were not tested for (the materials) or because they did not produce visible colony growth (VBNC microorganisms).

Because AFUs measure heretofore undetected microorganisms and materials, CFU and AFU counts cannot be assigned a standard offset. Nevertheless, certain trends are generally, though not definitively, correlated between the CFU and AFU data, and, for this reason, statistical process control (SPC) may be applied to these data. This approach has the benefit of allowing both the traditional and alternative methods to be used in concert with each other, informing the appropriate microbiological sampling activities to be undertaken when upward trends in autofluorescent particles are detected.

OWBA APPLICATIONS

Understanding the scope of justifiable OWBA implementation is a key factor in a smooth and successful implementation of OWBA monitoring in a facility. Specifically, one must understand:

- The pathway for validation and regulatory acceptance of an alternative microbiological method that detects more objects than the compendial method it is intended to supplant
- The scope of the testing that can and cannot reasonably be replaced with an OWBA
- The requirements imposed as a consequence of OWBA implementation into systems with high regulatory standards and expectations, such as water for injection (WFI) systems

It is also important to understand that the bioburden in a water system may not only be composed of homogeneously distributed microorganisms but also may include nonhomogeneously distributed microorganisms in the form of biofilms. These biofilms can release bacteria into the free-floating state and can slough off in large mats. OWBAs can detect free microorganisms and mats. The fact that bioburden is not homogenously distributed in a water system should be considered when performing a risk assessment–based analysis of the feasibility of reducing sampling frequencies.

It is reasonable to rely on an appropriately validated and regulatorily accepted OWBA as a continuous monitor of GMP water quality on a loop. Just as online TOC and conductivity meters have allowed facilities to reduce the number and frequency of water samples used for monitoring TOC and conductivity, OWBAs act as continuous monitors that, with appropriate trending analysis and risk-based assessment, offer the possibility of reducing the number and frequency of loop water samples.

However, it is not reasonable at the current time to believe that an OWBA can fully replace loop samples, as the OWBA's meter readings must be periodically compared to data from classical water testing methods to ensure ongoing control of both the loop and the meter. Continued monitoring, system characterization, and regulatory buy-in may allow future wholesale replacement of loop grab samples.

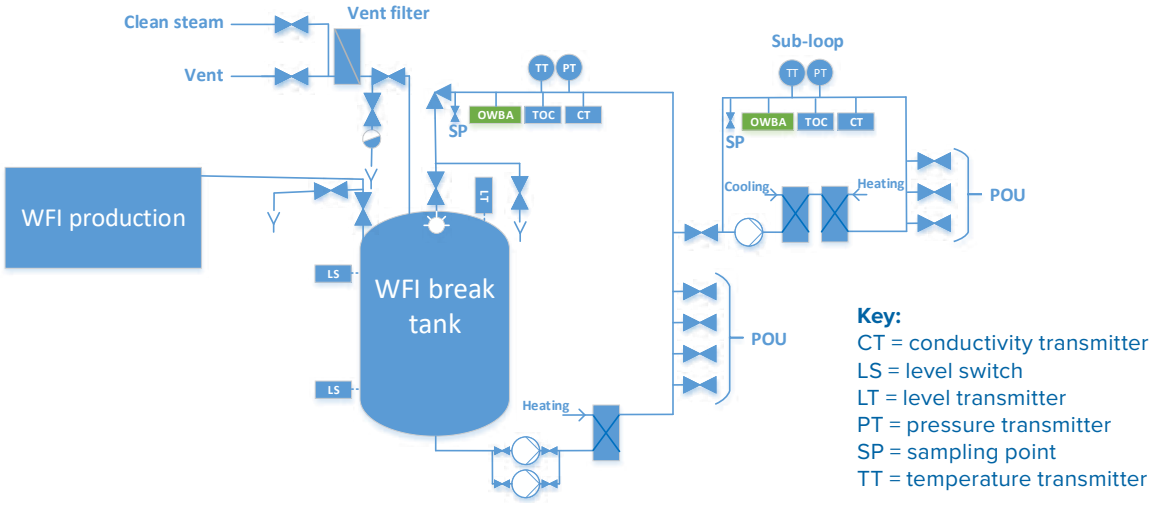
An OWBA monitoring the loop will also not replace required point-of-use (POU) samples due to the potential influence of the piping between the loop and the POU. It would typically be impractical to manifold POUs to an analyzer. It is, however, possible to set up a meter to read in both online and sample injection modes. In this way, a meter could be used in both continuous monitoring and POU sample modes. This approach is not as straightforward as it might seem because introduction of artifacts through injected grab samples is a significant concern. Two recent publications [11, 12] review the sources of grab sampling and analysis artifacts and discuss methods for minimizing them in OWBA analyses. There are practical challenges in switching from online to sample injection modes that must be overcome. Among these are ensuring that there is no backflow into the loop and ensuring smooth and consistent injection events.

Regulatory standards and expectations regarding the water quality analyzed by the OWBA dictate the required level of scrutiny that must be applied to OWBA data and installation. OWBA implementation in less-stringent scenarios is relatively straightforward. An example would be purified water. The regulatory limits for purified water are ≤100 CFU/mL. There is a gap between the limit of detection (LOD) of a typical OWBA and the point at which the sensors become overloaded by the amount of signal present. Typical purified water specifications are within this range, so the gap allows a bandwidth in which an OWBA system can operate. Because OWBAs detect more than classical CFUs, the precision of the OWBA measurement, as compared to classical compendial methods, has an inherent span of uncertainty within the operating range. Monitoring could be performed on an SPC basis with event-triggered capture of water samples for microbe identification in the case of an exceeded limit. As one is inherently dealing with higher limits and larger numbers of microorganisms in low-stringency applications, the chance of missing capture of an excursion would be relatively low.

It should be appreciated that water samples that are too low in microbiological quality may have so many detection events that the analyzer becomes either saturated or nonlinear. Untreated surface water, sewage, and untreated drinking water would not be good candidates for analysis with currently existing OWBA options.

Application of OWBAs is possible in waters with the most stringent requirements (e.g., WFI, which has a regulatory limit of ≤10 CFU/100 mL). However, it is especially difficult in these high-stringency applications to demonstrate control and capture and identify contaminating microorganisms. Depending on the inherent background AFU detection level (including detection of artifacts like Teflon and Viton particles), the in situ LOD of a typical OWBA on a given high-stringency loop may not be sufficient to adequately resolve microorganism concentrations to the required levels: unless the background AFU level in the water is very low, the analyzer might not be useful for detecting whether CFUs exceed the regulated limits. Those considering such an application should pre-assess whether their system's inherent background AFU count would allow detection of microorganisms at the required levels. The low numbers of putative microorganisms in these waters must be captured for identification to

Figure 1: Example of OWBA installation in a WFI system.



exclude objectionable microorganisms and ensure knowledge of the type of microorganisms in the water. As a result, such installations require a robust and thoroughly tested capture system for excursions.

RETURN ON INVESTMENT

OWBAs have the potential to reduce ongoing costs in facilities. For example, they may help reduce energy usage by optimizing sanitization cycles, reducing water sampling and associated testing costs, and potentially reducing the number or duration of water-associated process deviations. The following are hypothetical examples of OWBA costs and potential savings:

- Instrument purchase, installation, and full qualification: ~$180,000
- Savings from reducing sampling and testing frequency from daily to weekly: ~$30,000/year/sample point
- Energy cost savings through sanitization every second day instead of daily: ~$55,000/year
- Savings from reducing the number of investigations: ~$20,000/event

Any actual evaluation of individual costs, savings, and return on investment should be based on the details of the planned installation.

INSTALLATION GUIDANCE

OWBAs can be installed on purified water systems. Care should be taken to ensure that installation does not compromise the GMP status of the system and the water produced by the system. This typically means ensuring that the OWBA is sampling a slipstream that goes to drain subsequent to the OWBA instrument (i.e., the water is not returned to the loop and the slipstream is not subsequently used for GMP purposes).

Figure 1 depicts OWBA installation in a WFI system with a main loop and subloop. OWBAs can be installed in other steps in water systems to meet user needs; however, the following points apply:

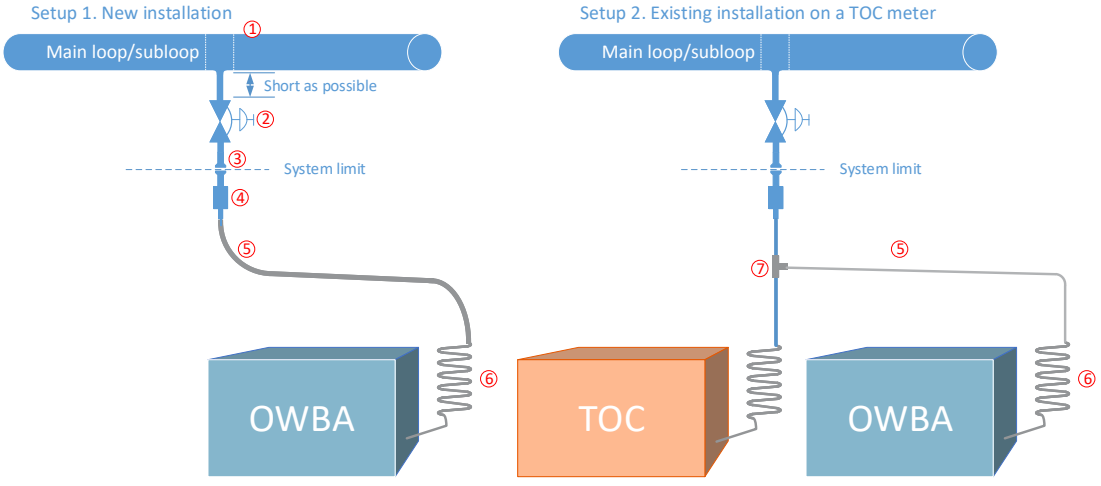
- The optimal installation point on a water loop to cover and represent the loop is at the return of the loop.
- The OWBA can directly replace some process control (PC) sampling at loop return.
- The OWBA can reduce PC sampling to some extent.
- An OWBA installed in a loop cannot cover the POU directly and therefore cannot, by itself, substitute for quality control (QC) sampling of the POU.

It is reasonable to accept that demonstrating continuous PC can lead to a reduction in loop QC sampling.

The following are other issues that must be considered and/or addressed when choosing where to install OWBAs:

- The cost of having an OWBA installed at each POU would be tremendous and would often cause more trouble than benefit due to issues related to installation space, process equipment functions during sampling, and other factors.
- Because OWBAs use sensitive measuring technologies, there is a high risk that the instruments could be damaged if they are moved. This may be a substantial concern if the intent is to use an OWBA at multiple locations (e.g., moving it to various POUs).
- Using one OWBA to cover multiple POUs would require a multiport valve and connecting piping system. This is seen as a difficult alternative to achieve due to the cross-contamination risks and complex validation requirements.
- Grab sampling at the POU and conducting analysis through an OWBA external sample port presents problems that are not readily obvious. Primarily, this effort could inadvertently introduce particulates or other artifacts during sampling,

Figure 2: Example connections for an OWBA on a water loop.



sample prep, and/or sample injection. Recent publications have addressed methods and points of concern for minimizing artifacts in OWBA grab sample collection and injection [11, 12].

- Installing a non-GMP instrument on a GMP system, even if it samples a slipstream that goes to drain, can result in inspection questions.

Product (Water System) Risks

Connection of an OWBA on a water system raises the risk of backflow or microbial growth in tubing. It is therefore important to understand and minimize such risks and determine whether a temporary or continued connection requires a change request.

A change request may not be necessary (depending on local requirements) if changes are not made to the water system. An example is a temporary connection of a silicone tube to a sample valve (or drain valve) to mount the OWBA equipment without any intervention on the system itself (loop, valves).

Materials used for connections must be approved and cleaned. Examples of suitable materials are silicone tubing (the same material that is often used in production); fluorinated ethylene propylene (FEP) or perfluoroalkoxy alkane (PFA) tubing (equivalent to polytetrafluoroethylene [PTFE] tubing); stainless steel cooling coils (supplied by the OWBA supplier to provide an analysis temperature compatible with the instrument); and stainless steel fittings.

There is no risk of liquid backflow if the OWBA cannot produce a higher pressure than the supply pressure. This ensures that there is no overpressure in the OWBA system itself and no overpressure in the loop.

The single and greatest backflow risk is a blocked drain. If the drain is installed with "open" flow, there is no risk of backflow. This can be ensured with an air gap.

Any internal pump used in conjunction with an OWBA must be installed and hardwired to ensure that the pump cannot accidentally change flow direction.

Instrument Qualification

Standard instrument qualification practices as required in relevant internal and regulatory guidances are used to perform instrument qualification. The standard user requirement specification (URS) published by the OWBA Working Group [6] is recommended as a foundational document for the instrument qualification. Its use helps ensure that no appropriate requirements are overlooked. However, users are cautioned that local requirements may require additional specifications beyond those in the URS. If the user has additional specific user requirements, it is necessary to carefully consider the characteristics and capabilities of the specific OWBA to ensure that the requirements can be fulfilled. OWBAs are "off-the-shelf" instruments and should generally not be custom redesigned to fulfill specific user needs or wishes.

OWBA-Loop Connection

Connecting an OWBA to a loop is relatively uncomplicated. It is recommended that flexible tubing is used from the connection outlet to the OWBA. During engineering studies, the connection could be temporary, using an existing outlet if one is available. Figure 2 shows two examples of how the analyzer could be connected to the loop.

The following are points for consideration regarding components and design (note that for reference, the points are labeled in Figure 2):

1. When a new valve is installed, it is preferable to cut the loop and install a "T" piece or expanded "T." This will ensure proper sanitary design.

2. A valve must be installed on the loop so the water supply to the OWBA can be cut off. The valve could be a manual valve, or an automatic valve or a manual valve with automatic override could be considered, especially for long-term installations.
3. The valve outlet should be finished with a clamp connection, preferably a mini tri-clamp ferrule connection. This connection will also serve as the system boundary. This means that the components and piping (Figure 2, parts 1–3) will be a part of the water system; therefore, standard installation requirements or GEP must be fulfilled according to company's requirements for
   - Piping and instrumentation (P&I) diagrams and component/instrument data
   - Construction materials
   - Welds
   - Surface roughness
   - Sanitary components, instruments, and bulk goods
   - Dead legs
   - Drainability
   - Initial cleaning
   - Pipe marking
   - Insulation and cladding
4. The next component consists of a mini tri-clamp connection and a fitting to connect the flexible tube. The fitting may need to be custom designed because a sanitary component (the mini tri-clamp ferrule) is coupled with a nonsanitary component. However, if a sanitary quick clamp–to–compression tube fitting is used for the nonsanitary component, a custom design is not needed because this is an off-the-shelf component. These couplings often use metal gasket face seal fittings, which are also often used on TOC instruments. So, even though this arrangement is not considered a fully sanitary design, it is probably the best design option available.
5. Flexible tubing should be used to ensure the optimal inner surface roughness. The recommended types are transparent; therefore, it is necessary to block out light. Simply take a piece of larger-diameter black tubing and run the PFA/FEP tubing through it so that it is fully covered. To ensure proper drainage and support the tubing, pipe supports can be installed. Given the risk of particle shedding, tubing must be a part of planned maintenance; changing tubing on a yearly basis is also recommended.
6. The spiral coil, which is often a part of the purchased OWBA package, is required to help lower inlet temperature because some OWBAs are sensitive to higher temperatures. The OWBA may be able to operate in temperatures up to 40°C. It is important to mount the coil as close as possible to the OWBA equipment to ensure that most of the flow path will be sanitized. Sanitization of the flow path should be a part of routine water distribution sanitization. The frequency and method to be used will depend on the characteristics of the water system and construction materials.
7. The "T" piece (Figure 2, part 7) is inserted in existing tubing/piping for the existing TOC instrument. This installation might be an easier alternative compared to a new installation. Stainless steel compression fittings are recommended.

Points 4 through 7 should comply with installation requirements or GEP, according to company's test/validation strategy for the following:

- P&I diagrams and component/instrument data
- Construction materials
- Surface roughness
- Drainability
- Pipe marking

Wiring and Signal Interfaces

When implementing an OWBA, it is very important to determine how the data will be transmitted from the unit. The two primary means to send data from the unit are (a) via a 4-20 mA connection and (b) use of a transmission control protocol/internet protocol (TCP/IP) connection. The important difference between the two relates to the scale of the data that will be trended. A 4-20 mA connection is typically an easier connection to support, as most processing equipment use this data transmission method and it can be easily integrated into the automation process. The limitation with using this method is the decreased sensitivity or scale associated with this method. For example, with data that range from a baseline average of 300 AFUs to a potential peak of over 100,000 AFUs, the 4-20 mA method will reduce the sensitivity at the lower end to accommodate the higher counts, thus losing the capacity to differentiate changes at lower counts. Furthermore, because significant differences in counts from one loop to another are experienced, permanent default settings may not be appropriate for all or most water loops/systems. Defaults settings may not result in the accuracy that end users are expecting. If analog is still chosen, tailoring output ranges to suit the specific system is recommended. This should be done to some extent to optimize accuracy.

If digital inputs are available on the OWBA, it is recommended that the inputs be used to start and stop sampling on the OWBA. This will allow external control of the OWBA from a supervisory control and data acquisition system. This feature can benefit the user during start-up of the water system.

IT Considerations

The instrument must be compliant with 21 CFR part 11 and EU Annex 11. Before operational qualification can be started, the company must assess whether the OWBA instrument presents a risk to the company's IT system and how OWBA use can comply with the company's IT conduct regulations. For example, the instrument may be designed to transfer data via a portable storage device (e.g., USB drive) but the company prohibits use of such devices. As data integrity awareness penetrates the marketplace, these disconnects between instrument requirements and user restrictions should diminish or disappear.

Computer validation is required because all data are generated and handled in the OWBA system software. The analyzers

typically generate a large amount of data. This validation process includes specification of user requirements, specification of functional requirements, development of a test plan, execution of the test plan, and demonstration that all requirements have been fulfilled. Data integrity should also be evaluated given its prominence in recent regulatory audits and discussions.

Method Validation

The final required element before the OWBA can become operational is method validation, which also constitutes performance qualification because the instruments are intended for continuous monitoring. For an overview of the method validation process, see the 2018 *Pharmaceutical Engineering* article by Nissan Cohen [7].

Several guidance documents are relevant to OWBA method validation, including ICH Q8(R2) [8]. Additionally, because OWBAs are an alternative microbiological method, it is important to refer to *USP<1223>: Validation of Alternative Microbiological Methods* [9], which provides overarching guidance for method implementation. For companies producing for the European market, European Pharmacopoeia Chapter 5.1.6 [10] applies, and for all markets, the Parenteral Drug Association's Technical Report 33 [11] provides guidance on implementation of rapid microbial methods.

Fundamentally, these guidance documents require demonstration that the alternative assay method is not inferior to the compendial methods it is intended to replace. This hurdle is not to be taken lightly: Because OWBA instruments report AFUs and compendial methods report CFUs, comparison of the methods, outside of highly controlled experiments [12, 13] is typically only possible using statistical trending methods.

SETTING LIMITS

Once an OWBA is installed, qualified, and validated, an extended period of operation is needed to characterize the behavior patterns of the system being monitored. This data set will be useful in delineating definable bioburden-independent changes in OWBA response. As an example, during sanitization cycles, the elevated temperatures in the water system may trigger the OWBA to report an apparent increase in AFUs. Conditions that are clearly definable as not being dependent on bioburden levels may, with documented justification, be excluded from routine ongoing bioburden trend analyses.

An extended period of monitoring is also needed to provide sufficient statistical robustness of the data set used for analysis. Simple rules of thumb, such as a minimum of 30 observations being sufficient for characterizing normally distributed data, do not take into account potential longer-term variations such as seasonal variation. For this reason, it is suggested that preliminary provisional limits may be calculated after a reasonable period (determined by a risk assessment that takes into account a number of factors, including frequency of sampling and known operational impacts to a system); however, OWBA system action and alert limits should be reassessed on a routine basis. Demonstration of ongoing system control may be shown through SPC principles [14, 15].

REGULATORY HURDLES

Although OWBAs clearly have utility and can be installed, qualified, and validated for use in GMP service, there are regulatory hurdles to their widespread implementation:

- As noted previously, OWBAs report units that are different from, and not directly correlated with, the units used in traditional methods. This raises concerns for regulators and inspectors. In turn, companies have internal concerns that agencies might not approve OWBA technologies or products relying on such technology, and these concerns can result in delays or supply disruptions. In fact, the relevant compendial chapters provide clear pathways to adoption of alternative methods, including those that use different methods of measurement.
- OWBA validation methods will vary from those used for traditional instruments because OWBAs detect more objects typical of water streams than those enumerated by classical plate count methods (e.g., VBNC microorganisms, dead microorganisms, and polymer particles that fluoresce at the same wavelength as bacteria). We propose that validation via the compendial chapters and demonstration of control via SPC methods are suitable means for demonstrating continued control.

- There is a lack of clear guidance as to how or where to file the use of OWBA technology. In the case of a new installation, a properly installed and qualified OWBA could be incorporated into the facility from the ground up and could be qualified and documented as part of initial water system qualification. Implementation in existing facilities is more complicated due to the need to pilot the instrumentation to collect data and set limits, while not affecting the GMP status of the water system and, by extension, the products manufactured with that water. The FDA guidance on process analytical technology [16] addresses how to implement instrumentation into GMP systems for the purpose of evaluating and qualifying the instrumentation. OWBA technologies are used primarily for environmental monitoring of facilities; therefore, we propose that the site master file is the appropriate place to file the use of these technologies in existing facilities. If the technology is officially listed on filed and previously reviewed documentation, it should be less of concern for regulators. This approach should therefore reduce company fears that individual inspectors who are unfamiliar with OWBAs might feel compelled to do a complete re-review of the technology at each inspection. Appropriate change control and notification procedures for incorporating the OWBA into the site master file should be followed to remove risk to continued production.

CONCLUSION

With appropriate implementation and validation, OWBAs can function as real-time monitors of water system quality and operation. Implementation of OWBAs should follow a classical instrumentation qualification, operational qualification, process qualification (IQ, OQ, PQ), and method validation format. OWBA applications must take into account the stringency of the specifications and the quality of the water being measured. Current regulatory concerns regarding OWBA implementation can largely be resolved through early and frequent dialog with the relevant regulatory authorities prior to using the instruments for GMP purposes.

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Jesper Hjorth was educated as a marine engineer and has worked since 2006 as a Utility Professional at Novo Nordisk, where he is mainly responsible for supply of black and clean utilities. His support for Novo Nordisk sites within the clean utility area has ranged from daily support tasks to projects. He currently works on testing of OWBA proofs of concept, with the goal of company OWBA implementation. Jesper has been an ISPE member since 2011.

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WELCOME THE 2020–2021 ISPE INTERNATIONAL BOARD OF DIRECTORS

The 2020–2021 ISPE International Board of Directors began their term at the Member Meeting on 5 November during the 2020 ISPE Annual Meeting & Expo.

In her address to the membership, Joanne R. Barrick, RPh, Chair, noted that in 2021, implementation of the second year in ISPE's current Strategic Plan will continue. "While we are changing the 'how' we deliver the strategic plan, the plan and our content priorities remain a solid foundation for our Society," she emphasized. Digitization will enhance content and information availability, and Women in Pharma® and workforce development training programs will remain strong. The Society will continue to seek to expand its impact by increasing its global footprint, Barrick said, noting the recent addition of the Mexico and Eurasian Affiliates. She added that the ISPE Foundation is now poised for significant growth and will include the pursuit of initiatives targeted at increasing diversity in the pharmaceutical industry.

In addition, ISPE will continue to emphasize integration of conference, training, and guidance document offerings and place more emphasis on regulatory topic impact and activities, she said. Opportunities for more interface with the ISPE Board through conferences and participation in Chapter and Affiliate events can be expected.

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