PHARMACEUTICAL ENGINEERING®

The Official Magazine of ISPE

March/April 2024 | Volume 44, Number 2

Navigating the Asia Pacific Pharmaceutical Landscape for Global Impact

Evolving China's Regulatory System in Alignment with ICH

Digital Display Labeling in Clinical Supplies for Clinical Trials

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MARCH/APRIL 2024

12 NAVIGATING THE ASIA PACIFIC PHARMACEUTICAL LANDSCAPE FOR GLOBAL IMPACT

The Asia Pacific region (APAC), like any large territory, encompasses a blend of well-established and early-stage economies, diverse healthcare systems, and differences in language, culture, politics, and technology adoption. APAC's size and complexity has created new challenges and opportunities for the pharmaceutical industry as nations work together to meet the manufacturing needs for medical products.

20 EVOLVING CHINA'S REGULATORY SYSTEM IN ALIGNMENT WITH ICH

With the Chinese government initiating drug regulatory reform in 2015 and China joining the International Council for Harmonisation (ICH) in 2017, a significant number of measures have been implemented by the government. The aim is to make fundamental changes to China's drug regulatory administration system so it can facilitate pharmaceutical development and better meet patient needs in the country.

33 DIGITAL DISPLAY LABELING IN CLINICAL SUPPLIES FOR CLINICAL TRIALS

Digital display labels (DDLs) offer an alternative solution to eliminate manual relabeling in the clinical supply chain, optimizing label content updates through a simple, system-controlled approach while providing new, uncharted opportunities. With increased efficiency in making regulatory-compliant changes and enhanced flexibility in the clinical supply chain, DDL technology has the potential to revolutionize drug development and to increase and expedite patient access to therapies.

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DEPARTMENTS

6 MESSAGE FROM THE CHAIR
A Regional Focus for 2024

10 WOMEN IN PHARMA® EDITORIAL
Women's Participation in the Pharmaceutical Industry in Mexico

11 EMERGING LEADERS EDITORIAL
Personalized Medicine in the US

PEOPLE + EVENTS

42 ISPE Affiliates and Chapters Span the Globe

43 Ireland Affiliate Creates Opportunities for Members

44 Meet the ISPE Staff: Alexis Thomas

45 Introducing the New ISPE Baseline® Guides: Biopharmaceutical Manufacturing Facilities (Third Edition) and Pharma 4.0™

46 Community of Practice Leader Profiles
46 Tammy Spain, Project Management Community of Practice Chair
47 Nathan Temple, Commissioning and Qualification (C&Q) Community of Practice Chair

48 2023 ISPE Pharma 4.0™ and Annex 1: Keynote Presentations

49 Save the Date: International Women's Day Is 8 March

100 Ad Index/Classifieds

TECHNICAL

51 MIXING VALIDATION
Risk- and Science-Based Media and Buffer Mixing Validations
The validation of media and buffer mixing is a continuing area of resource constraint in the pharmaceutical industry. These validations require materials, validation associates' time, and the use of equipment and processing areas. This article proposes a risk-based life cycle for minimizing mixing validation resource inputs, with the objective of optimizing validation efforts through the use of recipe bracketing and predictive methods to identify the worst-case recipes that should be validated.

56 SURFACE QUALIFICATION
Electrochemical Techniques for Onsite Surface Qualification
Pharmaceutical critical utilities are typically built of 316L stainless steel; nevertheless, surface degradation has been reported due to the occurrence of different phenomena. This article aims to explain how field electrochemical techniques using a portable tool can be an effective method for surface inspection, qualification, and monitoring. The surface finish assessment considered different average roughness, obtained by mechanical polishing and electropolishing, and whether the surface was chemically passivated or not, to generate distinct passive films. This was done to prove the sensitivity of the field electrochemical tool using corrosion techniques.

66 CONTAINMENT EQUIPMENT
Selection Criteria for Pharmaceutical Containment Equipment
Pharmaceutical manufacturing facilities produce a variety of products, including highly potent products that require safety measures to prevent adverse health effects on patients and operators. To ensure safety, these facilities use containment equipment to minimize the risk of contamination. This article presents criteria for selecting containment equipment, considering both cross-contamination and industrial hygiene risks.

77 STEAM QUALITY MANAGEMENT
A Sustainable Approach to Steam Quality Management
The world is beginning to grasp the huge challenge of achieving net-zero carbon emissions, or carbon neutrality, by 2050. Many countries have committed to achieving this ambitious goal. As a major global industry, the pharmaceutical sector has a significant role to play. For thermal energy–intensive industries, such as pharmaceutical manufacturing, the long-term future options to maintain current manufacturing processes are few and look to significantly increase energy costs. Optimizing current systems and considering new strategies is necessary.

85 VALIDATION 4.0
Concluding Compliance Challenges with Validation 4.0
As the pharma industry moves to an ambitious Validation 4.0 paradigm, computerized systems play a pivotal role in enabling the rapid transition. Innovation and agility in computerized system validation (CSV) received a strong push in the second half of 2022 with the publication of the FDA draft guidance on "Computer Software Assurance for Production and Quality System Software" and the *ISPE GAMP® 5 Guide: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition).*

94 COMPUTER SOFTWARE ASSURANCE
Computer Software Assurance and the Critical Thinking Approach
In 2022, the US Food and Drug Administration (FDA) issued their draft guidance "Computer Software Assurance for Production and Quality System Software" [1] to enhance the computer validation process required by predicate rules, either in the pharmaceutical or medical device space. The critical thinking approach was introduced by ISPE GAMP® Guides and emphasizes a focus on clear thinking through a plan, then creating documentation from a process perspective. These methods combined create the optimal replacement for computer system validation (CSV).

ISPE

PHARMACEUTICAL ENGINEERING

Volume 44, Number 2

ISSN 0273-8139
Pharmaceutical Engineering is published six times a year by ISPE and is online at ISPE.org/Pharmaceutical-Engineering

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Stock Photography and Illustration
iStock

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

Printing
Sheridan NH

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

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Article reprints can be ordered through Sheridan Content Solutions at sheridancontentsolutions@sheridan.com

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US Postmaster
Send change of address to:
Pharmaceutical Engineering Magazine
3001 North Rocky Point Drive East
Suite 200-242
Tampa, Florida 33607 US

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

Canada Postmaster
Send change of address and undeliverable copies to:
Pharmaceutical Engineering Magazine
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By Scott W. Billman


Scott W. Billman

A Regional Focus for 2024

ISPE has started 2024 with great momentum, having two technical conferences in the first quarter, the 2024 ISPE Facilities of the Future Conference in San Francisco, California and the 2024 ISPE Aseptic Conference in Vienna, Austria.

We will continue that momentum with the 2024 ISPE Europe Annual Conference in Lisbon, Portugal, 16–18 April. This conference will bring together regional ISPE membership and industry leaders to continue discussions on topics like digital transformation and GAMP® 5, while also discussing learnings and case studies in the regulatory and GMP inspections space. I look forward to meeting and speaking with many of you at that conference.

REGIONAL FOCUS

ISPE membership is a global ecosystem of industry professionals and students. Our membership engages at local, regional, and international levels through attendance at conferences, trainings, and networking events. In this issue of *Pharmaceutical Engineering®*, we focus on the regional aspect of this global organization and industry.

Like many of our members, I began my involvement and volunteer engagement with ISPE at the local Chapter level. The Chapters and Affiliates offer a vast array of opportunities for local and regional members and companies to engage in dialogue and learn about global topics and then apply these to their local needs and their network. Building a strong local community of industry contacts who can learn from each other and support the industry is a key value to members and the broader industry.

ISPE membership is a global ecosystem of industry professionals and students.

Part of the ISPE 2023–2025 Strategic Plan—and a focus area for the current International Board of Directors—is to grow engagement and increase offerings in the emerging market areas. With more than 50% of the world's population living in the Asia Pacific (APAC) region, the industry and ISPE will also continue to focus on building technical knowledge and workforce capabilities in this region of the world.

We have strong Affiliates in the APAC region that are doing great work at expanding industry engagement and knowledge sharing. Geopolitical pressures, inflation, and supply chain challenges drive the need for our industry to continue to innovate and to clear the hurdles that prevent us from getting lifesaving therapies to patients.

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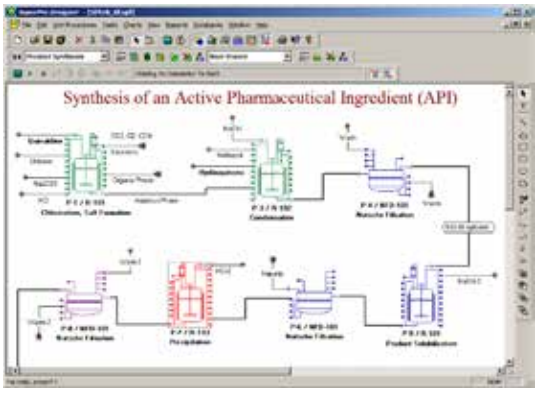
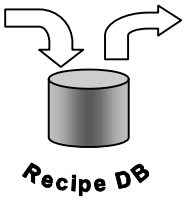
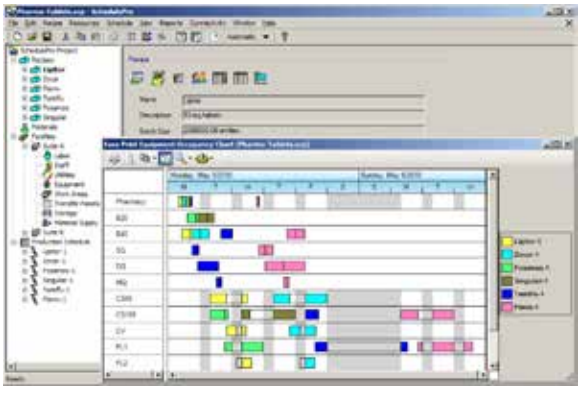


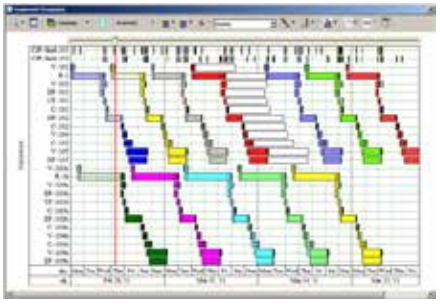
Use SuperPro Designer to model, evaluate, and optimize batch and continuous processes



SchedulePro®

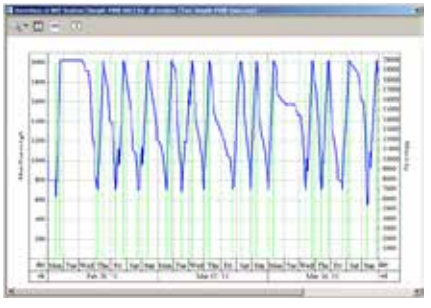


Migrate to SchedulePro to model, schedule, and debottleneck multi-product facilities



Easy production tracking, conflict resolution and rescheduling

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



Managing inventories for input, intermediate, and output materials

SuperPro Designer is a comprehensive process simulator that facilitates modeling, cost analysis, debottlenecking, cycle time reduction, and environmental impact assessment of integrated biochemical, bio-fuel, fine chemical, pharmaceutical (bulk & fine), food, consumer product, mineral processing, water purification, wastewater treatment, and related processes. Its development was initiated at the Massachusetts Institute of Technology (MIT). SuperPro is already in use at more than 500 companies and 900 universities around the globe (including 18 of the top 20 pharmaceutical companies and 9 of the top 10 biopharmaceutical companies).

SchedulePro is a versatile production planning, scheduling, and resource management tool. It generates feasible production schedules for multi-product facilities that do not violate constraints related to the limited availability of equipment, labor, utilities, and inventories of materials. It can be used in conjunction with SuperPro (by importing its recipes) or independently (by creating recipes directly in SchedulePro). Any industry that manufactures multiple products by sharing production lines and resources can benefit from the use of SchedulePro. Engineering companies use it as a modeling tool to size shared utilities, determine equipment requirements, reduce cycle times, and debottleneck facilities.

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AFFILIATE/CHAPTER GROWTH FUND

A critical component of the One ISPE framework is the Affiliate/Chapter Growth Fund. This central fund is established through financial contributions from the various Affiliates and Chapters, then matched by ISPE International each year. These funds are held separately and are designated for the strict purpose of supporting ISPE's global mission and vision at the local level. The disbursement of funds is administered by a committee composed of ISPE members from the International Board of Directors and the Chairs of each Regional Affiliate Council.

Affiliates and Chapters can submit proposals for projects to use these funds to further membership outreach and engagement. Some examples of how the funds are being used in the first year of the program are in-person Women in Pharma® workshops and events, educational sessions to increase membership recruiting, new local student chapters, specific training for members in response to FDA industry feedback, and sponsorship of ISPE educational sessions for operating companies.

With the submissions, applicants are asked to do something different, be specific on what the funding would go toward, and set goals for how it will grow and retain members at the local level. If you have an idea, we encourage you to reach out to your local ISPE Affiliate or Chapter board.

BIOTECH IN THE NORTHEAST US

As we enter the second quarter of 2024, we will look to engage in another impactful region as we meet for the 2024 ISPE Biotechnology Conference in Boston, Massachusetts, 17–18 June. The Northeast region of the US has been a concentrated center for the biotechnology industry for decades and biotechnology continues to be a strong growth area for patient therapies.

Bringing industry experts together to discuss the interaction of the various topics and their impact on the biotechnology industry is critical for us to meet the increasing demands on supply, quality of medicines, and sustainability goals. ISPE continues to expand the Communities of Practice (CoPs) around these areas to ensure we provide forums for learning, debate, and knowledge sharing.

This issue of PE has articles spanning topics like regional regulations, systems validation, digital display labeling for clinical trials, and sustainability. The breadth of topics covered by the article contributors, CoP members, and staff—all in one publication—shows the complex network that is the pharmaceutical industry. I hope you continue to see value in the content and topics. Happy reading!

Scott W. Billman is Vice President of Engineering for Pharmaceutical Services at ThermoFisher Scientific and the 2023–2024 ISPE International Board Chair. He has been an ISPE member since 1996.

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By Fatima Jacoba Mancilla Islas


Fatima Jacoba Mancilla Islas

WOMEN'S PARTICIPATION IN THE PHARMACEUTICAL INDUSTRY IN MEXICO

Over time and with effort and determination, women in key leadership positions have proven that these positions are genderless for individuals with the correct set of abilities and knowledge.

Although equity and diversity are promoted in companies, barriers still exist related to obsolete prejudices that prevent progress in the equal development of women. Professional growth must be increased and promoted on equity, diversity, and integration, which directly impact and help develop good performance. We must continue to strengthen and incorporate the efforts so far as part of our daily organizational strategy.

ACHIEVING GENDER PARITY

In Mexico's pharmaceutical industry, 46.5% of personnel are women [1], which could be considered a high percentage. However, only an average of 38% of women occupy key leadership positions in industry [2], including the pharmaceutical industry. Although it was a 3% increase from 2017 (35%) to 2020, it is a small increase. These statistics represent a challenge to achieve gender parity, not only in the pharmaceutical industry, but in all economic sectors.

To accelerate women's participation, it is necessary to promote programs in companies for empowerment. To accomplish this, it is necessary to develop and promote different initiatives within industry and at a cultural level. Mexico is well-known for maintaining stereotypes and granting superiority to the masculine identity and the attitude that men "should have" over women. Although some think that this view has decreased, obstacles persist. The following would help address this issue:

- Stimulate high aspirations in childhood and encourage professions that are not specific to a gender. Allow girls to explore health science careers so they can aspire to be scientists, engineers, and other professionals within the pharmaceutical industry.
- A strong foundation of support offered at a younger age will likely increase the number of women in careers related to STEM, which all relate directly to the pharmaceutical industry. In Mexico, currently 14% of STEM graduates are women. In addition, leadership and preparation for a competitive professional life must be reinforced.
- The push for equal representation must continue. Although there has been a 3% increase of women´s representation in key positions the objective should not only be to reach equal representation, but to maintain it. This can be made possible if policies and strategies focused on equity are developed.

Considering that women only occupy 38% of these key positions, their influence on decision-making at the management level is limited and the value that women's leadership brings is not fully considered. The inclusion of women broadens the contribution of ideas to establish strategies for improvement and problem resolution.

WOMEN IN LEADERSHIP POSITIONS

Increasing women's participation in executive leadership positions in the pharmaceutical industry can be managed from different points. Companies should create egalitarian policies to include and develop both men and women, in such a way that the same job opportunities are created in salaries, hiring, and representation in corresponding levels. These policies should involve general management, operational directors, and all company leaders so that the policies are created in an integral way.

A second goal is to implement programs for professional growth, such as mentoring and sponsorship programs. These can be created within companies, by associations related to the pharmaceutical industry, and within universities. Sponsor programs (such as the ISPE Mentor program) pair an experienced person with a new learner to strengthen the learner's skills and abilities.

Professional growth programs directly involve and develop newer generations within the pharmaceutical industry and support the development of more egalitarian policies, which helps establish more women in executive leadership positions. These actions will reduce the discrepancy because when women fill leadership roles, they serve as examples of equity and promote inclusion and diversity.

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By Monique L. Sprueill


Monique L. Sprueill

PERSONALIZED MEDICINE IN THE US

Personalized medicine provides a treatment alternative that utilizes patients' genetic material to produce therapeutics. According to Market Research Future, the US currently accounts for the largest share of the personalized medicine market, and it is expected to reach US $27.5 million by 2030 [1]. This will significantly impact how pharmaceutical companies develop, test, market, and distribute drugs in the future.

Chimeric antigen receptor (CAR) T cell therapies are an example of personalized medicine. Since 2017, the US Food and Drug Administration (FDA) has approved six CAR T cell therapy products. In the US, they are regulated in the same manner as biologics. Due to the complexity of these products, changes are often required. The FDA has issued draft guidance to manage these modifications titled "Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products" [2]. This guidance provides the FDA's perspective on managing manufacturing changes and assessing the potential impact those changes have on product quality.

US manufacturing facilities are continuing to develop innovative ways to produce and distribute personalized medicine. As this is an evolving class of drugs, there are opportunities to shape the industry. There are many opportunities for an Emerging Leader (EL) to help provide personalized lifesaving therapeutics to patients. EL is a community that consists of college students, recent graduates, and professionals who are transitioning into the pharmaceutical industry. As scientists and engineers, we work in areas such as process development, operations, research, project management, and facility design.

ISPE Communities of Practice (CoPs) offer platforms for industry professionals to discuss topics of interest. Advanced Therapy Medicinal Products, Biotechnology, and Pharma 4.0™ CoPs also provide a wealth of information on drug development, processes, and how to use analytics to present performance data.

Taking advantage of opportunities to advance your skills and increase your network will increase your visibility in your organization and the industry. Get involved with your local Chapter or Affiliate and participate in EL events.

Participation in ISPE Hackathons at your local level and at the Annual Meetings allows Emerging Leaders to interact with professionals from different regions while working on case studies. The ISPE Foundation provides professional development grants for conference and travel expenses to the ISPE Annual Meeting & Expo and ISPE Europe Annual Conference. Women in Pharma® also sponsors a mentoring program to connect Emerging Leaders with seasoned pharma professionals and the Foundation partners with corporations to attract talent for internships. Emerging Leaders are encouraged to apply for both.

There are many advantages to joining EL:

- Professional development
- Access EL member-only resources
- Opportunities to establish and grow your network
- Exposure to thought leadership events
- Participation in Hackathons
- Career solutions to promote advancement

If you are not a member of ISPE, join today at ispe.org and:

- Actively participate in EL activities in your local Affiliate or Chapter
- Access Good Practice Guides and educational resources
- Join CoPs and connect with other industry professionals
- Add content, ask questions, and post your ideas on Engage
- Write a blog or article
- Talk with your manager and colleagues about presenting your project at a conference or local program

For more information about ISPE's EL community, visit ispe.org/membership/emerging-leader

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NAVIGATING THE ASIA PACIFIC PHARMACEUTICAL LANDSCAPE for Global Impact

By Scott Fotheringham, PhD

The Asia Pacific region (APAC), like any large territory, encompasses a blend of well-established and early-stage economies, diverse healthcare systems, and differences in language, culture, politics, and technology adoption. APAC's size and complexity has created new challenges and opportunities for the pharmaceutical industry as nations work together to meet the manufacturing needs for medical products.

COMPLEXITY OF APAC

"I'd say almost everything about APAC is unique," said Charlie Wakeham, Director at WakeUp to Quality in Australia and a pharmaceutical quality and compliance expert. "It's convenient to stick a tag on the map and call it Asia Pacific, like it's one entity, but it isn't. It's a vast geography, with language barriers, geographical challenges, and a sliding scale of technology adoption."

From Japan and South Korea to Australia and New Zealand, it is indeed vast, and the range of capabilities, strengths, and challenges of the pharmaceutical industry is difficult to summarize. The particularities that exist throughout APAC significantly affect the pharmaceutical landscape and have challenged nations to meet both domestic and global needs for medical products. Efforts to address these challenges—for example, through collaborative regulatory initiatives and the adoption of technological advances—is fueling a burgeoning pharmaceutical industry.

"API [active pharmaceutical ingredient] export manufacturers from a country like South Korea are very sophisticated," Wakeham said. "To compete in the global market and sell in places like the US, they know they have to invest in the necessary technology. At the other end of the scale are countries with less automation and networked equipment."

"The range within APAC really interests me," said Maurice Parlane, Director at New Wayz Consulting in New Zealand and Director and Partner, CBE Pty Ltd in Australia. "The industry in some countries, like Singapore, is outwardly focused. Then there are many other economies, like Indonesia, Malaysia, and Thailand, striving to build capacity in the local manufacturing network for domestic consumption. Vietnam has a lot of foreign investment coming in from Japan and Korea and other overseas markets. In Indonesia, big pharma companies want to have a presence because the market is so large. Korea is also a large market, but focuses more on the US market and has taken a different tack than Singapore, which attracted foreign pharma companies to build large manufacturing facilities, whereas South Korea established a biotechnology center in Osong. There are many startups there and a lot of biosimilar work in that area. It seems that they have critical mass. As you see, each country is different."

Exploring the complexities within the region highlights the ways APAC continues to develop as an important nexus for the worldwide supply of drugs.

INDUSTRY CHALLENGES IN APAC

The pharma industry must meet the challenges that arise from the geographical and cultural constraints within APAC. Language, of course, can be a barrier to cooperation and trade. The lingua franca for many manufacturers in APAC countries is English, given their desire to supply drugs to markets in Europe and the US. This includes places like Malaysia, Singapore, Indonesia, and Thailand. For other countries, like South Korea and Japan, there may be a more relevant second language than English.

Most of APAC sits on the Ring of Fire, a band of volcanoes and tectonic activity in the Pacific Ocean that is prone to earthquakes and tsunamis (see Figure 1).

"Because of the risk of natural disasters, business continuity requires careful consideration about where to store materials off site," Wakeham said. "In Australia, it might be enough if you're located in Sydney to have backup data in Melbourne, but those nearer the Ring of Fire have to think bigger. This could mean choosing an offshore data center on a separate tectonic plate."

Complex historical relationships and ongoing political tensions can adversely affect the free flow of goods and services. "Also, most countries are proud of their domestic manufacturing capabilities," Wakeham said. "They may choose internal over external providers based on this."

While these challenges exist for manufacturers in any industry, there are two big challenges particular to the pharmaceutical industry: the need to bridge the regulatory regimes that exist country by country and the wide range of technology adoption and capabilities. On both fronts, APAC is making significant gains.

HARMONIZATION OF QUALITY AND COMPLIANCE

Given the large number of APAC countries involved in the industry, there has historically been a patchwork of regulations that makes it challenging for manufacturers to export to other countries in the region. Wakeham also noted that the level of knowledge and expertise varies across APAC. Fortunately, there is now a common GMP standard that most countries follow.

ALIGNMENT TO PIC/S GMP STANDARDS

The Pharmaceutical Inspection Co-operation Scheme (PIC/S) is a non-binding collaboration of regulatory authorities, each of which adheres to a similar GMP inspection system, to align inspection approaches globally. Currently, there are 56 participating regulatory agencies globally. PIC/S members within APAC include the regulatory authorities of Indonesia, Singapore, Malaysia, Thailand, Australia, New Zealand, Japan, South Korea, Hong Kong, and Taiwan. Although the regulatory agencies of India and China are not PIC/S members, both countries have large numbers of export manufacturers working to PIC/S GMP standards to access global markets, and China has applied for PIC/S membership.

"By providing a common standard across the region, PIC/S GMP standards are of tremendous importance within Asia Pacific and to facilitate access to the wider global market," Wakeham said.

In addition, the Association of Southeast Asian Nations (ASEAN), which includes the Philippines, Singapore, Thailand, Vietnam, Indonesia, and Malaysia, are signatories to a mutual recognition agreement to harmonize on PIC/S GMP irrespective of their national GMPs [2]. This greatly simplifies trade between these nations. If a manufacturer has a GMP certificate from a PIC/S member regulatory agency (e.g., the Australia Therapeutic Goods Administration [TGA]), other PIC/S members may choose to accept their products without their own further inspection.

Figure 1: The Ring of Fire in the Pacific Ocean.

Map courtesy of USGS [1].

Governments are promoting this because it makes them more compatible with international markets.

"While it's a step forward, it's not yet a perfect system," said Bảo Nguyễn, a quality control manager in Vietnam. "Responding to regulations of countries in the region can still be difficult. The level of requirements can vary greatly throughout Southeast Asia, and a Vietnamese company may encounter different regulations despite the application of the same standards. For example, although they all participate in PIC/S, the regulations in Thailand, Malaysia, and Indonesia are different in terms of registration dossiers. There are also some special local regulations, like Halal in Indonesia."

REGULATORY EXPERTISE CAN BE VARIABLE

"The level of knowledge and expertise in the regulatory agencies is variable across the region," said Wakeham, who has provided training directly to many regulatory agencies in the region, including Australia, Indonesia, Malaysia, Myanmar, New Zealand, South Korea, Philippines, Taiwan, Thailand, and Vietnam. "Some entrenched attitudes are difficult to break, such as the insistence among some regulators to keep a paper copy of an approved electronic copy of a paper record."

Parlane, who is an ISPE trainer, knows that learning about regulations and quality requires understanding the reasons for the rules. "Success is not about regurgitating a guide. It's about learning the 'why' behind a rule. It's even more important to have a culture that sees the importance of the why. Embracing PIC/S shows the industry recognizes the need to gain knowledge and the incredible growth in membership of APAC ISPE Affiliates reflects

this. I see Malaysia, Thailand, and Indonesia being close to being able to export significant amounts of medicines."

"There needs to be a mindset shift," said Shanshan Liu, Technical Director, No deviation Pte Ltd, a consultancy in Singapore providing industry support for commissioning, qualification, and validation, as well as engineering. "Countries are recognizing the need to put quality by design in place and use the best equipment. But what's even more important is the systems implemented in their facilities—the quality system and procedures. The way they operate and maintain the equipment makes all the difference."

DIGITALIZATION IS ON THE HORIZON

"It's only now that there's a need for digitalization in much of APAC," Wakeham said. "Earlier manufacturing in the region was focused on domestic or local markets and depended on low levels of automation and connectivity. As ambitions grow, so have quality standards and expectations."

This has raised the collective regional knowledge and expectations, making the time ripe for GAMP® in APAC. GAMP, a community of practice (CoP) within ISPE, is focused on computerized systems quality and data integrity and the use of automated systems in the industry. Wakeham set up GAMP South Asia, a CoP for the region. She is currently the chair of both the GAMP Global Steering Committee and the GAMP South Asia CoP. GAMP South Asia provides a unique blend of collaboration and knowledge sharing, allowing Asian countries to tap into the education ISPE offers.

"The digital needs in Asia Pacific are unique," Wakeham said. "APAC needs a local focus by local people because it's not the same as making pharmaceuticals in the US or Europe. We need that level of knowledge sharing and mutual upskilling to get the best out of computerized systems. While it's getting better, there are still challenges with IT infrastructure. While most cities have good connectivity and bandwidth, locations with unreliable connectivity hinder companies from using software as a service (Saas) in the cloud for their daily operations. This can impact something as imperative as the need to transition from paper records to digital records."

THAILAND

Thailand has a vibrant biopharmaceutical industry due in part to the size of its domestic market. By revenue, oncology drugs are the most lucrative products manufactured in the country [3]. Government policy has promoted affordable healthcare, leading to a shift toward generic drug manufacturing. Tax incentives attract significant foreign investment with seven of the top 10 companies in the industry being multinationals, including GSK, Pfizer, and Novartis. The government has also facilitated research and development of innovative treatments through the establishment of the Thailand Center of Excellence for Life Sciences.

The ISPE Thailand Affiliate

The Thailand Affiliate has been active for more than 20 years and has 460 members. It collaborated with industry and others in the country to become a member of PIC/S GMP in 2016. The Affiliate was an important advisor to the government initiative to develop a roadmap for manufacturing advanced therapy medicinal products (ATMPs).

INDONESIA

Parlane noted that vaccine manufacturing is growing in Indonesia and thinks the market for innovative drugs is particularly appealing in a country that has more than 270 million people. Large pharma companies are attracted to the market but, due to government regulations, must partner with a domestic company.

"Supplying Indonesia makes sense given the size of the market and the fact that it's an ASEAN member," Parlane said. "While BPOM [the Indonesian regulatory agency] is PIC/S accredited, it doesn't lead to a lot of exports. Sometimes it's easier to import a drug into the country than it is to make it there."

The ISPE Indonesia Affiliate

The ISPE Indonesia Affiliate is very active and has been in existence for over 20 years. They run a well-attended annual conference which includes topical GMP themes. The 2023 conference ran over 2 days with over 300 industry attendees. The theme of the conference was "Technology Innovation–Adhering to Ethical Behavior and Ensuring Patient Safety." Outside of the conference, the affiliate is very active with events most months, often featuring international subject matter experts. Badan POM, the Indonesian GMP regulator, was one of the first APAC authorities to be PIC/S approved in 2012 and actively participates and supports the local Affiliate.

INDIA: PHARMACY OF THE WORLD

The Indian pharmaceutical industry is a major player, not only in APAC, but globally. Some estimates value it at US $50 billion and expect rapid, continued growth, supplying as much as 20% of the world's generic medicines and 60% of global vaccine demand [4]. Indian companies received almost half of the 742 abbreviated new drug application approvals from the US Food and Drug Administration (FDA) in 2022 [5].

Interest in complex generics is burgeoning and has the potential to enhance long-term growth for pharmaceutical manufacturers in India. The challenges of developing successful manufacturing processes limits competition and offers a higher return on investment for companies in this sector, which includes Dr. Reddy's, Zydus, Glenmark, Aurobindo, Torrent, Strides, Lupin, Cipla, and Sun.

SINGAPORE

Singapore has a well-established pharmaceutical infrastructure, with manufacturers such as Roche, Pfizer, Novartis, and Amgen having set up shop and introducing innovative technologies (e.g., continuous manufacturing, Manufacturing Execution Systems, and Process Analytical Technology) to the country.

"Singapore has invested heavily in biologics and other complex, high-value products, like personalized medicines,"

said Liu. "This emphasis is in both research and development and manufacturing."

Liu noted that the strength of the industry—eight of the top 10 pharmaceutical companies operate in the country—led to the government putting greater emphasis on research. The country has invested to develop an entire system supporting advanced therapies, including pharmaceutical companies and contract development and manufacturing organizations (CDMOs), clinicians investigating new therapies, and tertiary institutes like the Agency for Science, Technology, and Research (A*STAR) and the National University of Singapore. It also created the Advanced Cell Therapy and Research Institute (ACTRIS), a significant investment in infrastructure that aims to be a center of excellence in the region for the discovery, development, and production of cell therapies.

"Singapore is an attractive destination for talent from places like the States and Europe," Liu said. "The politics are stable and regulatory policies are beneficial for the pharma industry. The concentration of industry provides a centralized pool of talent and resources, making it efficient for companies to plan."

It also has a resilient supply chain, with multiple ports and good relationships with different nations and suppliers. The government developed a biomanufacturing center on the western end of Singapore. Tuas is a densely contained base for large-scale manufacturing of small molecules and traditional antibody therapies. Manufacturing facilities for Novartis, Lonza, GSK, Amgen, Abbott, Roche, MSD, and Pfizer are located there.

> Success is not about regurgitating a guide. It's about learning the "why" behind a rule. It's even more important to have a culture that sees the importance of the why.

One domestic company is CellVec, a CDMO that develops and produces viral vectors for both clinical and commercial applications in cell and gene therapy (C&GT) within its GMP-certified manufacturing facility. It is located in south Singapore near a container terminal, alongside high-tech companies like Google.

"Singapore has a long history as a pharmaceutical manufacturing powerhouse, with the kind of supply infrastructure that makes it a good place to set up a CDMO like CellVec," said Lucas Chan, Founder and Chief Scientific Officer, CellVec. "As a major trading

Establishing a GMP-accredited capability in the region is an important step toward self-sufficiency and means we can improve access to these transformative therapies within Southeast Asia and the wider region.

partner to the US, Europe, and Japan, we're easily able to import the raw materials we need to develop our cell and gene therapies."

"Despite ongoing technological advancement in gene transfer technologies, viral vectors remain a staple and critical enabling component to both the development and commercialization of C&GT products, and supplies continue to be a significant bottleneck in Europe, America, and in Australia," Chan said. "Establishing a GMP-accredited capability in the region is an important step toward self-sufficiency and means we can improve access to these transformative therapies within Southeast Asia and the wider region." He added there are ongoing C&GT development efforts in many APAC countries, including Australia, New Zealand, Thailand, and India, all of which require a stable supply of GMP-compliant viral vectors.

The small size of Singapore gives it the advantage of needing only one centralized regulatory agency, the Health Sciences Authority (HSA), making harmonization much simpler. Singapore, as a member of PIC/S, shares mutual recognition of GMP standards with regulators in other jurisdictions, such as Australia's TGA. This has led to scientific collaborations within the region and beyond, including a partnership between CellVec and the Peter MacCallum Cancer Centre in Australia to provide viral vectors for the center's clinical development pipeline of autologous cell therapies.

"Another advantage Singapore has is at the established level of regulatory standards, through Singapore's regulatory agency, HSA. This has resulted in the international recognition of the quality of biomanufacturing in the country," Chan said. "Establishment of these standards and practices requires a significant level of infrastructure investment from the government, and Singapore has done a lot of this over the last 20 years. Being a GMP-accredited manufacturer has enabled us to export clinical C&GT vectors for both the wider region and internationally."

The ISPE Singapore Affiliate

Shanshan Liu is chair of the ISPE Asia Pacific Affiliate Council whose members include Malaysia, Philippines, Indonesia, Thailand, Australia, Japan, South Korea, and India. There are local affiliates throughout APAC, including the ISPE Singapore Affiliate, which has 300 active members. Liu is President of the ISPE Singapore Affiliate. The ISPE Singapore Affiliate's mission is to provide accessible educations to the workforce and to connect the industry. The Affiliate provides education sessions within the country and helps organize educational events in other countries in the region.

"We have really close working relationships with each other," said Liu, who is qualified as an ISPE instructor for Commissioning and Qualification (C&Q) and ATMP modules, among other subjects. "Often two countries will collaborate on official ISPE training, so we can make the traveling of instructors more efficient and share the license fee."

The Affiliate hosts the annual ISPE Singapore Conference & Exhibition, bringing together participants from around the world to hear keynote addresses, attend workshops, and visit an exhibitor hall. Regulators from the World Health Organization, European Medicines Agency, and other agencies also offer presentations. The 2023 conference saw more than 1,500 participants attending on-site, making it the biggest conference so far.

"We offer packages to attract more people, such as C&Q training," said Liu. "This way they can experience the technical and networking benefits of becoming members of the Singapore Affiliate."

MALAYSIA

"The pharmaceutical manufacturing sector in Malaysia is primarily focused on generics," said Zarina Noordin, Quality and GMP Consultant, and President of the ISPE Malaysia Affiliate. "Patented products from multinational companies are mostly imported. Areas of growth include vaccine production and cell and gene therapies. Medical device manufacturing is also growing, especially during the pandemic, with many players opening new factories."

The medical device market has a projected revenue of more than US $3 billion in 2023, with cardiology devices at the forefront [6].

"While the Malaysian pharmaceutical industry has a well-educated workforce, most of whom speak English, there's a significant brain drain to neighboring countries," Noordin said. "There's also a lack of skilled personnel in biotech and biopharma. We see ISPE playing an important role to fill this gap with our publications, education content, and global network."

"It is the larger companies that have the resources needed to meet GMP and market demands for new modalities," Noordin said. "Even then, the decline in the value of the Malaysian ringgit makes it a challenge to innovate and invest in digitalization and technology to meet Annex 1 requirements."

Two examples of large, local companies investing in biotech, digitalization, and innovative technology are Pharmaniaga Berhad and Duopharma Biotech, which have multiple sites in Malaysia and throughout the region.

The ISPE Malaysia Affiliate

This Affiliate provides education on topics such as biotech, C&GTs, and new advances in manufacturing, and assists smaller players

in the fundamentals of GMP. There is interest in good distribution practices (GDP) training for small- to medium-sized companies, requested by the National Pharmaceutical Regulatory Agency (NPRA).

"The Malaysian pharma industry is a relatively small one," said Noordin. "The Affiliate has a vibrant program to help develop the human capital needed in Malaysia. We provide a professional platform for industry—companies, regulators, government agencies, academics, students, and vendors—to network and learn through monthly webinars, in-person GDP and vendor seminars, social events, and the annual conference. ISPE Malaysia is looking at approaches and knowledge required to ensure compliance and patient safety within the context of our nation."

The ISPE Malaysia Annual Conference provides participants and members with information on trends and technologies. In 2023, an entire session was devoted to regulatory trends and updates, with presentations by the NPRA, the Medical Device Authority, the Malaysian Green Technology and Climate Change Corporation, and the Malaysian Industrial Development Finance Berhad. The presentations updated participants on the latest developments in their respective agencies, as well as opportunities for assistance.

"The ISPE Malaysia event is unique in bringing all the agencies together in one conference," Noordin said. "We had a lot of positive feedback and will continue with the regulatory track in our next conference. ESG [environmental, social, and governance] and sustainability are additional areas of great interest right now with publicly listed companies having to comply with lower carbon emissions and other targets by 2030. The ISPE Malaysia Affiliate has been asked to assist in developing technical documents and calculation tools to help pharmaceutical companies."

PHILIPPINES

"Over the last few years, the pharmaceutical industry in the Philippines has shown significant market growth potential," said Arnel Cabungcal, Operations Services and Technology, Unilab, Inc., and past president of the ISPE Philippines Affiliate. "This is highly reliant on the government's interest in developing the local drug manufacturing sector. Growth in Philippine healthcare is driven by a favorable demographic profile, rising chronic disease burden, and continued government commitment to universal healthcare. This is driving drug sales and is augmented by a government subsidy and increased private sector participation."

Regulatory compliance in the country continues to improve with membership in ASEAN and an evolution toward PIC/S GMP standards. Despite these improvements, the domestic pharmaceutical industry relies almost solely on imports for the bulk of its supply for a growing population exceeding 117 million. Two-thirds of the pharmaceutical products supplied to the domestic market, and virtually all raw materials and APIs used to manufacture or formulate drugs are imported, with India being the largest supplier of pharmaceuticals to the country [7]. The value of the country's exports was only US $50 million in 2017, the last year for which data is available [7]. As of 2016, the largest pharmaceutical company in the local market was Unilab, which had a market share of 25% [7].

"All API supply and most raw materials are imported," according to Vivien Santillan, Regional Director, Asia, Novatek International. "This high dependency on importation leads to drug shortages and the high cost of drugs. Multinational pharmaceutical companies have a presence, but only for distribution or through engagement with CMOs [contract manufacturing organizations] for repacking or production. The Philippine industry consists predominantly of generic manufacturers, typically for small molecule drugs. There are limited government incentives for local manufacturing but efforts from the Department of Trade and Industry through the Board of Investments have been established to spur adoption of Industry 4.0."

Other than the challenge of building up domestic manufacturing, a state-of-the-industry report from the Philippine Competition Commission outlined several other challenges for the pharmaceutical industry in the country, notably that the regulatory environment in the country appears to be more stringent than others in the region [7]. The challenges the report highlights include the following:

- A slow drug registration process that hampers getting products to market
- Lack of dialogue between industry and the Philippines Food and Drug Administration (PFDA)
- The presence of counterfeit drugs on the market
- Struggles to hire, and keep, qualified workers
- Large variations in drug prices depending on the seller or hospital

"Growth headwinds include challenging sustainability of the healthcare system, lack of healthcare facilities and workers, and low levels of intellectual property protection," Cabungcal said. "Greater collaborative efforts by government and industry to suppress counterfeit drugs continue to provide an upside to locally developed generics."

The ISPE Philippines Affiliate

"Since its creation in 2008, the ISPE Philippines Affiliate continues to drive the mission and vision of ISPE at the regional level, elevating members of our community as we create opportunities for collaboration and networking," Cabungcal said. Representatives from regulatory authorities and government agencies make up 39% of the membership of the Philippines Affiliate, while 52% are students and recent graduates. "To help nurture the future workforce for the pharma industry, we collaborate with academic institutions, the industry, and professional organizations to foster capability of young professionals, conduct internship programs for pharmacists, and mentor students and emerging leaders."

According to Cabungcal, the ISPE Philippines Affiliate, which won the Affiliate and Chapter Excellence Award in 2021, collaborates with the PFDA and industry associations to:

- Build technical competencies in GMP and other pharmaceutical technologies
- Explore anti-counterfeiting solutions and drug shortage prevention
- Develop pharmacovigilance and adverse event monitoring

"While there are different maturity levels with respect to technology and regulatory adoption within the APAC region, there is engagement with government agencies to incentivize local manufacturing," Santillan said. "The technical trainings provided through the ISPE Philippines Affiliate help update the industry on the trends, technologies, and the latest regulations."

VIETNAM

Vietnam has a long history of pharmaceutical manufacturing. For example, Sanofi, which operates a GMP facility in Ho Chi Minh City, has had a presence in Vietnam for more than 70 years.

"The pharmaceutical market in Vietnam still has growth potential with our population of more than 100 million," said Bảo Nguyễn. "There has been a shift in production from other countries in the region, such as Indonesia and China, to Vietnam, and there is significant foreign investment in domestic companies."

This includes SK Group (South Korea), which took control of Vietnamese drug manufacturer Imexpharm [8], ASKA Pharmaceutical Co., Ltd. (Japan), which invested in Ha Tay Pharmaceutical [9], and Samil Pharmaceutical (South Korea), which opened a new facility in Ho Chi Minh City in 2022 to produce eye drops for global distribution [10].

"Most companies focus on simple manufacturing techniques and low-value OSD [oral solid dosage] medicines, like paracetamol," said Huy Nguyễn, Quality & Validation Engineer III, Terumo Blood and Cell Technologies. "There are more than 200 local pharmaceutical companies that can contribute to the medical security of Vietnam's healthcare system."

This is good news for the Vietnamese pharmaceutical industry, the value of which is pegged to reach US $8 billion in 2023 [9]. There are investments in technology for high-tech products, such as vaccines and pellets. Many of the manufacturers are CMOs for large pharmaceutical companies, including Pfizer and AstraZeneca.

According to Bảo Nguyễn, the industry's challenges include strong pricing competition from other countries in the region. Raw materials are mainly imported, with price and quality varying from batch to batch because Vietnamese companies often buy in small quantities. "As well, the layout of many facilities follows older concepts, requiring considerable investment to meet cross-contamination control requirements. There are limited human resources to follow GMP requirements, especially in small localities. Training is still limited, much of the hardware is old, and the processing is still manual and, as a result, has a lot of human errors."

Huy Nguyễn agrees. "There are few people with the knowledge of quality and validation, which is a prerequisite to get GMP certification. There's a lack of appropriate levels of investment in quality management systems, manufacturing equipment, and facility design. This results in low quality management and, unfortunately, compliance issues. The unique challenge is the willingness of leadership to invest in quality."

A case in point. The Drug Administration of Vietnam recently sanctioned a pharmaceutical manufacturer of methotrexate for quality violations [11].

"I'm hopeful these challenges can be met by building a quality system to meet new requirements, learning from training courses from organizations around the world, and taking advantage of human resources from global companies in Vietnam, like Sanofi," said Bảo Nguyễn. "We can also invest in new hardware systems and research products with high economic value."

AUSTRALIA AND NEW ZEALAND

Australia and New Zealand are blessed with a highly skilled labor market, along with strong research and development (R&D) in science and technology at universities that drives innovation, including clinical-scale ATMP production and chimeric antigen receptor T cell innovation. Both countries are attractive spots to run clinical trials because they are English-speaking and, in Australia's case, the government offers a significant tax break on clinical projects. As a result, contract research organizations are prevalent. Combined with their proximity to the abundance of relatively cheap labor in Asia, this means the traditional biopharmaceutical industry is quite small in both countries.

"It's true, we can't compete in terms of low-cost labor," Wakeham said. "Ten years ago, I would have said pharmaceutical manufacturing was in decline in Australia when we lost some of the global multinationals."

"Over recent years, there was an exodus of larger manufacturing companies from New Zealand and Australia," said Parlane. Some have recently shut down sites in Australia, including Pfizer and GSK, which closed its Boronia site at the end of 2022 after 50 years of operation. "The extended amount of time without larger firms manufacturing in New Zealand means there is a lack of technical expertise and recent experience, making it difficult to stand up even modest-sized projects in that country." Australia has critical mass in terms of its industry and local regulators.

There are, however, signs of a resurgence in the industry. Australia continues to have a strong biotech and R&D sector, with many research facilities. Moderna announced in 2021 that it will produce millions of doses of mRNA vaccines annually, and BioNTech has plans to open a research center and manufacturing site. The New South Wales government is building a large viral vector manufacturing facility, which will be put out to tender for a private company to operate.

New Zealand has established vaccine manufacturing capabilities since COVID-19, albeit on a small scale. And, in both Australia and New Zealand, the rise of the medicinal cannabis industry has seen expansion of GMP manufacturing. In Australia, for example, the number of new patient receiving a prescription for medical

cannabis in the first six months of 2023 more than doubled over a similar period in 2022 [12]. Although sales were estimated at only US $67.4 million in 2022, the market is projected to continue to grow rapidly over the next decade [13]. In addition, Tasmania is the largest producer of legal opioids, including morphine, thebaine, and codeine [14].

"And New Zealand continues to be a hub for veterinary medicine manufacturing," said Parlane. "We have also seen steady growth in GMP manufacturing of low-risk listed medicines—primarily for the Australian market."

Quality and compliance are also strengths. The TGA is an active and respected partner in many regulatory forums, including PIC/S and the International Medical Device Regulators Forum. This means TGA approaches are usually well-aligned with GMPs from both the US and Europe.

"TGA hosts inspector trainings that are open to other regulators in the region, helping to raise the overall standard of inspection throughout the region," Wakeham said. "I've presented at their inspector training sessions and found regulatory acquaintances attending from Thai FDA, Medsafe, and others."

JAPAN

Japan is the third-largest pharmaceutical market in the world, though it is expected to shrink while the rest of the global market grows [15]. Despite the size of its pharmaceutical market, Japan's production of new drugs declined in recent years with only one of the top 20 drugs, by revenue sales in 2020, having been developed in the country [16].

Despite this, the industry does exhibit strengths. There has been a renewed focus to improve the country's drug discovery system and exports have increased dramatically since 2020 [15]. Japan's biopharmaceutical market is projected to grow despite the downturn of Japan's total pharmaceutical market, and the industry's use of artificial intelligence in drug development is significant [15].

"Japan has robust intellectual property protection laws, encouraging innovation and providing a supportive environment for pharmaceutical companies to invest in R&D without significant concerns about intellectual property theft," said Hirokazu Kisaka, Vice President, Kyowa Kirin Co., Ltd, and ISPE Japan Affiliate chair. "Japanese pharmaceutical companies have a strong track record in R&D. We invest significantly in innovative and cutting-edge research, leading to the discovery and development of novel drugs and therapies."

Kisaka noted that, like many jurisdictions around the world, the Japanese pharmaceutical industry may face shortages of skilled professionals. "Training, attracting, and retaining talent is essential for the continued success of the pharmaceutical sector."

The ISPE Japan Affiliate tries to help meet this challenge. "Our purpose is to contribute to revitalizing the industry and increasing competitiveness in the world," Kisaka said. "We can provide the opportunity for members of the pharmaceutical industry to gather to exchange the latest information on business environment, technology, regulatory, and overseas affairs."

CONCLUSION

The biopharmaceutical industry throughout APAC is developing rapidly, propelled by strong government support, regulatory reforms and international cooperation, an influx of venture capital, and a desire to adopt technological innovations. Its ability to evolve and adapt to meet challenges continues to mean it can deliver legacy drug products and develop innovative therapies to supply both domestic and global markets.

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EVOLVING CHINA'S REGULATORY SYSTEM in Alignment with ICH

By Charles C. Tong, PhD, Zhengyu Wu, Yang Gao, PhD, Meng Yang, PhD, and Mingping Zhang

With the Chinese government initiating drug regulatory reform in 2015 and China joining the International Council for Harmonisation (ICH) in 2017, a significant number of measures have been implemented by the government. The aim is to make fundamental changes to China's drug regulatory administration system so it can facilitate pharmaceutical development and better meet patient needs in the country.

INTRODUCTION TO THE REGULATORY SYSTEM IN CHINA

This article introduces these important regulatory changes, adaption of ICH guidelines, and key considerations for drug development in China, particularly those in chemistry, manufacturing, and controls (CMC), quality, and engineering areas. In addition, major challenges and opportunities will be discussed for innovative drug product development covering small molecules, biologics, and cell and gene therapy (C&GT) in China.

National Medical Products Administration (NMPA)

The State Administration for Marketing Regulation, which is directly under the State Council of China, administers the NMPA. The NMPA is China's national regulatory authority for drugs, medical devices, and cosmetics. It was originally founded in 1998 as the State Drug Administration, joined ICH as a regulatory member in 2017, and was elected and reelected as a member of the ICH management committee in 2018 and 2021. The key functions and responsibilities of drug supervision are handled by internal departments and affiliated institutions under the NMPA during new drug clinical development and marketing authorizations.

The Center for Drug Evaluation (CDE)

The CDE is responsible for the acceptance and technical review of applications for drug clinical trials and drug marketing authorization. Two regional CDE centers are established in the Yangtze River Delta region and the Guangdong-Hong Kong-Macao Greater Bay Area to reach out to the pharmaceutical industry in these regions.

The National Institutes for Food and Drug Control (NIFDC)

The NIFDC is responsible for the sample testing and the method and specification verification according to the CDE's review needs of new drug applications (NDAs). The sample testing by the NIFDC is rarely required by the CDE for clinical trial applications, except for some vaccines and certain types of special biological products, e.g., some C&GT products. The NIFDC may allocate the testing and verification to the Provincial Institutes for Food and Drug Control for NDAs of small molecules.

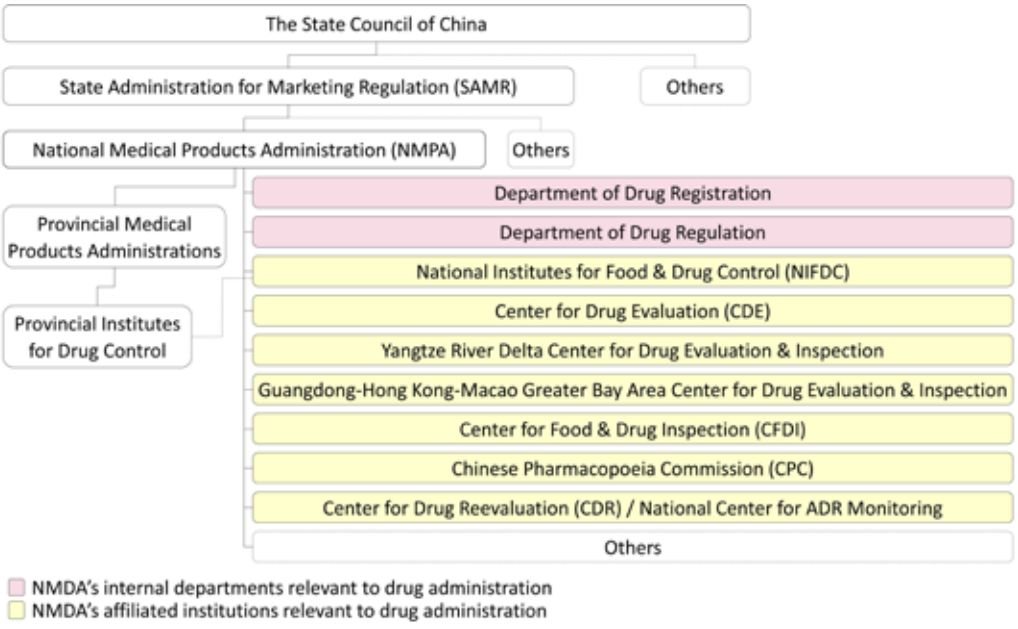
The Center for Food and Drug Inspection (CFDI)

The CDI undertakes the preapproval inspection of the research and development site(s) and manufacturing site(s) as well as the for-cause inspection required by the CDE during the review of NDAs. It also coordinates the co-inspection if the GMP compliance inspection to the domestic manufacturing site(s) is initiated by the Provincial Medical Products Administrations (PMPAs) together with the preapproval inspection. The CFDI may authorize the preapproval inspection to the PMPAs.

The Chinese Pharmacopoeia Commission (CPC)

The CPC publishes the national drug standards, including the Chinese Pharmacopoeia and other national drug standards. The national drug standards are mandatory for the drug products approved in China. Compliance with Chinese Pharmacopoeia is critical during the review, testing, and inspection of NDAs.

Figure 1: Organizational chart of the NMPA relevant to drug administration.



The Department of Drug Registration and the Department of Drug Regulation

These departments of the NMPA are responsible for interpretation of the laws and regulations to address the policy and regulatory and administrative issues raised by the CDE or the CFDI during the review and inspection of NDAs.

Provincial Medical Products Administrations (PMPAs)

Prior to the submission of a new drug application, the PMPAs are responsible for authorizing domestic manufacturing site(s) and the applicant that will be the marketing authorization holder (MAH) when the drug application is approved. PMPAs may initiate the GMP inspection together with the preapproval inspection of NDAs. Following approval of the new drug application, PMPAs supervise the drug production, distribution, pharmacovigilance, and most of the activities and obligations of the MAHs that take place at the PMPAs' administrative areas.

Other Ministry-Level Departments

In addition to the NMPA, other ministry-level departments directly under the State Council are also relevant to drug research and development. For example, the ethics review of clinical trials is also subject to the relevant requirements supervised by the Ministry of Science and Technology (MOST) and the National Health Commission (NHC). The collection and research of human genetic resources during clinical trials need to be approved by the NHC (formally by the MOST), the human stem cell and gene diagnosis and therapy technology related drug clinical development is subject to the Special Administrative Measures on Access to Foreign Investment (Negative List) issued by the Ministry of Commerce (MOFCOM), and the technology exportation is subject to the Catalogue of Technologies Prohibited or Restricted from Export, issued by the MOFCOM as well.

Changes to Drug Administration Law and Implementation Rules

The Drug Administration Law (DAL) [1] is the basis of drug administration in China, which was initially adopted in 1984 and revised in 2019 by the Standing Committee of the National People's Congress. This revision consolidated the improvements and outcomes of the drug regulatory reform since 2015 and established the MAH-based regulatory supervision system throughout the life cycle of drugs. Specifically, the following improvements have been expected by the industry for a long time:

- Policies encouraging the development of innovative drugs with a new mechanism of therapy, for life-threatening or rare diseases, multitargeted systematic intervention, and pediatric use.
- Conditional approval of drugs for life-threatening diseases without effective treatment or for urgent needs for public health, which are supported by predictable clinical value by available data on efficacy.
- Priority review and approval of drugs for pediatric use, drugs on shortage for urgent clinical needs, or new drugs for prevention and treatment of serious infectious diseases and rare diseases.
- Completion of clinical trial application review within 60 working days from the acceptance of application is stipulated, and expanded access and compassionate use of investigational drugs can be considered.
- MAH may have its drugs manufactured by their internal or contract manufacturing facilities, distributed by itself or by contactors;

Table 1: Regulatory differences between domestic and imported drugs.

Regulatory Practices	Domestic Drugs	Imported Drugs*
Nationality of the applicant of clinical trial application and new drug application	Domestic sponsor	Foreign sponsor with its appointed local registration agent
Manufacturing authorization	The manufacturing license is granted to both the MAH and the manufacturer	N/A
Nationality of drug MAH	Domestic holder	Foreign holder with its appointed local agent
GMP compliance inspection	Inspected by PMPAs as part of routine supervision	Inspected by CFDI as the for-cause supervision called overseas inspection
Preapproval inspection of the manufacturing site(s) for new drug application	Initiated by the CDE and inspected by the CFDI or PMPAs for most new drug applications	For-cause initiated by the CDE and inspected by the CFDI for a few NDAs
Notification of moderate and above post-approval changes	Submitted to and reviewed by PMPAs	Submitted to and reviewed by the CDE
Review and approval of drug renewal	Submitted to, reviewed by, and approved by PMPAs	Submitted to, reviewed by, and approved by the CDE

* For a chemical drug product, the imported drug means the drug product is produced at the foreign manufacturing site(s) and it must be held by a foreign entity (applicant/MAH). For a biological product, the imported drug means both the drug product and its drug substance(s) are produced at the foreign manufacturing site(s) and the drug product must be held by a foreign entity (applicant/sponsor/MAH).

however, the MAH's due obligations throughout the life cycle of drugs from research and development to use in patients are enforced and regulated.

Data Exclusivity and MAH in China

Based on the revision of the DAL, numerous regulations, standards, guidelines, and administrative working procedures have been updated or newly developed as a result of the drug regulatory reform. One of the most significant legislative programs is the draft revision of Regulations for the Implementation of DAL [2], with the following specific considerations for encouraging drug innovation and drug accessibility:

- Six-year regulatory data protection over the undisclosed trial data and other data of some drugs (to be further clarified by the authority) is expected.
- Up to seven-year market exclusivity for new drugs treating rare diseases is expected.
- Up to 12-month market exclusivity for pediatric-specific new drugs, new dosage forms, new strength, and the extension of pediatric indications or usage and dosage is expected.
- 12-month market exclusivity for the first generic drug succeeding in patent challenge is expected.
- Cross-border holding of marketing authorization is not yet allowed but may be expected in the future for innovative drugs with special considerations for urgent clinical demands.

The separation between the MAH and the manufacturer is one of the essential aspects of the MAH system regulated by the revision of DAL, in that MAH certificate of a drug product may be the same as the drug manufacturer or a different entity. However, due to the historical reasons, China's drug regulatory requirements and practices for imported drugs and domestic manufactured drugs are somewhat different (see Table 1). Both the MAH and the manufacturing site(s) must be from one side of the border; that is, an imported drug can only be held by an MAH outside of China, and a domestic drug can only be held by a domestic MAH.

Designations to Expedite Development

China has established three pathways in 2020 to expedite development and regulatory approval for medicinal products that have the potential to address unmet medical needs: breakthrough therapy, conditional approval, and priority review, which were described in the new Drug Registration Regulation [3]. These pathways provide opportunities for developers to engage regulators during the development process and participate in accelerated review programs. Table 2 summarizes the qualifying criteria and key features for these three expedited pathways.

There is also another accelerated regulatory pathway called special review, which is available for public health emergencies, e.g., COVID-19 products.

Regulatory Interactions Between Health Authorities and Sponsor

The CDE has strengthened its resources to support innovation to ensure patient safety and efficacy while increasing patient access. Development of innovative investigational products, such as C&GT products, can introduce unique challenges due to unknown safety profiles, complex manufacturing technologies, the incorporation of innovative devices, and the use of cutting-edge testing methodologies. In recognition of the complex nature of C&GT products, the CDE has introduced preliminary informal consultations to allow sponsors to obtain feedback to facilitate product development and clinical study planning. These early meetings are in addition to the conventional CDE and sponsor meetings. During the life cycle of drug development, sponsors may seek advice from the CDE regarding several topics, including, but not

Table 2: Expedited pathways in China.

	Breakthrough Therapy	Conditional Approval	Priority Review
Qualifying Criteria	• New therapeutics for condition with no current treatment options OR with major therapeutic advantage over existing treatments AND preliminary clinical evidence indicating the potential to produce significant benefits for patients with unmet medical needs and hence deemed "major interest" from a public health and therapeutic innovation perspective	• New therapeutics fulfilling unmet medical need AND addressing seriously debilitating or life-threatening disease, rare disease, or for public health emergencies AND has a positive benefit–risk balance (benefits of immediate public access outweigh risks of incomplete data) AND it is likely the sponsor will be able to provide comprehensive data at anticipated time point in the future	• New therapeutics of major interest in terms of public health, particularly therapeutic innovation
Key Features	• Early dialogue to reinforce scientific or regulatory advice, optimize development, and enable priority review • CDE project manager appointed for a product at proof-of-concept stage • Kickoff meeting with multidisciplinary input from CDE experts to discuss development plan and regulatory strategy • Iterative scientific advice at major milestones • Advice on NDA preparation and submission • Use of priority review: procedure to speed CDE review	• Allows use of surrogate or intermediate end points to measure clinical benefit (i.e., tumor shrinkage versus overall survival) • Allows use of foreign clinical data when ethnically insensitive	• Reviews NDA in 130 days (versus 200 days for products without priority review)

limited to, regulatory, clinical pharmacology, safety, product quality, and nonclinical subjects.

Generally, important milestone meetings include the pre-investigational new drug application (pre-IND), end-of-phase 1 (EOP1), EOP2, and pre-NDA) meetings. These meetings are categorized to three types of meetings related to the development and review of investigational new drugs and biologics: Type A, Type B, and Type C, the purpose and rule of which is very similar to the US Food and Drug Administration (FDA) meetings. For cutting-edge technology such as C&GTs, the CDE also provides pre-pre-IND meetings, similar to the US FDA INTERACT meeting, to address their consideration on nonclinical studies and CMC studies at the very early stage to help avoid uncertainty and waste of resources.

Pre-Pre-IND Meeting

Sponsors can obtain a preliminary informal non-binding consultation with the CDE through the pre-pre-IND meeting prior to a pre-IND meeting. Pre-pre-IND meetings are available for innovative investigational products at an early stage of development on issues that are not yet at the stage of pre-IND meeting. It is important to note that the pre-pre-IND meeting validates the CDE's recognition of the complexity of such products.

Although a pre-pre-IND meeting is not mandatory, it may be highly valuable to drug development. This meeting is non-binding in nature, which means that a sponsor is not bound to pursue a particular regulatory pathway. This also means that the CDE feedback can change depending on information or updates the sponsor may provide in the future. Sponsors can obtain non-binding advice regarding different aspects during the development process, such as planning initial clinical development strategies, CMC, pharmacology/toxicology development, and clinical aspects of the product development program.

When seeking a pre-pre-IND meeting, identifying optimal timing for such a meeting relative to product development might be the sponsor's greatest challenge. The meeting request might be declined if it is raised too early in the process at a point when a clear pre-clinical study design has not been established, or when it is considered too late, such as after a clinical development plan has already been defined. Nevertheless, sponsors are advised to apply for the pre-pre-IND meeting earlier rather than later because this meeting is the only opportunity to engage the CDE prior to the pre-IND process. If agreed, the CDE will hold the pre-pre-IND meeting within 60 working days upon receipt of the meeting request.

Pre-IND Meeting

The pre-IND meeting is a Type B meeting and meant to communicate the understanding of the action mechanism and discuss whether the available CMC, nonclinical data, or ongoing studies can support the early-phase clinical trials. The pre-IND meeting is not mandatory by regulation. However, in practice, it is expected if an IND involves the following topics: a product not previously approved, a new active pharmaceutical ingredient (API) with a novel pharmacologic mechanism, a product critical to public health, or a new indication.

Table 3: Regulatory category of chemical drug.

Regulatory Category	Category Explanations	Conditions
1	Innovative drugs not approved in and outside China	Drug substances and their drug products containing new compounds with definite structure and pharmacological actions and possessing clinical value.
2	Improved new drugs not approved in and outside China	2.1 Drug substances and their drug products containing optical isomers with known active ingredients made through such methods as separation or synthesis, or esterification of known active ingredients, or saltification of known active ingredients (including salts containing hydrogen bond or coordinate bond), or the alteration of the acid radicals, basic groups or metal elements, or the formation of other noncovalent bond derivatives (complex, chelate, or clathrate) and possessing significant clinical advantages.
		2.2 Drug products of new dosage forms containing known active ingredients (including new administration systems), new formulation processes, and new routes of administration and possessing significant clinical advantages.
		2.3 New combinations containing known active ingredients that can bring significant clinical advantages.
		2.4 Drug products of new indications containing known active ingredients.
3	Drugs generic to original drugs approved abroad but not yet approved in China	Drug substances and their drug products possessing the same active ingredients, dosage forms, strength, indications, routes of administration and dosage, and method of administration as original drugs.
4	Drugs generic to original drugs approved in China	Drug substances and their drug products possessing the same active ingredients, dosage forms, strength, indications, routes of administration and dosage, and method of administration with original drugs.
5	Applications of drugs approval abroad for marketing in China	5.1 Applications of original drugs marketed overseas (including drug substances and their drug products) for marketing in China.
		5.2 Applications of non-original drugs marketed overseas (including drug substances and their drug products) for marketing in China.

SUBMISSION CONTENT

Common Technical Document (CTD) or electronic CTD (eCTD)

The CTD or eCTD submission structure developed by the ICH provides the backbone for providing information regarding CMC, nonclinical, and clinical in structured modules. The CDE requires that all types of drug products use CTD or eCTD for IND and NDA.

The NMPA also stated that for clinical trial applications and marketing authorization applications for therapeutic biological products and preventive biological products, applicants should follow the "M4: Common Technical Document (CTD) for Registration Application of Drugs for Human Use" [4] (hereinafter referred to as CTD) to prepare application dossiers.

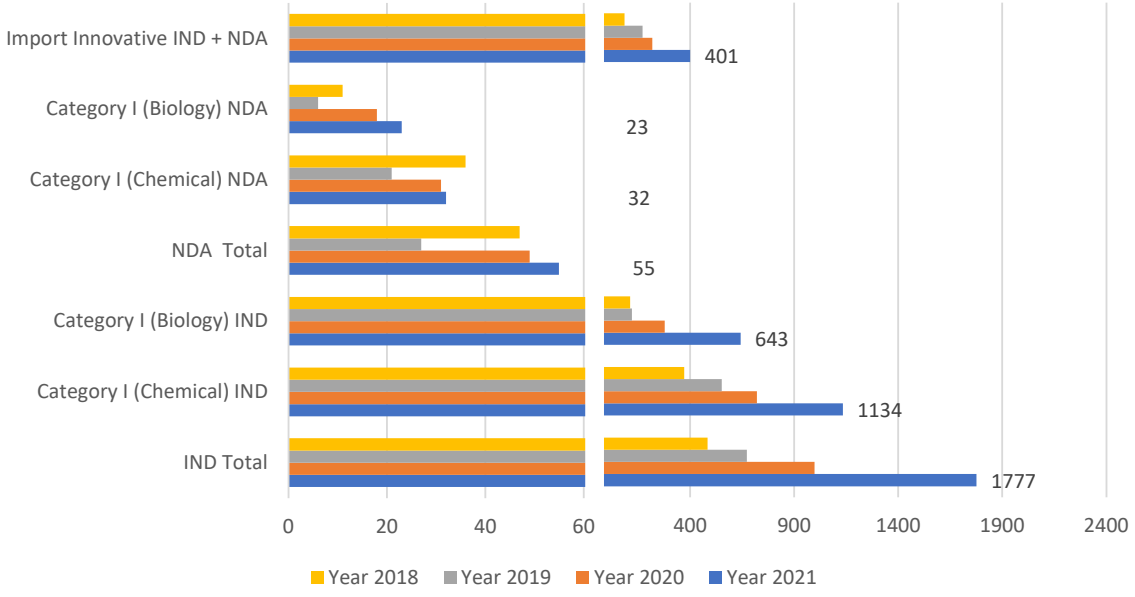
Submission of IND and NDA to the CDE

Sponsors that wish to conduct a clinical trial or market product in China must submit an IND or NDA. The CDE's review of the IND takes 60 working days. The CDE will focus on determining whether there are any reasons to believe the manufacturing or controls for the clinical trial product present unreasonable health risks to the subjects in the initial IND trials; as always, safety is the key concern for a reviewer. When filing an initial IND, details about the following CMC information are presented in the CTD structure and should include drug substance; drug product; placebo, if applicable; and labeling information for the labeled products relevant to the investigational drug.

If the CDE identifies any unresolved safety issue in the IND during the review, or if the CDE identifies such an issue arising during clinical study, the agency will issue a clinical hold on the clinical study. Regulations require the CDE to attempt to discuss and satisfactorily resolve any resolvable issue that may not result in the clinical hold with the sponsor before issuing the clinical hold. Once an IND has been deemed safe to proceed by the CDE, multiple studies can be conducted under the same IND, which are not limited to one specific indication at the early phase of development.

There are two main regulatory checkpoints: the clinical trial application (CTA) and the NDA. The CTA usually only requires the CDE's review and approval decision. For the NDA, the CDE leads the other two functions (the NIFDC and CFDI) under the NMPA to make the technical decision and the NMPA makes the

Figure 2: 2018–2021 China innovative drug application (chemical and biological) number comparison.



administration decision. During the review of the NDA of C&GT products, the NMPA's CFDI has oversight of Good Laboratory Practice (GLP), Good Clinical Practice (GCP), and Good Manufacturing Practice (GMP) compliance and conducts on-site preapproval inspection. The NMPA's NIFDC reviews the analytical method validation and tests the C&GT products per registered specification. All data and results from the CFDI and the NIFDC go to the CDE for comprehensive review and decision.

Life Cycle Management

The NMPA established a three-level change management reporting system according to the risk level of changes. One of the challenges to innovation is the burden of global change management. Thus, the ICH developed the ICH Q12 Lifecycle Management Guidance: "Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management," which provides a framework to facilitate management of postapproval changes in CMC. The NMPA started implementation of the ICH Q12 guidance since 25 Aug 2023 [5]; and 24-month transition period has been set.

CHEMICAL DRUG DEVELOPMENT

New Category of Chemical Drug

In March 2016, the NMPA announced the new chemical drug regulatory categories [6], as shown in Table 3. There are three key changes in the new category:

- The "innovative" definition changed from "not launched in China" to "not approved inside and outside of China."
- The concept of Category II has similarity with 505b(2) [7] in the US, but with emphasis that it should demonstrate "significant clinical value."
- The "generic" requirements changed from "quality similarity" to "quality and efficacy should be similar to the originator."

In June 2020, the NMPA [8] further specified the regulatory category of chemical drug and the corresponding China submission document requirements should follow "ICH M4: The Common Technical Document," signifying that ICH M4 was adopted in China.

Under the new regulation, because the "generic" concept has changed from "quality similarity" to "quality and efficacy similarity," the NMPA initiated the "quality consistency reevaluation" program in February 2016 [9], followed by the generic injection product "quality consistency reevaluation" program in May 2020 [10]. Drugs that pass the reevaluation program will have priority to be enlisted in the China National Essential Medicine List. Drugs that fail the reevaluation program will be removed accordingly [11]. In addition, Chinese regulations required all the market products to have license renewal every five years, with generic product license renewals being rejected if it fails the reevaluation program.

Innovative Chemical Drug Development in China

Small molecule drug product development has had a high growth rate in the past five years. Based on the 2021 CDE annual review report [12], 1,886 innovative drug applications (IND and NDA) were accepted, with a year-on-year increase of 76%. Note that foreign companies contributed a significant number of these innovative drug applications.

Among all drug types, chemical drugs still dominate, and application numbers increased significantly: from 2,979 applications in 2017 to 6,788 applications in 2021, among which there are

China officially joined the ICH in June 2017. As of March 2023, 59 of 63 ICH guidelines in safety (S), efficacy (E), quality (Q), and multidiscipline (M) have been formally adopted. Among 151 ICH guidelines (including annexes and Q&As), 124 guidelines have been translated into Chinese and are available on the CDE website.

1,166 innovative chemical drug applications (1,134 Category I INDs and 32 NDAs) belonging to 508 products, as one product may have different strength or dosage form, or different clinical trial applications. As revealed in the 2021 CDE annual report, there is a significant increase in regulatory applications with 35% in IND, 68% in NDAs, and 82% in Abbreviated New Drug Application (ANDA) compared to 2020.

Major CMC issues are identified for generic products, including:

- There were serious defects in CMC, which cannot prove controllability for product quality.
- Proof for quality consistency between a generic and its reference drug was not established.
- Drugs used in different development stages, meaning that CMC variations were not comparable.
- Stability result and selection of starting materials for API did not meet technical requirements.
- Sourcing of APIs are not coming from validated supplier.
- Sample testing results were out of specification or analytical methods had serious deficiencies.

Adaption of ICH Guidelines

China officially joined the ICH in June 2017. As of March 2023, 59 of 63 ICH guidelines in safety (S), efficacy (E), quality (Q), and multidiscipline (M) have been formally adopted. Among 151 ICH guidelines (including annexes and Q&As), 124 guidelines have been translated into Chinese and are available on the CDE website.

For the quality series of guidelines, 17 ICH guidelines have been implemented in China, except for the following three guidance documents:

- Q4B Pharmacopoeias
- Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products
- Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

It is noted that Chinese Pharmacopoeia Committee has already put pharmacopoeia alignment with ICH as one of its top priorities.

CHALLENGES AND SOLUTION

Chinese Pharmacopoeia

Different requirements by different pharmacopoeia are always an issue for global development. For example, because ICH Q4B [13] and Q6B [13] are not implemented in China, some test method differences (e.g., microbial enumeration tests, bacterial endotoxins test, and abnormal toxicity test) can pose issues for product registration in China. Moreover, differences in pharmacopoeia become critical under new registration regulation, which suggests that all sponsors need to complete registration sample testing before NDA submission; alternatively, the registration sample testing will be initiated by the CDE, which will make the registration process more unpredictable.

The sample testing issue may cause significant delays for the NDA approval. To deal with this issue, a CMC team should have a good understanding of Chinese Pharmacopoeia and relevant guidelines, which will assure that product specification meets the specific China registration requirements. This kind of challenge has been acknowledged by the health authority. The CPC plans to take a stepwise approach to adopting ICH guideline requirements in Chinese Pharmacopoeia 2025 [14], including adopting ICH guidelines into general chapters of Chinese Pharmacopoeia; for example, adopting the ICH Q1 concept by revising the Chinese Pharmacopoeia stability general guidance; based on ICH Q3A [13] and Q3B [13], the Chinese Pharmacopoeia impurity analytical guidance has incorporated the reporting threshold, identification threshold, and qualification threshold concept, as well as the "Decision Tree for Identification and Qualification."

Preapproval Inspection

Another challenge for innovative small molecule product development in China arose from Article 34 in the new Drug Registration Regulation [3], which required, "After having completed studies including CMC, pharmacological and toxicological studies and drug clinical trials supporting the drug marketing registration, established the specification and completed commercial-scale manufacturing process validation and manufacture for drug registration inspection and testing, the applicant shall file a drug marketing authorization application and submit related study data as per application dossier requirements. The application shall be accepted when the application dossiers comply with requirements and pass the administrative check."

It will bring challenges to the pharmaceutical company, because "completed commercial-scale manufacturing process validation" before NDA/marketing authorization application (MAA) submission means early CMC investment with more uncertainty and sacrifice of the shelf life of the validation drug product batches.

Table 4: Regulatory classification of preventive biological products.

Regulatory category	Category explanations	Conditions
1	Innovative vaccines not approved in and outside China	1.1 Vaccines for the disease without effective prevention methods.
		1.2 Neoantigen forms developed based on marketed vaccines, such as new recombinant vaccines, new nucleic acid vaccines, and new conjugate vaccines prepared based on marketed polysaccharide vaccines.
		1.3 Vaccines containing neoadjuvants or neoadjuvant systems.
		1.4 Multicombined/polyvalent vaccines containing neoantigens or neoantigen forms.
2	Modified vaccines developed by modifying domestically or overseas approved vaccine products	2.1 Vaccines with obvious clinical advantages that are obtained by changing the antigen spectrum or type based on domestically or overseas marketed products.
		2.2 Vaccines with major technical improvements, including the improvements of the bacterial or viral strain/cell matrix/production process/dosage form of the vaccine.
		2.3 New multicombined/polyvalent vaccines composed of marketed for similar vaccines.
		2.4 Vaccines with obvious clinical advantages that are obtained by changing the administration route.
		2.5 Vaccines with obvious clinical advantages obtained by changing the immunizing dose or immune procedure.
		2.6 Vaccines with changed applicable populations.
3	Domestically or overseas approved vaccines	3.1 Overseas marketed manufacturing on oversea, domestically unmarketed vaccines to register for marketing.
		3.2 Overseas marketed and domestically unmarketed vaccines to register for domestic manufacturing and marketing.
		3.3 Domestically marketed vaccines.

It is not a major issue if the China NDA happens years later than another country or region, or if there is global simultaneous submission in multiple countries, including China. It will become a challenge if China is selected as the first country for the NDA. As a result, China-specific process validation requirements should be taken into consideration in a global CMC development plan.

BIOLOGICAL DRUG DEVELOPMENT

Definition and New Category of Biologics in China

In 2020, the NMPA [16] clarified the definition and classification of biological products as products that are manufactured from microorganisms, cells, animal- or human-derived tissues, body fluids, etc. as starting raw materials made by biological technologies, used for preventing, treating, and diagnosing human diseases. Biological products are further classified as three subgroups: preventive biological products, therapeutic biological products, and in vitro diagnostic reagents managed as biological products.

Preventive biological products are vaccines for human immunization to prevent and control the occurrence and prevalence of diseases, which are further divided as immunization program vaccines and non-immunization program vaccines (see Table 4). Therapeutic biological products are used for treating human diseases, including proteins, polypeptides, and their derivatives prepared from engineering cells (such as bacteria, yeast, and insect, plant, and mammalian cells) with different expression systems; C&GT products; allergen products; microecological products; biologically active products extracted from human or animal tissues or body fluids or prepared by fermentation (see Table 5).

In vitro diagnostic reagents that are biological products are regulated as therapeutic biological products, including in vitro diagnostic reagents used for blood source screening and radionuclide labeled in vitro diagnostic reagents.

It is noted that under the new regulatory classification system, a Class 1 new drug is defined as when the biologics license application (BLA)/NDA application is submitted in China and the product has not been marketed inside or outside China. Once the classification is determined, it will not be affected by product marketing authorization abroad. Therefore, this new registration classification system encourages simultaneous development and marketing authorization.

Table 5: Regulatory category of therapeutic biological products.

Regulatory Category	Category Explanations	Conditions
1	Innovative biological products not approved in and outside China	Domestically and overseas unmarketed biological products for therapeutic.
2	Modified biological products developed by modifying domestically or overseas approved biological products	2.1 Biological products with obvious clinical advantages that are obtained by optimizing the dosage form and administration route based on marketed products.
		2.2 Biological products with new indications that were not approved domestically and overseas and/or with changed applicable populations.
		2.3 New combination composed of marketed biological products.
		2.4 Biological products with major technical improvements made based on marketed products.
3	Domestically or overseas approved biological products	3.1 Overseas marketed and manufactured in oversea, domestically unmarketed biological products to register for marketing.
		3.2 Overseas marketed and domestically unmarketed biological products to register for domestic manufacturing and marketing.
		3.3 Biosimilar.
		3.4 Other biological products.

In 2022, the total acceptance number and approval number of NDAs for innovative drugs declined, but those corresponding numbers for biological products are on the rise, indicating the continued boom in the development of biological products in China [16].

Introduction to the Development of Biological Products in China

The CDE annual report [12] shows a boom in the regulatory applications for innovative biological products in China since 2017, reaching a peak in 2021 when CDE accepted 860 IND applications for biological products in 2021, up 48% from the previous year, including 643 IND applications for innovative biological products; and accepted 178 NDAs, up 41% from the previous year, including 23 NDAs for innovative biological products.

In 2021, the CDE recommended the approval of 764 IND applications for biological products, up 52.8% year from 2020, of which 449 were applications for anti-tumor indications. Applications for other indications included 44 for preventive vaccines, 41 for dermatology and ear, nose, and throat (ENT) medicines, 37 for anti-rheumatic and immunologic drugs, 35 for drugs acting on the endocrine system, 30 for anti-infective, and 29 for drugs for neurological diseases (see Figure 3).

In 2021, the CDE recommended the approval of 149 NDAs, up 67.4% year from 2020, of which 60 were applications for anti-tumor drugs, making up the majority. Applications for other indications included 26 drugs for hematologic disorders, 23 for drugs acting on the endocrine system, 14 for preventive vaccines, and eight for drugs for dermatology and five for sense organs (see Figure 4).

In 2022, the total acceptance number and approval number of NDAs for innovative drugs declined, but those corresponding numbers for biological products are on the rise, indicating the continued boom in the development of biological products in China [16].

IMPLEMENTATION OF ICH GUIDELINES AND HARMONIZATION OF OTHER RELATED REGULATIONS

Implementation of ICH Guidelines

As described previously, China has made significant progress in the implementation of and harmonization with ICH guidelines

Figure 3: Approved biological INDs: Statistics by indication.

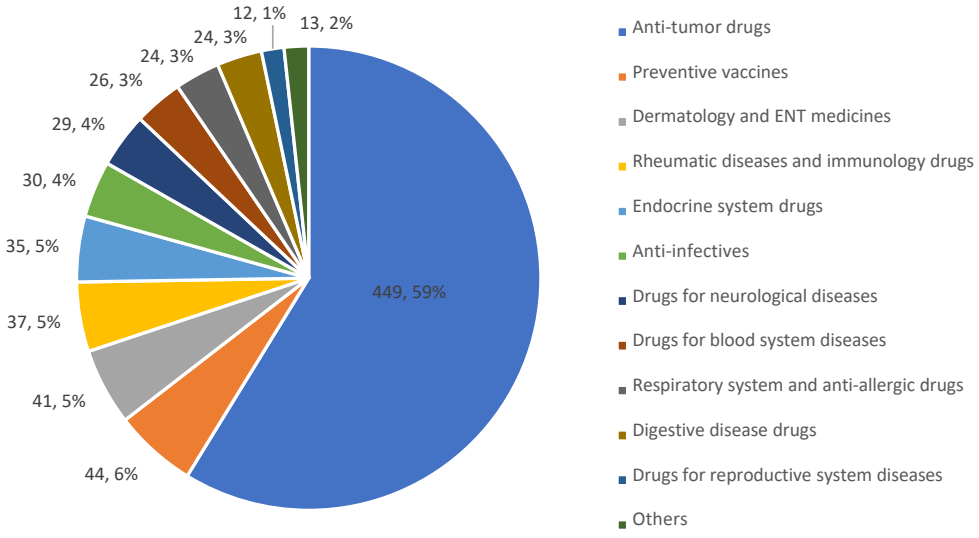
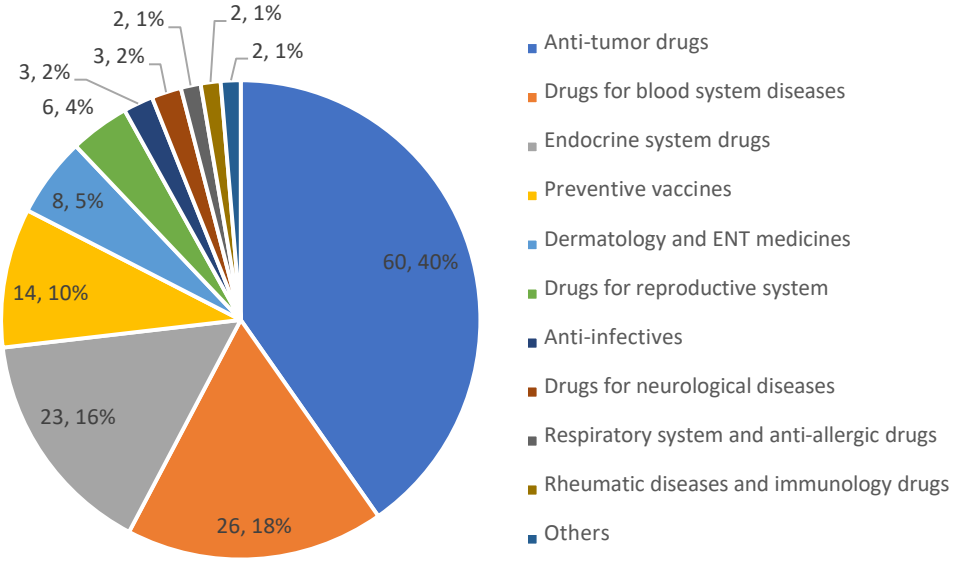


Figure 4: Approved BLAs: Statistics by indication.



over the past few years, and the ICH Q5 series of guidelines [13] related to biological products have all been implemented. For biological products with a global presence, the biggest challenge emanates from the harmonization of the Chinese Pharmacopoeia with ICH Q6B [13]. How to scientifically explore and justify what test items should be included in the release specification based on the principles of ICH Q6B guidelines is currently a major issue for the development and approval of biological products in China.

In addition, how to resolve the contradiction with the Chinese Pharmacopoeia is also an issue posed to the implementation of ICH Q6B. For example, the tests for host cell protein residues and host cell DNA residues should be performed as required by "General Monograph of Recombinant DNA Protein Products for

Human Use," "General Monograph of Recombinant Monoclonal Antibody Products for Human Use" and other monographs concerning recombinant products in Chinese Pharmacopoeia [17]. There are other issues for Chinese Pharmacopoeia to be harmonized with ICH guidelines, such as cell banks and viral safety with ICH guidelines Q5A, Q5B, and Q5D [13].

SPECIAL CONSIDERATIONS FOR VACCINES

Quality Control of Vaccines

In general, testing for abnormal toxicity is required in the Chinese Pharmacopoeia, and more stringent limits are specified for residual process impurities, such as inactivator, host cell protein and host cell DNA. Meanwhile, process validation and quality control are emphasized in the EU and US Pharmacopoeias, and some testing items (such as organic solvent residues and special immunities that can be effectively removed upon process validation) may be exempted; finished products may be exempt from some testing items (such as preservative content, residual solvent, protein impurities, and toxicity test) if intermediate products are qualified upon verification.

However, more emphasis is put on the final release testing for products in the Chinese Pharmacopoeia, and so there are more testing items for finished products than those defined in the European Pharmacopoeia (Ph. Eur.) and the US Pharmacopeia (USP). Finally, due to different identification methods, the requirement of the Chinese Pharmacopoeia for antigen content in vaccine products is higher than that of other pharmacopoeias.

Dossier Requirements for Vaccines

For vaccine clinical trial applications and marketing registration applications, dossiers should be prepared in accordance with ICH M4. The requirements for biological products in ICH M4 are mainly aimed for recombinant products. According to the characteristics of vaccines, there are more considerations regarding the CMC part of a dossier [15].

- If applicable, the data and information of virus used for production should be submitted in section 3.2.S.2.3.
- Verification reports of the batches of strains (virus) seeds used for production and the batches of cell matrix seeds used for production by the NIFDC or a third-party agency recognized by the drug regulatory agency should be provided in 3.2.S.2.3.
- For adjuvants, an overview of adjuvants should be submitted in 3.2.P; Comprehensive pharmaceutical research information should be submitted in 3.2.A.3, including raw materials, processes, quality attributes, testing methods, stability, etc.
- For the safety evaluation of exogenous factors, the target virus inactivation validation data should be submitted in 3.2.S.2.5. The validation data of removal/inactivation of non-target viruses should be submitted in the section 3.2.A.2.

Challenges

There are many challenges in the review and approval of biological products, with the biggest one perhaps from sample testing. According to the new Drug Registration Regulation [3], registration sample testing is not required in an application for clinical trials of biological product, but subject enrollment for clinical trials of a vaccine product should be initiated only after vaccine product meets registration sample testing. In terms of NDAs, all biological products are required to have three batches manufactured at commercial scale for registration sample testing, and the marketing approval may be granted after they pass the testing. It is undoubtedly a very challenging requirement for high-cost biological products, especially products for rare diseases.

Furthermore, attention should be paid to registration testing involved in supplemental applications for post-approval changes. As specified in the new Drug Registration Regulation [3], the decision to initiate registration testing for major post-approval changes should be made based on risk assessment. However, the published regulations and regulatory documents are not clear about what post-approval changes entail the initiation of registration testing or what risk assessment model a decision-making is based on.

Moreover, once registration testing is initiated, the review timeline for major post-approval changes will be extended from 60 to 200 working days [18]. Besides, the specific testing requirements are not clear, for example, sample size, batches, considerations for sample representativeness, and scope of the registration testing. It requires the applicant to discuss and reach an agreement with regulatory authorities on these issues in a timely manner, making post-marketing changes more difficult and uncertain.

In addition to sample testing associated with registration applications, imported biological products that have been granted marketing authorization are subject to import testing in compliance with the Administrative Measures for Import of Drugs [19] issued in 2003. The customs may release such import biological products upon passing the testing prescribed in the registration specification. This requirement also increases the cost of drugs and prolongs the lead time for supply.

Another challenge is related to the segmented manufacturing and MAH cross-border holding. MAH is a new concept introduced in China's regulatory framework in 2019. China health authorities are working on how to implement this concept to encourage innovation. There are many discussions about how the MAH can be held accountable for product quality, and segmented manufacturing is considered a high-risk practice.

Regarding the cross-border holding, at a practical level, the MAH, drug substance manufacturing site(s) and drug product manufacturing site(s) of imported biologics should all be located outside China. For example, except for insulins, it is not acceptable to ship drug substance to China and have drug product manufactured by a local factory, even if that factory is a member of the MAH group. Obviously, this is a big limitation for multinational corporations with global manufacturing networks and supply chains. However, given that the MAH system is still in its infancy in China, it is understandable that regulatory authorities still need to explore the most suitable management approach.

Table 6: Guidelines related to C&GT in China.

	Guideline	CMC	Nonclinical	Clinical	GMP
1	Guidance for Clinical Trial Design of Gene Therapy for Hemophilia			x	
2	Guidance for Clinical Trials of Immune Cell Therapy Products (Trial Version)			x	
3	Guidance for Clinical Risk Management Plan for Marketing Authorization Application of Chimeric Antigen Receptor T Cells (CAR-T) Therapy Products			x	
4	Guidance for Long-Term Follow-Up Clinical Studies of Gene Therapy Products (Trial Version)			x	
5	Guidance for Nonclinical Studies of Gene Modified Cell Therapy Products (Trial Version)		x		
6	Guidance for Nonclinical Studies and Evaluation of Gene Therapy Products (Trial Version)		x		
7	Guidance for Research and Evaluation of Cell Therapy Products (Trial Version)	x	x	x	
8	Guidance for CMC Research and Evaluation of Immune Cell Therapy Products (Trial Version)	x			
9	Guidance for CMC Research and Evaluation of In Vivo Gene Therapy Products (Trial Version)	x			
10	Guidance for CMC Research and Evaluation of In Vitro Gene Modified Systems (Trial Version)	x			
11	Guidance for Cell Therapy Product GMP				x
12	Guidelines for CMC Research and Evaluation of Human Stem Cell Products (Trial)	x			
13	Guidelines for Clinical Trials of Tumor Active immunotherapy Products (Trial)			x	
14	Guidelines for CMC Research and Evaluation of Oncolytic Virus Products (Trial)	x			
15	Guidelines for Clinical Trials of human stem cells and their Derived cell Therapeutic Products (Trial)			x	

Regulatory Framework for C&GT Products in China

In China, C&GT products are classified and regulated under the umbrella of biological products. Unlike the FDA Office of Therapeutic Products (OTP) or the EMA Committee for Advanced Therapies, the CDE does not have an integrated and special office or committee to provide oversight of the quality, safety, and efficacy. Instead, this is assessed by pre-clinical, biological CMC, clinical, and biostatistics and clinical pharmacology departments within CDE.

The novel and diverse nature of C&GT products has resulted in evolving regulatory activities specified to support these products. In the past three years, guidance documents addressing CMC, nonclinical, clinical, and GMP for C&GT were drafted and published by China authority (see Table 6). The list of guidelines initially constructed regulatory and technical requirements and is still growing.

As for the supervision of a clinical trial of C&GT products, China has two main regulatory authorities that are independent agencies with distinct roles—the NMPA/CDE, which supervises the clinical trial for registration purpose, and the NHC, which supervises the investigator initiated trial (IIT) for exploratory research purpose of new medical technology. IIT is mainly reviewed and approved by hospital's ethics board and requires less CMC and nonclinical data than a CTA at NMPA/CDE. IIT pathway provides an opportunity for the sponsor to look at the efficacy and safety potential of their innovative C&GT designs before they invest more resources on CMC and nonclinical studies.

Considering C&GT is so innovative that regulatory framework is not as mature as small molecular and large molecular drugs, sponsors can obtain a preliminary informal non-binding consultation with CDE through the pre-pre-IND meeting prior to a pre-IND meeting.

Summary of C&GT China Regulatory Status

The regulatory framework governing C&GT products can pose a large degree of complexity for developers. In addition, in comparison to more traditional biopharmaceutical products, the field is relatively immature. Therefore, both development efforts and regulatory guidelines are evolving. CDE provides a range of opportunities for developers to meet, discuss, and gain clarification on various aspects of the C&GT product development process, including topics relating to early phases of development, CMC, and clinical trials.

In addition, references specific to C&GT products are starting to be addressed within the ICH [20]. Materials developed and released by the ICH will provide guidance on a more general level

and can be referenced as development progresses. Furthermore, CDE offers a number of expedited regulatory pathways to support and facilitate the innovation and therapeutic value promised by C&GT products. As the C&GT field continues to mature, it is expected that the corresponding regulatory structures and systems will continue to gain knowledge and experience from accumulated data, which will, in turn, allow both developers and regulators to move forward to ensure that patients are given access to the safest and most efficacious products possible.

CONCLUSION

The regulatory reform launched in 2015 has brought profound changes to the pharmaceutical industry in China and facilitated the adoption of ICH guidelines. As a result, innovative drug development has flourished in recent years, as evidenced by a significant number of small molecule biologics and C&GT products that have entered clinical development or gained marketing authorization in China. Nevertheless, technical or regulatory challenges present in pharmacopoeia, process validation, sample testing, or MAH should be overcome to support sustained drug development and patient accessibility. However, we are confident that through dialogue, the regulatory authorities and the industry can work together to address those issues as the China regulatory system continues to evolve in alignment with ICH.

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DIGITAL DISPLAY LABELING in Clinical Supplies for Clinical Trials

By Members of the Clinical Supply Leadership Forum (CSLF) Digital Display Label Community of Practice

Digital display labels (DDLs) offer an alternative solution to eliminate manual relabeling in the clinical supply chain, optimizing label content updates through a simple, system-controlled approach while providing new, uncharted opportunities. With increased efficiency in making regulatory-compliant changes and enhanced flexibility in the clinical supply chain, DDL technology has the potential to revolutionize drug development and to increase and expedite patient access to therapies.

This article introduces a groundbreaking solution known as DDLs which have the potential to revolutionize the labeling process in the clinical supply chain for the pharmaceutical industry. Furthermore, this article advocates for industrywide alignment in adopting this solution, harmonizing its implementation, and collaborating with regulatory bodies to optimize its use in various scenarios for the ultimate benefit of patients.

THE NEED TO MODERNIZE THE SUPPLY CHAIN

As global focus on patient safety and accessible information increases, along with the need to address drug shortages and promote diversity, equity, and inclusion in the healthcare industry, there is a growing demand for the digitization of the clinical supply chain and the utilization of real-time data. The pharmaceutical industry recognizes the importance of leveraging innovative technology to streamline and expedite the development of new medicines.

However, with the rapid pace of new drug development, it is vital to modernize current clinical supply chain operations to reduce lead times and resource requirements, enhance flexibility, and minimize waste. The digitalization and streamlining of clinical supply chains will work to achieve these goals, which provides an opportunity for increased access and reduced burden for the patient.

A DDL is an electronic component with an e-paper display of the required label information, which replaces the traditional paper label on investigational medicinal products (IMPs) used in clinical trials. This digital solution enables the clinical supply chain (global clinical supplies, vendors, depots, and clinical sites) to eliminate manual relabeling. It also allows for easy and on-demand updates of label content and other information to patients and their caregivers, as well as clinical study personnel.

Although DDLs have been widely used in other industries for many years, this technology is projected to become more prevalent in the pharmaceutical industry, specifically during the execution of clinical trials. Key stakeholders such as patients, clinical study personnel, sponsors, and health authorities will benefit from the digitalization and clinical supply chain innovation, which will provide opportunities to improve patient access, safety, and the clinical trial experience.

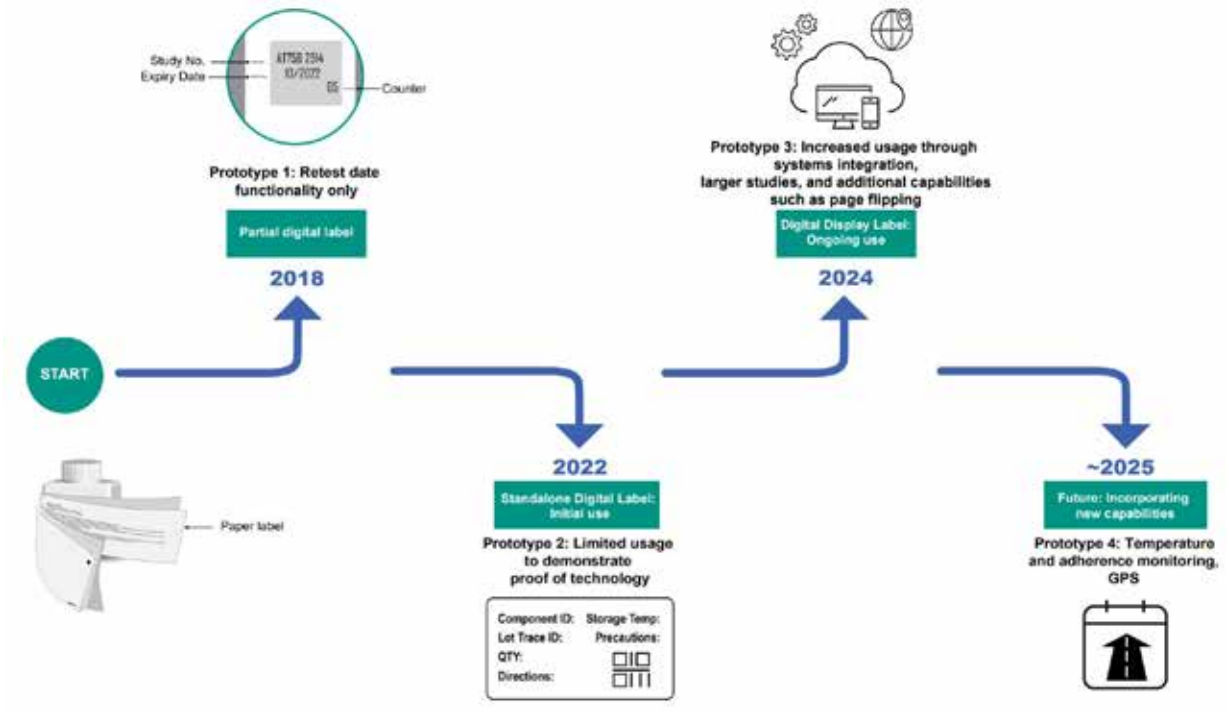
TRANSFORMING THE IMPS LABEL

As highlighted by a 2018 *Pharmaceutical Engineering*® feature, digital labels have been used in sectors outside of the pharmaceutical industry for over 40 years [1]. Leveraging this technology to label investigational clinical supplies for clinical trials is a novel application. DDL in clinical supply has been in development and has undergone several prototypes, which is shown in Figure 1.

Prototype 1

In 2018, the "partial digital label" was created as prototype 1, featuring a digital expiry/retest date but with most of the clinical label content remaining static on a traditional booklet label. The

Figure 1: Transforming the IMPs label: A case study [2].



digital functionality provided an opportunity to efficiently update clinical labels with a retest date, making use of near-field communication (NFC) technology. To evaluate the technology and eliminate regulatory conflicts, a US-only pilot was conducted with prototype 1. This pilot included two expiry extension updates in different settings, one in a nonclinical setting and the other at a clinical trial site. The pilot demonstrated the value of leveraging this technology to perform a label update, significantly reducing the lead time from months to one day [1].

Prototype 2

Lessons learned from prototype 1 enabled further innovation and opportunity, resulting in prototype 2, the "standalone digital label." The standalone digital label included a select number of clinical label aspects: component identification number (CID), lot trace ID, quantity, and directions (administration of IMP, storage temperature, and precautions). However, this label was supported by a restricted, standalone system, which limited the software functionality and potential to scale and industrialize the solution. This solution has been tested in a nonclinical environment.

Prototype 3

Prototype 3 reached complete digital content capability by allowing full control over the digital display in text or image format through a company enterprise resource planning (ERP) system. In addition, capabilities such as paging (multipage labels) and using parent-child connected label updates (multilevel labels) were added to dramatically increase the amount and synchronization of information to be stored and displayed on the digital label. Further developments in software functionality are aimed at integration with third-party supply chain management systems to enable scalability.

Prototype 4

There is now an aspiration to evolve to prototype 4, or the "smart pack." As a platform solution, prototype 4 could potentially enable the integration of temperature monitoring, as well as tracking and traceability of clinical supplies, while also providing opportunities to leverage digital technologies such as adherence monitoring via smart phones.

In the future, as DDL technology continues to advance, it will be beneficial to expand the content agility of the label and to broaden its physical capabilities. Furthermore, it is advantageous to address the overall environmental impact of introducing electronics into the pharmaceutical industry. This can be achieved through further developments that minimize the environmental impact of DDLs at the component level.

Additionally, to fully optimize the potential of DDLs, systems supporting clinical supply chains can be integrated with DDL update capabilities across their current reach. This means expanding the use of DDLs beyond traditional healthcare facilities and exploring new locations such as patient homes. This

integration can enhance the efficiency and effectiveness of the clinical supply chain, while improving the patient experience by reducing clinical trial burden and increasing access to real-time information.

CLINICAL LABEL REGULATORY LANDSCAPE

IMP labels are a regulatory requirement, but labels also play a critical role in providing clinical trial participants, caregivers, and investigators with the information needed for safe and compliant use of the investigational product. Universal guidance on labels used for IMPs in clinical trials has not been established globally.

Regulatory requirements for clinical supply labels vary from region to region. A typical IMP label may require as many as 19 different regulatory elements [3]. Some requirements shared by several regions include, but are not limited to, drug name, batch or lot number, storage conditions, country-specific language, and a unique "for clinical trial use" phrase (e.g., in the US, the following CFR statement must be included: "Caution: New Drug - Limited by Federal (or United States) law to investigational use" [4]).

Clinical supply labels may also have additional country requirements, depending on the therapeutic modality being investigated. For radioligand therapy and cell and gene therapy trials, the label must bear radioactive symbols, cryogenic symbols, and special cautions ("contains genetically modified organism," "autologous use only," etc.). For personalized medicines, the label may need to include patient-specific information.

DIGITAL LABEL INNOVATIONS ACROSS THE LANDSCAPE

Digital innovation to streamline labeling and supply chain operations has gained interest in both the clinical and commercial space. For commercial products, information can be accessed digitally through the use of a quick response (QR) code and an external device (e.g., smartphone). This can provide health care professionals with the most up-to-date prescribing information (e.g., medication guides, package inserts) as well as with live media content, such as videos.

In the clinical space, the concept of an e-label to simplify labeling of IMPs was explored. The solution proposed for the universal paper label would include a simplified, language-agnostic printed label conveying minimal information needed for identification, safety, and dispensing. It would direct the user to the e-label/QR code for the remaining details, which would be accessible through an electronic device.

One of the challenges companies faced when engaging with health authorities to deploy the e-label concept was the reduction in content on the IMP paper label not complying with existing regulations, which require text to be visible and human readable on the label. The e-label solution relies on technology to access this information, and health authorities felt that it was not currently universally accessible and, therefore, could result in noncompliance with regulations [3].

In contrast, the DDL displays all required content on the digital IMP label itself as human readable text, ensuring compliance with the regulatory requirements without the need for additional technology, devices, or QR codes to access the regulatory content of the label. Any QR code or additional device available would be intended to augment and enhance the user experience and supplement the compliant content currently displayed on the label, rather than replace it.

PAPER LABEL CHALLENGES

Alongside the limitation of paper labels being updated at clinical sites, the restricted space available on small units, like vials or syringes, leads to font sizes that are not easily readable. Additionally, the use of lengthy, multipage booklets makes it challenging to search for specific information [5]. New technology and approaches provide an opportunity to improve the clinical trial experience for patients.

The utilization of paper clinical labels can pose limitations on effective management of clinical supplies. Content on paper labels is static, in contrast to the dynamic nature of clinical development. Developing, printing, and applying paper labels is labor intensive and long lead times limit flexibility when study designs evolve.

Paper clinical labels can require significant lead time to create and apply, whereas much of the study design continuously evolves, e.g., clinical timelines, study design, drug delivery, expiry date, retest date. This requires significant agility to ensure clinical label updates are implemented at least four weeks prior to packaging and labeling operations.

Additionally, the need for relabeling to update shelf life presents a particular challenge in supply management. Relabeling must be executed in facilities qualified for manually adding labels or reworking the finished package. This process results in increased waste and poses risks to the supply chain, because units must be periodically removed to undergo physical relabeling, which can compromise the label content and is not inherently traceable.

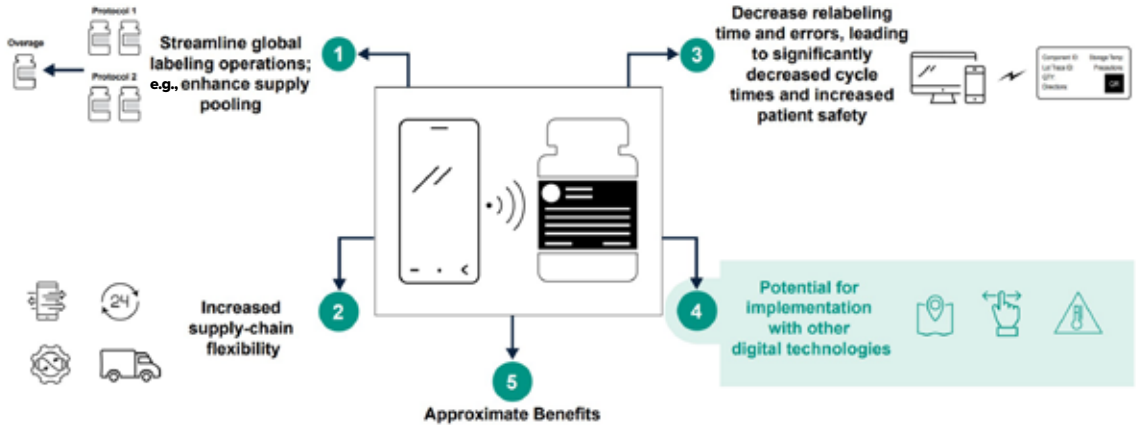
All of these challenges are a barrier to achieving operational efficiency, due to significant relabeling work of early expiring supplies, and hinder efforts toward waste reduction, due to impractical label changes. Paper clinical labels limit the ability to efficiently manage supply inventory, resulting in delays and reduced patient access and presenting a barrier to achieving waste reduction.

DDLS AS THE SOLUTION

Due to their dynamic nature, DDLs have the potential to add efficiencies to clinical supply chains and benefit key stakeholders, including patients, clinical study personnel, and health authorities. DDLs provide flexibility and increased agility within the clinical supply chain, improving and optimizing labeling and distribution operations. This can ultimately reduce the risk of delays and shortages and, thus, increase the assurance for patient access.

DDLs also present opportunities to enhance diversity, equity, and inclusion in clinical trials by tailoring the clinical supply label to the patient's preferred language. With DDL, it becomes possible

Figure 2: Potential benefits of the DDL in clinical supplies [2].



to easily customize the label at the site to display information in the language most comfortable for the patient.

This flexibility allows for seamless language changes based on patient preferences, ensuring clarity and understanding throughout the trial. By reducing the need for multilingual booklet labels or country-specific IMPs, the DDL also contributes to a reduction in waste, aligning with sustainability goals and promoting environmentally friendly practices. Overall, the DDL's ability to tailor the label to patients' preferred languages fosters inclusivity and offers an efficient and ecofriendly solution.

The fluidity of the DDL provides more real estate to increase information, which addresses patients' needs. For example, prototype 3 (see Figure 1) has a page-flipping capability to dramatically increase the amount and synchronization of information to be stored and displayed on the digital label. This provides the ability to adjust font size, provide additional information (e.g., specific notes from the clinical site), and add universal icons, which are easily recognized by the patient, to supplement directions for use or storage conditions: for example, a sunrise to denote AM, a moon to denote PM, or a snowflake to denote the need to refrigerate. This increases patient safety and adherence, and clinical site efficiency.

Prior to implementation, ensuring the accessibility and legibility of information presented on the DDLs is paramount. Keeping the user and use environment in mind throughout development, stakeholder feedback has been elicited from a variety of users, such as patients and clinical study personnel (e.g., pharmacists, nurses) across various settings (e.g., the patient's home, clinical and sponsor sites).

For prototype 2 (as shown in Figure 1), a legibility study was conducted on a diverse, small patient population and compared the DDLs to conventional paper label controls in both bright and dimly lit room conditions. The DDL performed similarly compared to a traditional paper label, and these outcomes serve as a foundation for further improving DDL technologies, while also highlighting the safety and effectiveness of DDLs as a viable alternative to paper labels. Additional legibility studies will be conducted iteratively as design changes occur, to ensure the readability and safety of DDLs.

INPUT ON LABEL DESIGN

Patients and Caregivers

The feedback and studies aim to gather input from patients and caregivers who will be directly impacted by and interact with the DDL. They have been conducted specifically to obtain insights on the design of label content and various features of the DDL. By incorporating these inputs, the DDL can be carefully crafted with a patient-centric approach in mind, while ensuring no additional risks are introduced such as impacting health care personnel's ability to reconstitute or administer.

The aim is to develop features that optimize the clinical trial experience for patients and alleviate any burdens they may encounter. It is anticipated that the patient insight and pharmacist and nurse studies will be completed by the end of the first quarter of 2024.

Clinical Personnel

To ensure the design of the DDL does not introduce risk or administrative burden to clinical study personnel at clinical sites, initial assessments have been conducted at three different clinical settings located in the northeast region of the US. The feedback received was positive overall, with additional considerations to ensure success in these settings. These assessments will continue to be conducted to ensure input collected represents diverse geographical perspectives from different clinical site settings and patient care populations, as well as to capture differences in procedures and operations.

The use of DDLs enhances flexibility within the supply chain. Traditionally, changes in study design or protocols could have significant implications on the labeling and distribution of clinical supplies. Using the DDL, label modifications such as updating the IMPs reevaluation date (RED) (expiry date) can be made without

Figure 3: Operational efficiencies achieved with DDL.

manual relabeling, which reduces the risk of label inconsistences and errors, eliminates labor-intensive steps, and reduces administrative burden.

The DDL enhances supply pooling opportunities. Drug supply pooling is a method where clinical goods are centrally supplied and can be used for multiple protocols. Pooling moves the clinical supply chain from material- and labor-intensive protocol-specific packaging and labeling to a protocol-agnostic supply chain with reduced impact to the clinical site operations.

Leveraging just-in-time (JIT) labeling, the IMP can be labeled with the assigned protocol number just before it is needed. However, JIT labeling can be further streamlined with DDLs by simply updating the digital label to reflect the assigned protocol number or any other country-specific information, eliminating the need for manual labeling.

DDLs offer the flexibility to adapt and adjust more seamlessly, accommodating evolving study requirements and timelines. This increased agility in the supply chain contributes to faster drug development and facilitates quicker patient access to potentially life-saving treatments.

A notable advantage of DDLs is their ability to facilitate documented changes efficiently and in a manner that complies with regulatory requirements. A technical prerequisite for any use case is effective system integration. The initial placement or update of the label content is monitored, executed, and controlled remotely via the ERP IT-controlled environment, which captures and documents changes and therefore does not require a qualified packaging facility.

The content on the label can be "written" on the digital display via NFC technology. Finished product can be rereleased in real time after updating via NFC technology. Executing label updates through a system-controlled approach saves on lead times, expediting supply operations from weeks to a matter of days.

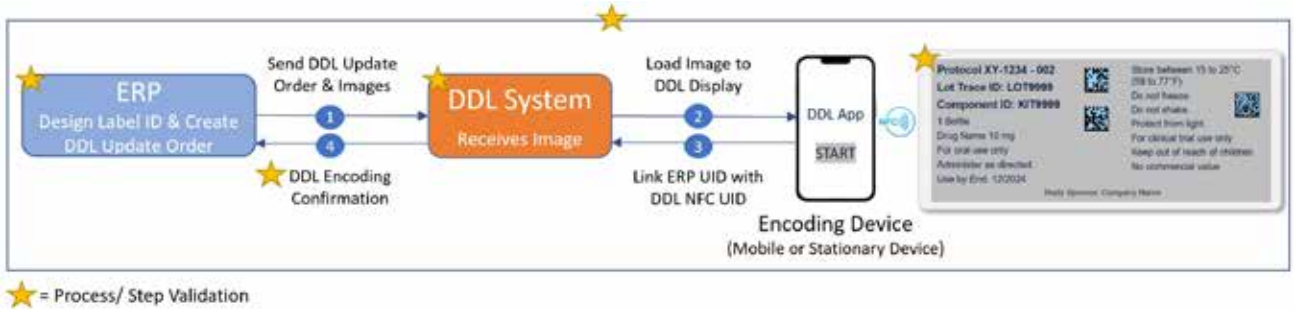
This estimated reduction is extremely beneficial when considering the supply planning for products which have a very short shelf life (e.g., radioligand therapy molecules have a shelf life of 72 hours). More DDL benefits will be presented as part of future publications. Figure 3 demonstrates how leveraging DDLs streamlines RED label updates to significantly reduce cycle times.

Looking ahead, the versatility of DDLs offers promising opportunities for further enhancing patient safety, adherence, and holistic patient care. As one example, including tracking mechanisms can enable temperature monitoring and geolocation. Integrating DDLs with other innovative technologies, such as smart packaging, allows for a shift from independent technologies to a comprehensive digital platform solution.

For instance, combining DDLs with smart dosing technologies can improve medication adherence by accurately tracking and monitoring medication adherence. Continuous patient monitoring through digital biomarkers and using digital platforms for patient engagement are also potential areas of integration with DDLs [6].

By integrating DDLs with a digital platform, various patient-centric features can be incorporated. This includes personalized patient experiences by capturing and displaying specific information such as visit schedules, appointment and dosing reminders, patient diaries to record symptoms and adverse effects, motivational messages to encourage therapy continuation, timely communication of critical safety updates, and enabling direct communication between patients and clinical sites through two-way communication channels. It is important to note that the development of such integrated technology is

Figure 4: How text is updated, displayed, and validated on the digital label.



subject to additional regulatory requirements and product classification considerations.

Overall, the adaptability of DDLs opens exciting possibilities for transformational advancements that prioritize patient safety, adherence, and comprehensive patient care by integrating with other digital technologies as a platform solution.

TECHNOLOGY BACKGROUND

To ensure reliable performance of the DDL, the development and implementation of hardware requirements should be rolled out in a phased-approach: for example, starting with a minimum viable product (MVP) that undergoes robust testing and hardware and software validation before development and implementation of commercial and reusable products. Considerations for a robust implementation strategy include addressing interoperability upfront, integrating existing standards, such as GS1 [7]. A target MVP should consider the following capabilities and attributes (not all-encompassing).

Package Types for DDL Integration

Consider the product portfolio and select the most prominent product formulation and primary packaging container (solutions for injection contained in a 2-mL vial, tablets that are packaged in a bottle, blister wallet, a combination product that is provided as a kit enclosed in a carton, etc.)

Image and Display Capabilities

How will the resolution and quality compare to traditional paper labels? How many and which languages need to be displayed? Consider local coding and serialization regulatory requirements such as barcoding, standards that the country follows or accepts (e.g., GS1, Health Industry Business Communications Council, International Council for Commonality in Blood Banking Automation), requirements for including ISO symbols on the product, etc.

CHALLENGES TO ADOPTION AND IMPLEMENTATION

Adoption of new technology is inherently challenging, especially in a highly regulated industry. This requires socialization and collaboration across industry and with regulatory bodies to further enhance development and optimize use cases for the ultimate benefit of patients.

Investment

Like any new technology, the initial investment required for adopting and implementing DDLs is higher compared to traditional paper labels. This is due to the need for additional hardware and software, as well as the establishment of operational infrastructure. However, as the technology gains widespread adoption across the pharmaceutical industry, the increased demand and established infrastructure will eventually lead to cost reductions.

Failures

Although there is the potential for breakage of the DDL, paper labels are also prone to failures such as the ink fading, flaking off, or the label itself falling off. The key is understanding such risks through testing in various conditions, addressing risks, and validating the integrity of the label to provide a higher level of confidence in its use.

Waste

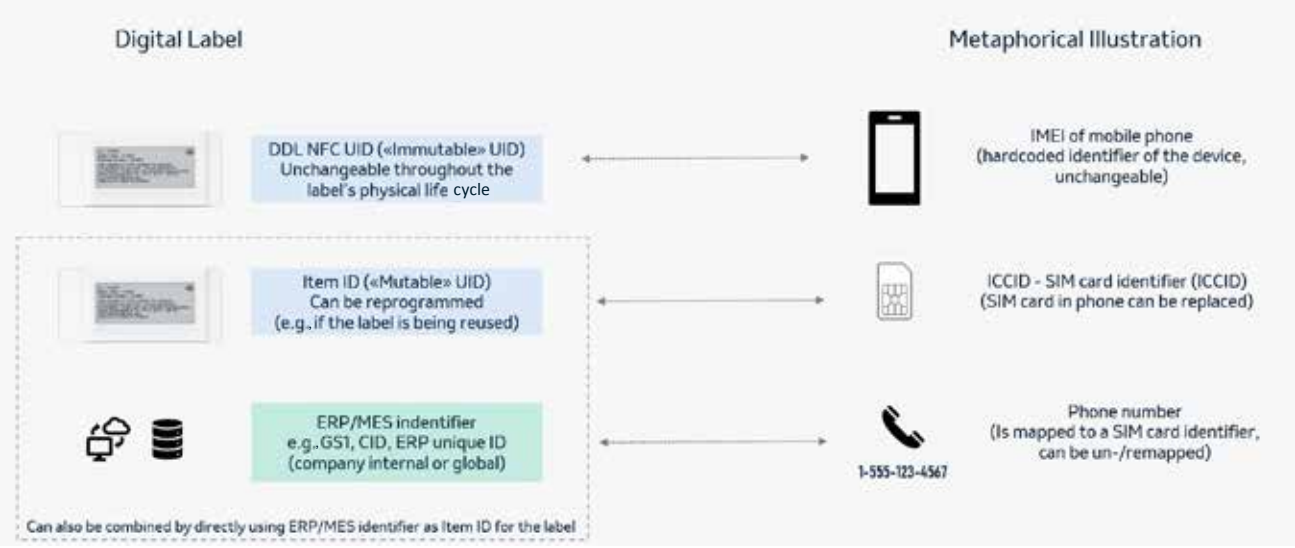
Although aiming for a sustainable solution, implementation of a global approach for the collection, reprocessing, and reissuance of DDLs to enable reuse of the technology can be challenging.

SOFTWARE AND SYSTEM INTEGRATION REQUIREMENTS

The steps to creating a label remain the same, whether the label is displayed on the DDL or printed on paper. For DDL, there is communication between the ERP system, where the DDL image is generated, and the DDL system, where the image is loaded and then displayed on the digital label (shown in Figure 4). Validation ensures that the DDL is secure, and final release of the approved digital label text is performed per normal label release procedures.

Any digital label solution will require mapping of unique identifiers (of the digital label and the data source). It will also require verifying that the DDL system is GxP validated and Part 11 compliant; the label always displays correct image for user

Figure 5: Mapping of unique identifiers.



ICCID: Integrated circuit card identification; IMEI: International mobile equipment identity; MES: Manufacturing execution system

acceptance testing (UAT); and that during the label image update, positive encoding confirms DDL was updated correctly. Figure 5 gives an illustration for such identifiers using a mobile phone as a metaphor in this example.

In more centralized system landscapes, this could consist of only two levels by writing the ERP/MES identifier as "mutable" unique identification number (UID) to the label and directly mapping the source to the label. In more complex environments (e.g., if there were parallel data source systems), there may be a need to have a third level in between, hence mapping the ERP/MES ID to this item ID in the source system(s), and the item ID to the NFC UID in the digital label system.

It is probably sensible to distinguish use cases between the two perspectives of the source system and the digital label system. The standard use cases to be implemented in the digital label system are relatively few (initial load, update, scrapping individual units, recycle the label), potentially with some additional functions to handle exceptions. From a source system(s) perspective, the use cases (triggers) may be a lot more versatile, but usually result in one of the standard use cases at the digital label system end. While in development, the goal is to have the DDL system available as a commercial off-the-shelf software, compatible across computer systems.

CONCLUSION

Although DDLs offer a wide range of benefits to patients, clinical trial personnel, sponsors, and health authorities, certain challenges must be addressed to realize the full benefits. These challenges include obtaining industry and regulatory acceptability, upfront investment costs, and implementing a global approach for reuse.

With increased efficiency in making regulatory-compliant changes and enhanced flexibility in the clinical supply chain, DDL technology has the potential to revolutionize drug development and to increase and expedite patient access to therapies. The transformative capabilities of DDLs, with opportunities for integration with other digital technologies to deliver a platform solution, pave the way for more efficient and patient-centered clinical trials in the future.

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Acknowledgments

The **Clinical Supply Leadership Forum (CSLF)** is a pharmaceutical industry global advisory group that is committed to providing leadership and strategic direction through the establishment of an open discussion on precompetitive critical technical issues and challenges; identifying opportunities for alignment, innovation, and promoting consistency; and seeking worldwide harmonization, where applicable.

The **Digital Display Label Community of Practice (DDL CoP),** as part of the CSLF, is dedicated to harmonizing the industry application of DDL for clinical supply, creating benefits for patients, health authorities, clinical sites, and sponsors.

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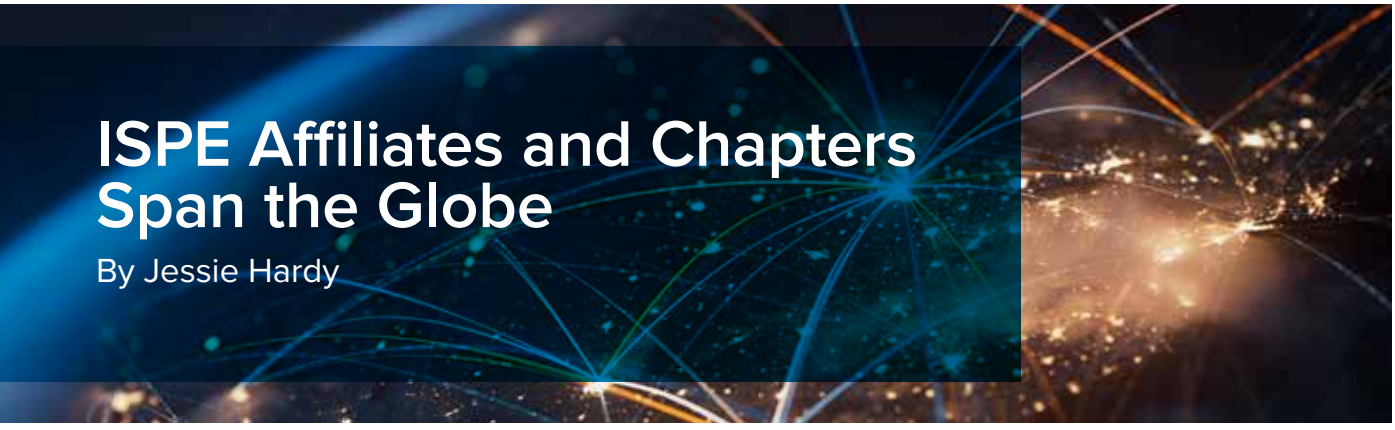

ISPE Affiliates and Chapters Span the Globe

By Jessie Hardy

ISPE has more than 21,000 members in more than 120 countries worldwide. As an ISPE member, you have access to this network, which can be exciting and overwhelming at the same time. Connecting at the local level unlocks the unique benefits that your local Affiliate or Chapter holds. Not only is this a career game changer, but it also opens doors of opportunity to experience your ISPE membership like you never dreamed possible.

As part of the ISPE membership process, you can join one of the 40 Affiliates and Chapters from around the world. It's the perfect way to gain lifelong experiences as an ISPE member and to get involved as a volunteer. There are various volunteer opportunities to choose from with each Affiliate and Chapter. Many Affiliates and Chapters also have openings for Chairs or Directors that lead other important committees, such as Students, Emerging Leaders, Events, Programming, and Women in Pharma®.

Affiliates and Chapters host various activities and events locally. This includes a variety of educational and networking opportunities that may be hosted in person or virtually. They also organize many activities for local Emerging Leaders and Women in Pharma.

Here are some fun facts about ISPE Affiliates and Chapters.

LEADERSHIP

- Each Affiliate and Chapter is governed by its local Board of Directors, which consists of a President or Chair, a Vice President, a Treasurer, and a Secretary.
- Affiliates and Chapters are governed by the same ISPE Charter that sets the operational framework. The only difference is that it is called a Chapter if it is within the US and an Affiliate if it is outside the US.
- Affiliates and Chapters provide leadership opportunities for members to get involved locally and to gain exposure internationally by working with the ISPE International Team.

LOCATIONS

- The newest US Chapter is the ISPE Southwest Chapter, which includes Arizona, Nevada, and New Mexico.
- The largest Chapter in North America is the ISPE Boston Chapter. In Europe, the largest Affiliate is the ISPE Germany/Austria/Switzerland (D/A/CH) Affiliate, and in Asia-Pacific, the largest Affiliate is the ISPE Japan Affiliate.

MEMBERSHIP AND GROWTH

- You can change your Affiliate or Chapter at any time by logging in to your account from the ISPE website.
- The Affiliate/Chapter Growth Fund provides funding for projects put forth by local Affiliates and Chapters. In 2022–2023, ISPE awarded US $122,921 in funding for 38 projects to support 18 Affiliates and Chapters.
- Each ISPE Student Chapter is sponsored by its local ISPE Affiliate or Chapter, which provides valuable support in the form of Industry Advisors to mentor students.

CONNECTION

- Each Affiliate and Chapter has a Board Liaison from the ISPE International Board of Directors.
- Each Affiliate and Chapter has their own website that details their events and other relevant information.
- You can follow your favorite ISPE Affiliates or Chapters on social media. Most have LinkedIn pages, and you can also find them on Facebook and Instagram.

You can learn more at https://ispe.org/membership/affiliates-chapters

Share your favorite Affiliate or Chapter memories and experiences with us. We look forward to hearing about your experiences getting involved locally.

Jessie Hardy is Senior Director of Membership and Chapter Relations at ISPE.

Ireland Affiliate Creates Opportunities for Members

By Marcy Sanford

Last year at the ISPE Annual Meeting & Expo, the Ireland Affiliate received the ISPE International Honor Award for Affiliate and Chapter Excellence. The award recognizes the outstanding work of the International Affiliates and Chapters as reflected by membership development and services, management, industry and society support, and innovation.

"The ISPE Ireland Affiliate won for their outstanding achievement in membership growth while increasing engagement through innovative approaches focusing on the needs of the local members. Events included a balance of educational and networking opportunities," said Tom Hartman, President and CEO of ISPE.

"They also focus on developing the workforce of the future and strengthening links and partnerships with regulators, special interest groups, and scientific bodies. They have proven success with their focus on the workplace of the future by connecting with students and Emerging Leaders (EL)."

Last year, the ISPE Ireland Affiliate grew their membership by almost 15%, had a strong focus on supporting students and Emerging Leaders, started a podcast series, established new groups and committees based on member interest, and actively engaged with regulators and vendors. It did this all while hosting more than 20 events covering a variety of topics and establishing a plan for continued success.

SUPPORTING STUDENTS

"We are committed to developing the workplace of the future by connecting with our students and Emerging Leaders," said Ireland Affiliate Board President Philip M. Gammell, Associate Director of Engineering, Astellas Pharma Inc. "Key to this is the development of Student Chapters and the introduction of the EduHub concept." At EduHub events, an industry leader provides a career talk and interactive demonstrations of technologies being used and developed in the life sciences sector which provides content for academic courses that reflect industry needs.

"Our aim is to have a Student Chapter in every third-level institution in Ireland. For each Student Chapter, an EL is assigned to support and mentor it. Typically, this will be the alma mater of the EL, so they will be giving back to their academic institution to support and mentor the students, who will become the future Emerging Leaders."

So far, Technological University Dublin, University College Cork, Munster Technological University, and Atlantic Technological University have all committed to building their student involvement with ISPE. Since 2021, each university student group has held two events each year and, in many cases, invited the other student groups to join. Additionally, an EduHub track runs in parallel at each live Ireland Affiliate event. The ISPE Ireland Affiliate plans to reach out to an additional three to four universities by the end of 2024.

PODCAST LAUNCH

The ISPE Ireland Affiliate Emerging Leaders started a podcast as an alternative method to deliver content that would benefit the ISPE network. The podcast focuses on different leadership styles, how to find your leadership style, and how to shape your career as a leader within the industry. It also offers career advice and markets the benefits of ISPE membership. Each episode features an ISPE leader and is linked from the ISPE EL LinkedIn page. Since its launch, the podcast has had listeners from more than 23 different countries tune in.

REGULATORY CONNECTIONS

Additionally, the ISPE Ireland Affiliate is helping connect members with the regulatory community. "We actively engage with regulatory bodies, primarily HPRA [the Health Products Regulatory Authority]," said Gammell. "There are currently over 20 regulatory members in the ISPE Ireland Affiliate."

"HPRA members regularly attend ISPE Ireland events and engage openly with the ISPE community in Ireland. For example, an HPRA Senior Inspector presented at a recent Annex 1 event in Ireland and engaged openly with attendees in a networking session regarding the revised Annex 1."

GAMP®

In addition to active Student Chapter, EL, and Women in Pharma® groups, the ISPE Ireland Affiliate has re-established GAMP Ireland, which had been dormant for a number of years and had its first live event, "Approaches to New Technologies in Life Science, Part 1" sell out. Pharma 4IReland was formed to promote Pharma 4.0™ in Ireland and has planned up to six events (virtual and live) and formed working groups like Labs 5.0. One of the goals of the Labs 5.0 working group is to develop a Labs 5.0 roadmap and identify the skills and competencies needed for current and future lab professionals.

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LOOKING TO THE FUTURE

ISPE Ireland Affiliate leaders have also put practices in place to ensure the future success of the Affiliate and its events. Attendees at every event are surveyed and then that feedback is incorporated into future events. A few examples of this are the opportunity for vendors to educate attendees about new technologies and services and networking sessions where speakers engage with attendees for informal Q&A in addition to networking sessions after presentations.

Strategic Plan and Meetings

"ISPE Ireland developed a strategic plan in 2020, which was refreshed in 2022. This sets out our vision of being the leading network for life sciences in Ireland and delivering unprecedented value and insights. As we look ahead, we will build on this vision, continuously innovating to serve our members better," said Gammell.

Monthly board meetings are held, which are attended by board members and the leaders of each subcommittee. In addition, a minimum of two hybrid meetings are held each year during which all board members and subcommittee members meet to review progress with current strategies and plans for future initiatives.

The EL committee is fully integrated with the main committee and participates in all board meetings—there is a clear succession plan, whereby EL members transition from the EL group and take up leadership and membership positions on subcommittees for different focus areas. This ensures that the EL group provides a continuous supply of members for leadership positions in the main committee.

Playbooks and Surveys

A series of documents have been professionally prepared for ISPE Ireland to support their initiatives and to ensure consistency of delivery among all ISPE Ireland Affiliate committee members:

- ISPE Ireland Playbook
- ISPE EduHub Playbook
- ISPE Ireland Student Chapter Playbook
- ISPE Ireland Member Roadshow

The playbooks provide detailed guidance for each focus area in an interactive and concise, easy-to-follow manner. These playbooks have been distributed to all ISPE Ireland committee members and uploaded to the ISPE Engage Ireland platform, where they are accessible by all ISPE Ireland members.

Meet the ISPE STAFF

Alexis Thomas

In each issue of *Pharmaceutical Engineering*®, we introduce a member of the ISPE staff who provides ISPE members with key information and services. Meet Alexis Thomas, Senior Chapter Relations Coordinator in Member Services.

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

Being the dedicated Senior Chapter Relations Coordinator of ISPE's Member Services team, I orchestrate Affiliate and Chapter relations daily, ensuring they all align seamlessly with ISPE's global initiatives. As the guardian of ISPE's Affiliate and Chapter ecosystem, I handle inquiries and concerns, keeping our Chapters updated with the latest information and promotions while ensuring compliance with ISPE's charter policies. Acting as a bridge between headquarters and Chapters, I facilitate a smooth flow of information, overseeing website management, providing membership reports, and showcasing local events globally. My event-planning skills shine in quarterly Regional Council meetings.

What do you love about your job?

I love meeting other passionate individuals at our conferences. My commitment to helping pharmaceutical professionals navigate their journey is reflected in every task I do. Knowing my day-to-day work is a piece of a larger puzzle that shapes the future of pharmaceutical engineering brings me immense satisfaction.

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

Beyond ISPE, I am a freelance, internationally published makeup artist and a dedicated full-time mom. I invest time in honing my artistic talents and supporting my children's endeavors. Away from work, you might also find me on Florida's beaches, embracing the therapeutic touch of vitamin D.

Introducing New ISPE Baseline® Guides

The newly released third edition of the *ISPE Baseline® Guide: Volume 6 – Biopharmaceutical Manufacturing Facilities* reinforces the concepts described in the second edition, provides examples of how these concepts can be put into practice, and details the value and benefits of the approaches described.

The revision also includes new topics and details regarding quality risk management, contamination control strategies, and the impact of closed processes on facility design. "The significant updates to the guide are centered around alignment of process closure, contamination control, and operations with a continued focus on product protection and risk mitigation," said Guide Co-lead Jeffrey Odum, Practice Leader for ATMPS and Biologics at Genesis AEC.

"I think this guide explores those topics more thoroughly than any other guide or industry publication I know of," Odum said. "The topics covered in this guide raise the bar and expand the body of knowledge for the industry. It should serve as a significant resource for companies developing new manufacturing assets and strategies."

The guide provides individuals and teams with tools to make informed decisions about layouts, area classifications, segregation strategies, project delivery approaches, and operational approaches, all aimed at creating compliant and cost-effective biomanufacturing facility assets.

"The tools and practices detailed in the guide apply to biopharmaceutical drug substance manufacturing, for both clinical and commercial scale, including large molecule [biologics] active pharmaceutical ingredients used in various biopharmaceutical products," said Guide Co-lead Brian Pochini, Principal Engineer at Sanofi.

"This guide should help to ensure a compliant approach aligned with current GMP guidance defined under 21 CFR Part 211 Current Good Manufacturing Practice for Finished Pharmaceuticals, EudraLex Volume 4 Annex 2, PIC/S Guide to Good Manufacturing Practice for Medicinal Products Annexes, and other globally recognized design and operational guidance."

NEW PHARMA 4.0™ GUIDE

The new *ISPE Baseline® Guide: Volume 8 – Pharma 4.0™* provides approaches for realizing lasting digital technology transformations. It contains tools and advice for companies to help them achieve their digitization and financial goals while maintaining and improving product quality and meeting regulatory requirements and expectations.

In addition, this guide outlines various starting points, prerequisites, governance structures, and strategies for achieving transformational success tailored to an organization's size, risk tolerance, flexibility, and maturity level.

"Pharma 4.0™ is a business transformation, not an IT project. As the pharmaceutical industry matures, it needs to evolve to operate in a volatile, uncertain, complex, and ambiguous world efficiently and effectively," said Guide Co-lead Christian Wölbeling.

"Applying emerging and digital technologies can lead to more robust and flexible manufacturing processes, which in turn can help the pharmaceutical industry respond to drug shortages, reduce interruptions in production and delivery of medicines, and ensure consistent clinical performance of products, among other benefits. This guide would be beneficial to any stakeholder involved in digital business transformation, from top C-level management to operators."

The guide describes areas of potential application for digital transformation and how to combine these with the high-level principles of Pharma 4.0™. Namely, what to consider when implementing a holistic control strategy in supply chain, manufacturing and packaging, validation, maintenance and engineering, automation, and quality, underpinned by a robust and flexible workforce.

A repository of technology definitions and technical principles, this guide also includes 35 real-world case studies to guide organizations that want to explore similar digital transformation opportunities. Companies can greatly benefit from the Pharma 4.0™ Maturity Model and Assessment Tool, which helps organizations monitor their transformation journey progress. It is a valuable resource for any size company to begin, reinvigorate, or advance their transformation journey.

For more information, visit ispe.org/Guidance-Documents

CoP LEADER PROFILES

TAMMY SPAIN, PHD, PMP

PROJECT MANAGEMENT COMMUNITY OF PRACTICE CHAIR

The impact people have on others' lives is not always obvious. For many, the Advil mini pill might not seem like a big deal, but for people who have trouble swallowing pills, like cancer patients, the tiny pill has made a huge difference in their ability to manage pain. It's projects like that, as well as treatments for bladder cancer and transthyretin amyloidosis, that Tammy Spain is most proud of up to this point in her career. "The projects I'm proud of are those that make a huge impact on people's ability to live and to live well."

Tammy started her career as a scientist, researcher, and analytical device developer for the US military before moving to the pharmaceutical industry as a project manager. Now, as Associate Director of Project Management at The FlexPro Group, she helps her clients with a wide variety of projects. "We try to get our clients over the finish line as quickly and safely as possible while staying on budget."

"Project managers are helpful in pharmaceutical engineering," she said, "because drugs and therapeutic treatments are expensive to develop and anywhere that you can find the opportunity to manage things better so that they take less time, or have more strategy behind how they're managed, the sooner you'll be able to get treatments to patients."

Because of her diverse professional background, Tammy can fully understand her clients' challenges and opportunities. She encourages anyone who is interested in pharmaceutical engineering project management to, "work in as many different functions of the pharmaceutical industry as you can. It is very helpful if you understand science, manufacturing processes, regulatory processes. The best project managers have a breadth of experience."

One way that Tammy sees project managers being able to help their clients in the future is by embracing the possibility of AI. She explains, "for example, right now, to identify potential resource problems in a project, we might be looking at data from 80 projects in a company's portfolio to see where resources are and what constraints there might be. We need to pull together the outputs of many data sources into an informative format."

"It can be time-consuming to develop a dashboard or format that can provide useful information about resourcing risks to any given project in a timely manner. To answer this problem, one of my clients is working on AI where you can put the specifics of what you need into the query line, the same way that people might do with ChatGPT, and the report you need will be generated for you. This would be a game changer—it will allow us to do our jobs much more intelligently and quickly and give us the time to ask higher-level questions."

Tammy says the Project Management Community of Practice (CoP) will be looking at this and other trends in the industry and that it hopes to present workshops and webinars in the future to give industry leaders a perspective on how project management can help their companies.

While her first introduction to ISPE was in 2019 through the *ISPE PQLI® Guide: Part 4 - Process Performance and Product Quality Monitoring System,* which she used as a reference for a project, she appreciates all the resources ISPE provides to the industry. She has found the CoP to be a wonderful networking resource and the ISPE Annual Meeting & Expo to be a great way to recharge her professional battery. "I've enjoyed getting to know other people in this field. They are all very interesting and I enjoy the camaraderie. It was great to meet in person at the Annual Meeting and share ideas. I came back ready to incorporate the knowledge and ideas I picked up there into my daily work."

In addition to her volunteer work with ISPE, Tammy is a member of the National Biodefense Science Board.

— Marcy Sanford, ISPE Publications Coordinator

NATHAN TEMPLE, PE

COMMISSIONING AND QUALIFICATION (C&Q) COMMUNITY OF PRACTICE CHAIR

Although he didn't know it at the time, Nathan Temple's service as a naval officer on the USS *Asheville* in Hawaii prepared him perfectly for a career in pharmaceutical engineering. "You learn so much, so quickly, on a submarine."

"You start off in the engineering plant and learn all the different systems and how they integrate, how to start up and operate a nuclear reactor and all the water, steam, support, and safety systems. If you make a mistake on a log entry in a nuclear power plant, you line it out, date, initial, and put the correct information. There's a lot of good documentation practices, and it is in fairly close alignment with the nature of the pharmaceutical industry."

Nathan started his civilian career at CAI. "At the time, they had about 50 employees and about two-thirds were former Navy nuclear trained. I was excited because it was an industry where I could continue to make a difference."

Twenty years later, Nathan is still making a difference as Global Director of Commissioning, Qualification, and Validation at CAI. He is in charge of strategy, consistency of method, and deploying best-in-class practices around commissioning, qualification, and validation. The 100% employee-owned CAI now has over 850 employees.

"The majority of our work is in commissioning, qualification, and validation, and we have put together a really exciting model that's focused on operational readiness and operational excellence—and commissioning and qualification (C&Q) is one element of that process—but we're focused on the full life cycle from the idea to market with the focus to get needed medicines to patients."

"I really enjoy working with clients looking at the full life cycle, whether it's a greenfield or brownfield project," Nathan said. "One recent client was an advanced therapy medicinal product project with only 10 employees, and they had 12 months to construct a facility to begin clinical trials and go into commercial manufacturing."

"It was really exciting to help them determine all the steps that it was going to take to deliver product to patients. The foundation for methodology comes from the *ISPE Baseline® Guide: Commissioning and Qualification (Second Edition)* and ASTM E2500. Authors from both of those guides are on the C&Q Community of Practice (CoP) Steering Committee, and it's exciting to discuss those methodologies with CoP members and then bring great ideas from the CoP to industry."

Members of the C&Q CoP Steering Committee regularly present at ISPE conferences, write blogs, and provide expertise on guidance documents. In the past year, they developed a C&Q benchmarking survey intended to provide a comprehensive view of the industry's current state—including the adoption rate of quality-risk-management-based integrated C&Q, C&Q best practices, and key performance indicators—and they are still working to compile data from it and present their findings.

They also have established a subcommittee exploring best practices in paperless validation. According to Nathan, "the future in our space is a full data model associated with product and process knowledge up front that translates through a much more efficient streamlined process, which means quicker to patient and less effort, duration, and cost. There are a lot of exciting developments in the industry in the C&Q space and ISPE is right there on the forefront."

Nathan encourages ISPE members, and especially Emerging Leaders, to participate in ISPE activities. "Get involved, because it is an investment in your future. We need people who are passionate and have good ideas about what we need to learn more about. You can get involved on any level. Sometimes it is good to step outside your comfort zone."

— Marcy Sanford, ISPE Publications Coordinator

2023 ISPE Pharma 4.0™ and Annex 1: Keynote Presentations

By Nada Elsayed

The 2023 ISPE Pharma 4.0™ and Annex 1 Conference was held in Barcelona, Spain, 11–12 December. Topics discussed included transforming operations, quality, and maintenance with Pharma 4.0™ principles and digitalization; strategies for implementing the latest Annex 1 version; the impact of automation on cutting-edge processes; and how rapid microbial monitoring enhances quality control precision and streamlines supply chains.

More than 425 attendees from 30 countries participated in the conference, which included 6 education tracks, networking opportunities and a vibrant exhibition area featuring 34 exhibitors. Participants also heard from industry leaders and regulators who shared their perspectives on the future of pharmaceuticals.

OPENING REMARKS WITH ISPE PRESIDENT AND CEO

ISPE President and CEO Thomas Hartman kicked off the meeting with a warm welcome to the attendees and shared ISPE's 2023 accomplishments, including the publication of the highly anticipated *ISPE Baseline® Guide: Volume 8 – Pharma 4.0™*. After his heartfelt opening speech, keynote speakers from different parts of the industry gave captivating talks. The speakers discussed a wide variety of topics, including innovation during COVID-19, regulatory topics, advancements in the industry, incorporating artificial intelligence (AI), and drug shortages.

KEYNOTE SPEAKERS

Quality Thinking in Lightspeed: People Making a Pandemic Vaccine

Christoph Prinz, Vice President Global Operational Quality, BioNTech

In his talk, Prinz gave a compelling presentation on how BioNTech was tasked with having to deliver the COVID-19 vaccine in the middle of the pandemic. Prinz discussed how, when faced with a nearly impossible task, the team had to rapidly find ways to maintain the highest levels of quality while also understanding that typical timelines were not at all feasible. To achieve this monumental task, Prinz had to streamline certain processes, ensure all team members were able to quickly adapt, and trust his team's ability to deliver.

Prinz described his approach as "quality thinking in light speed." He focused on the how instead of the why. Specifically, he focused on how to reduce complexity while increasing product quantity without taking any quality shortcuts. Using this approach, while also constantly reiterating the goal with each other, the team found innovative solutions to streamline the process and save precious time.

Some of the solutions they implemented included a single English label across all world regions to cut down on production time. In addition, the team implemented a multidose vial instead of a single-dose vial to reduce the production time. The health authorities also fast-tracked the FDA's investigational new drug. With all these innovative and streamlined processes, they were able to successfully reach a viable commercial vaccine in an astounding eight months.

Advancing Digitalization in Manufacturing: EU Initiatives

Evdokia Korakianiti, Head of Quality and Safety of Medicines, European Medicines Agency (EMA)

Korakianiti gave a riveting virtual talk on advancing digitalization in manufacturing. She discussed how the use of digitalization and automation is expanding and how it's important to make them "smart" to ensure that the highest quality levels are delivered. She urged the importance of investing in tech to help reduce or eliminate issues the industry faces: for example, drug shortages as demand increases to unprecedented levels.

Korakianiti noted that regulators have a big burden because they need to adapt quickly to the increasing innovations in digitalization. She explained that the EU is currently reviewing basic pharmaceutical laws to create the framework to promote technological innovation while also increasing patient access and drug availability.

In addition, the agency is also preparing for a future pandemic, should one happen. Regulatory sandbox tools are being implemented to test innovative approaches and the use of AI while safeguarding citizens. As recently announced in a press release, this is done using a risk-based approach. The EMA created a task force to balance guidance and AI use while leveraging current knowledge from other agencies. Korakianiti explained that, ultimately, the goal is to tear down boundaries and provide the best access to patients.

A National Competent Authority Perspective of the Legislative Momentum

María Jesús Lamas Díaz, Director, Agencia Española de

Medicamentos y Productos Sanitarios, the Spanish Agency of Medicines and Healthcare Products, (AEMPS)

Diaz gave a talk that touched on various pharmaceutical industry topics, including undeniable drug shortages experienced across the globe. The EU recognizes growing concerns, especially with drug demand increases coupled with supply chain shortages. The shortages are due to various factors, and some include disruptions related to environmental factors that cannot be solved easily by regulatory initiatives.

A first step to address shortages is to identify ahead of time where issues occur. For instance, the EMA identified a comprehensive list of nearly 500 of the most-used medicines. Over one-third of the active pharmaceutical ingredients (APIs) from that list are manufactured either in China or India. With that in mind, the agency is tracking manufacturing to help get ahead of possible shortages.

Legislators are also implementing incentives to manufacturers of these critical drugs. One incentive involves facilitating AI use in the life cycle management of drugs. Diaz echoed the sentiments of other keynote speakers, stating the importance of AI (if implemented correctly), having new legislations to support supply chain disruptions, implementing regulatory improvements focused on manufacturing, quality controls, and leveraging knowledge from other authorities to facilitate these initiatives and improvements.

ISPE Foundation

Teresa Minero, Founder and CEO, LifeBee – Digitalizing Life Sciences

Teresa Minero's energetic presentation about the ISPE Foundation rounded out the keynote session. Minero explained the foundation's mission to fuel global health equity by fostering access to knowledge and nurturing diverse talent. She discussed the foundation's philanthropic efforts, which include ISPE Knowledge Without Borders, student scholarships and grants, and supporting expansion of workforce diversity, among others. Before concluding, Minero showed how more than 180 students and Emerging Leaders from more than 30 countries were awarded a grant to attend different ISPE meetings in 2023, thanks to the ISPE Foundation's support.

The 2024 ISPE Pharma 4.0™ and Annex 1 Conference will be held in Rome, Italy, and virtually 10–11 December. For more information, visit ispe.org/conferences/2024-pharma-40-annex-1-conference

Disclaimer: This article contains an abridged, unofficial summary of presentations at an ISPE conference that has not been vetted by any agency or organization. The summaries are an informal and brief synopsis of the speaker views, and do not represent official guidance or policy of any agency or organization.

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Save the Date: International Women's Day Is 8 March

By Edyna Miguez

The new year is here and, with that, another International Women's Day approaches! This incredibly important global movement, which takes place every 8 March, celebrates women's achievements, raises awareness about discrimination, and advocates for accelerated equality and gender parity. ISPE's Women in Pharma® community strives to accomplish all these goals through regional and international programming.

Each year, those spearheading International Women's Day launch a theme that further drives the mission of the movement, and this theme serves as the jumping off point for ISPE's Women in Pharma international programming. In previous years, the themes were Break The Bias and Embrace Equity. This year, the theme is Inspire Inclusion.

Creating a more inclusive and equitable pharmaceutical industry is the driving force behind ISPE's Women in Pharma. In celebration of International Women's Day, Women in Pharma will host a series of in-person and virtual events throughout March, including webinars, Emerging Leaders Day, and networking events. Be sure to head to the Women in Pharma webpage (ispe.org/women-pharma) to see the calendar of events for this year's International Women's Day and learn how to get involved. You can also read about our work to create a more equitable industry for women and other marginalized groups.

For more information on ISPE's International Women's Day efforts, including past campaigns and this year's events, visit ispe.org/women-pharma/international-womens-day

Edyna Miguez is Manager, Membership Growth at ISPE.

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RISK- AND SCIENCE-BASED MEDIA and Buffer Mixing Validations

By Beth Fulton, MS, and Igor Gorsky

The validation of media and buffer mixing is a continuing area of resource constraint in the pharmaceutical industry. These validations require materials, validation associates' time, and the use of equipment and processing areas. This article proposes a risk-based life cycle for minimizing mixing validation resource inputs, with the objective of optimizing validation efforts through the use of recipe bracketing and predictive methods to identify the worst-case recipes that should be validated.

Often, manufacturers expend resources to validate mixing for media and buffer recipes that are not considered the most difficult to achieve a successful mixing endpoint (henceforth referred to as worst-case recipes). Further complicating validation efforts, successful endpoint of mixing is often gauged by visual assessment of dispersion, which is subjective.

Other variables may be used, (e.g., pH, conductivity, osmolality), although they also may not be perfect indicators of solution homogeneity if the solution has not achieved turbulent mixing (often described as vortexing). Calculations and modeling are presented as viable additional tools for prediction of dispersion to leverage theoretical estimations and to prevent the repeat work associated with failed validations.

It should be noted that the presented method is a "fit most cases" approach and may not be appropriate for all programs, manufacturers, or facilities. Similar approaches may be applied to more complex mixing tasks by making additional considerations for particle sizes, densities, and higher viscosity suspensions.

MIXING IN MEDIA AND BUFFER PREPARATION

In pharmaceutical media and buffer preparation, mixing is a method by which solid substances (solutes) and liquids (solvents) are combined to create a solution with uniform concentration [1]. The goal of creating a uniform solution is to minimize product variability and the impact on safety, purity, and the effectiveness of a drug to prevent adverse impacts to the patient.

In buffer and media mixing vessels, several mechanisms work individually or in combination to create a solution of uniform concentration. These mechanisms are best described in terms of the scale at which the mechanism is occurring: macroscale, mesoscale, or microscale.

Macroscale Mixing

Macroscale mixing occurs at a scale as large as the vessel itself [2] and, principally, involves a mechanism called bulk diffusion [1]. In bulk diffusion, the solute is dispersed within the solvent by the pumping action of the mixer's impeller. The objectives of macroscale mixing for solid–liquid mixtures are to suspend solute particles within the solvent (so that they are not sinking to the bottom or floating to the top of the vessel) and to uniformly distribute those particles within the solvent [2]. For liquid mixtures, the objective of macroscale mixing is to stop liquids from stratifying by density [1].

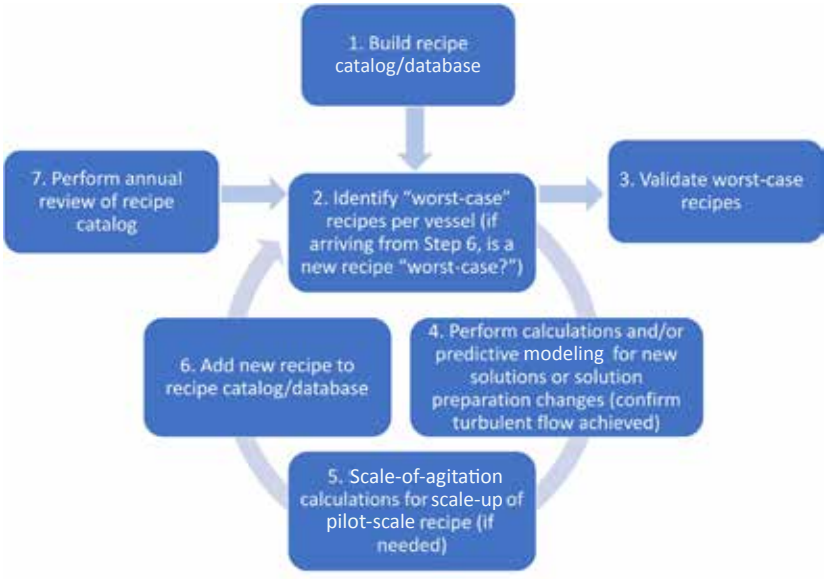
Mesoscale Mixing

Mesoscale mixing is the intermediate scale between the size of the vessel itself and the microscale. At this scale, a mechanism called dispersion occurs, which is facilitated by eddy currents that create drag that involves local velocity and shear-stress effects. At this mixing scale, the objective is to distribute clumps of solid particles into smaller groups or to decrease the size of liquid droplets, creating a homogeneous size distribution of droplets [2].

Microscale Mixing

Microscale mixing is mixing at the smallest scale, at which viscous dissipation, molecular diffusion, and surface effects become important [1, 2]. This mixing scale principally involves a mechanism called dissolution. In dissolution, solid particle components of the mixture decrease in size but retain their original characteristics, such as density and porosity, as they are incorporated as a solute in the liquid (solvent) portion of the mixture [2]. This is a

Figure 1: Efficient buffer/media/feed mixing validation life cycle.



mass transfer operation that is facilitated by the collision of solvent molecules with the surfaces of solute particles.

CHALLENGES WITH MIXING VALIDATION

The validation of mixing operations for all buffer, media, and feed recipes within a given organization can be a wasteful endeavor, for several reasons. First, repetitive validations are often performed. This is particularly a problem in the contract manufacturing organization space, where similar recipes are brought in by several clients, often using the same equipment configurations. Second, validations occasionally fail. Sometimes uniform mixing is not achieved with the proposed parameters and the recipe must be reformulated and revalidated.

Third, the use of an incompletely mixed solution can cause waste in the form of cost to quality due to a failed in-process control, critical process parameter, or quality attribute further down the line in the process. The quantification of successful mixing is often subjective (e.g., based on formation of a vortex or by visual judgement of dissolution) or is based on an orthogonal measurement (e.g., stabilization of pH or conductivity readings). None of these methods completely quantifies mixing at the macroscale, mesoscale, and microscale. Therefore, a small chance exists for a recipe to pass mixing validation even though the solution has not actually been uniformly mixed.

OPERATIONS AND MATERIALS IN SCOPE

This article discusses how to determine which buffer, media, and feed recipes should be selected for physical validation of mixing during make-up within stirred stainless steel vessels and single-use mixers, and activities that should be pursued prior to performing those physical validation efforts.

OPERATIONS AND MATERIALS OUT OF SCOPE

Mixing gas into liquid and mixing a solid into another solid sometimes occurs in the pharmaceutical industry. However, these mixes are not generally used for media, feed, or buffer preparation. Therefore, those methods are out of scope for this technical article and not discussed.

Mixing within piping is important in pharmaceutical operations, and induction mixing is occasionally used for buffer and media preparation. However, the scope of this article is limited to mixing within stainless steel vessels and single-use mixers, as that is the most common method for make-up of buffers, medias, and feeds.

Other chemical and physical manipulations of media, feed, and buffer solutions during formulation (e.g., heating, sparging) are out of scope for this discussion. Only mixing at a steady temperature will be discussed in this validation bracketing/prioritization approach; this strategy may not be suited to more advanced applications.

Finally, product mixing is also out of scope for this article, as that encompasses an almost limitless material scope (subject to other process- and material-specific concerns during mixing). The design of mixing operations (e.g., use of design space) and the execution of validation activities are out of scope for this article.

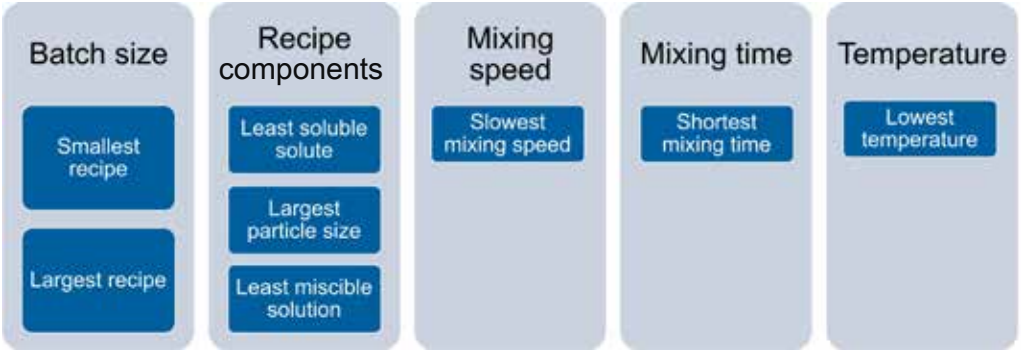
METHODS

This article describes ways of achieving efficiencies in mixing validation by employing a seven-step method for maintaining a risk-based mixing validation life cycle for buffer, media, and feed recipes, as shown in Figure 1.

Step 1: Build a Recipe Catalog

The first step in achieving efficiencies in an organization's mixing validation strategy is to create an internal controlled database

Figure 2: Examples of variables that represent the worst-case recipe(s) within a vessel or functionally equivalent vessels.



inclusive of all currently validated buffer, media, and feed formulations and to categorize formulations into families of which representative solutions may be validated, if required. Examples of these categorizations may include solutions with low and high concentrations, sera, low volume solutions, etc. A clear definition of each family should be established, along with criteria sufficient to sort each formulation into the correct category. This approach will make it possible to identify worst-case recipes within each family.

Step 2: Identify Worst-Case Recipes

This step requires identifying whether all worst-case conditions for mixing are represented within the currently validated recipes. This involves identifying what recipes represent the worst-case conditions (most difficult recipes in which to achieve successful mixing) within each vessel (and within a family of recipes).

Multiple vessels can be considered identical should they consist of the same equipment (e.g., same model/equipment ID and impeller type and dimensions) and configurational inputs (e.g., same process area, utility hookups, controller, software).

For a given vessel and impeller geometry and configuration, it is important to examine critical variables when determining which recipes that run in that vessel are worst case: e.g., batch size, solution components, mixing speed, mixing time, and temperature. Note that this list includes the most important variables, but, depending on the manufacturer's recipe catalog, other variables may also be important.

For batch size, it will be necessary to identify the smallest and largest volumes of solution to be prepared within the vessel(s). The worst-case recipe(s) should include the recipe(s) with the least soluble solute being added within the vessel(s), the solute with the largest particle size to be added within the vessel(s), and the least miscible solution to be added to the vessel(s). The worst-case recipe(s) should also include the recipe(s) with the slowest mixing speed, shortest mixing time, and lowest mixing temperature. Figure 2 depicts a summary of this approach. It includes critical variables that can inform a family approach/grouping of recipes.

Weighting may be applied to the variables indicated to demonstrate relative importance to product quality, e.g., formatting of the database as a custom cause-and-effect matrix or other similar criticality assessment tool. In the interest of efficiency, the current validation strategy should evaluate the fewest recipes possible that represent the worst case for critical variables within a given vessel geometry and configuration (i.e., solution family).

It should be noted that the structure of recipes matrix (database) will vary significantly for each manufacturer and will depend on recipe media/buffer family types, groupings of equivalent equipment, and variables chosen due to specifics of the recipes within a given family. Variables to be considered for grouping should include variables in Figure 2 as a starting point and then possibly include additional variables dependent on the recipe characteristics.

A cross-functional team should approve the finalized database, including experts from engineering, manufacturing sciences, quality assurance, validation, risk management, and manufacturing. However, the recipes evaluated must represent actual formulations for the process(es) being validated [3–5].

Step 3: Validate Worst-Case Recipes

If review of the recipe database revealed that some worst-case media, buffer, or feed recipes were not previously validated for a given vessel configuration, then mixing of those recipes should be validated.

Step 4: Confirm Turbulent Mixing Will Be Achieved

This step requires performing calculations and/or predictive modeling for new solutions, or when a solution preparation process changes, to evaluate whether turbulent mixing is going to be achieved. When changes to equipment, batch size, ingredients composition, etc. occur, affected recipe(s) should be subject to calculations or modeling that predict whether turbulent mixing will be achieved.

Dimensionless number (e.g., Reynolds number) calculations can be applied as previously described [1] to evaluate whether a new recipe is expected to achieve adequate (turbulent) mixing. A Reynolds number for a mixing environment can be calculated

Figure 3: Reynolds number formula.

$$N_{Re}=\frac{D^2\rho N}{\mu}$$

where

N = shaft speed (sec^{-1})
D = propeller blade diameter (cm)
ρ = density of solution dispersion (g/cm^3)
μ = viscosity of solution dispersion (g/[cm/sec])

Table 1: Summary of scale-of-agitation approach [1] for scaling up a recipe.

Variables Known	Variables to Be Determined	Necessary Assumption
• Specifications of small (pilot) tank (impeller and tank diameters, volume, horsepower) • Mixing speed of batch in pilot tank • Point density and viscosity of the solution • Volume (L) of the smaller (pilot) and larger (scale-up) batch • Specifications of available or already selected scale-up tank(s) (impeller and tank diameter, mixing speed range, volume, horsepower)	• Rotational speed of the larger vessel (rpm or 1/sec) • Horsepower requirements for the larger tank	The mixing time of the pilot and scaled-up batch is the same

using the equation in Figure 3, with a result greater than or equal to 2,000 indicating turbulent flow (indicative of better mixing) will be achieved during manufacturing of buffer and media.

It should be noted that a relationship exists between pumping number and Reynolds number within the turbulent range that is close to a straight line [1]. Therefore, linear extrapolation can be subsequently used to calculate the pumping number.

Performing these dimensionless number calculations in advance of starting mixing validation work will save effort overall because, if validation fails, the recipe design will need to be reevaluated. If lack of turbulent mixing is detected via dimensionless number calculations (prior to mixing validation), resources (e.g., equipment, suite time on the schedule, personnel hours, materials, etc.) will not have been wasted.

The authors have observed in the last few years a rise in the use of computer simulations and artificial intelligence applications that evaluate the mixing of solutions. This further strengthens the authors' message that these simulations are very useful. For example, numerous studies have been recently performed on fluid mixing simulation via computational fluid dynamics platforms validated for a specific equipment configuration in stirred tanks and bioreactors [6–9].

Modern software platforms can identify mixing dead zones within a vessel [6] and unwanted localized mixing effects (e.g., surface vortexing) [9]. If a computer simulation model is utilized, it must be validated by a quality-by-design approach prior to use to ensure that it is consistent with real-world results in the equipment and recipes within scope.

Step 5: Calculations for Scale-Up of Pilot-Scale Recipes

If scale-up of a new recipe is desired, once turbulent mixing of the pilot-scale recipe has been confirmed via dimensionless number calculations and/or a validated computational model, the scale-of-agitation approach can be used to determine scale-up batch parameters [1]. This will ensure that the exact mixing conditions from the pilot batch can be preserved in the production-scale batch [1]. Scale-down of recipes can be accomplished as well by similar methods, if necessary [10]. Table 1 summarizes the scale-of-agitation approach.

If the facility has a validated predictive modeling application in place, this again can also be applied to further confirm predicted mixing success of the scaled-up recipe.

Step 6: Add the New Recipe to the Database

Having received this confirmation that a new recipe is expected to achieve thorough mixing, the next step is to add the recipe to the database. Then, proceed back to step 2 to determine whether the new recipe is within the current recipe catalog/database bracketing design or represents a new worst-case recipe.

To understand whether a new recipe is represented within the existing bracketing strategy (or, alternatively, whether that recipe represents a new worst case that should be added to the current bracketing strategy), the following questions should be addressed. This will help identify if this recipe represents a new boundary condition for any of the critical variables previously discussed within the vessel(s) where it will be prepared:

- Does this new recipe represent a new smallest/largest volume of solution to be prepared within the(se) preparation vessel(s)?
- Is a solute in the recipe less soluble than the one that was previously considered as worst case for the(se) preparation vessel(s)?
- Does the new recipe contain a larger particle size than was previously evaluated in the(se) preparation vessel(s)?
- Is a new solution component less miscible than solution component(s) that were previously evaluated as worst case in the(se) vessel(s)?
- Is this recipe's mixing speed/time and/or temperature lower than those which were previously evaluated as worst case for the(se) vessel(s)?

If the answer is yes for any of these variables (or if the weight score is the new highest within a solution category), this recipe represents a new worst case and should be validated (proceed to step 3).

Step 7: Review Annually

It is recommended that the database or matrix of buffer, media, and feed recipes should be evaluated periodically based on a science- and risk-based rationale. This review period should not be longer than three years, according to existing regulatory expectations for validation of other systems (e.g., controlled temperature units) [11]. At a minimum, the following should be reviewed by cross-functional teams with quality assurance oversight: the introduction of new buffer or media formulations, removal of defunct recipes from the catalog, deviations, changes in process and/or equipment, any microbial excursions that may be associated with buffers and media, and other applicable criteria.

CONCLUSION

Efficiencies in mixing validation can be achieved by application of a life cycle approach. By developing a catalog of media, buffer, and feed recipes, it is possible to employ a bracketing approach in which only the worst-case recipes within a given equipment configuration are evaluated. New recipes or changes to existing recipes can be verified for turbulent mixing with calculations and/or predictive modeling prior to the occurrence of any physical mixing validation.

Where scale-up of a new recipe is needed, one may employ a scale-of-agitation calculation approach to ensure the mixing conditions from the smaller (pilot) batch are preserved. New or changed recipes can then be assessed to determine whether they represent a new worst case that must be validated for a given vessel or functionally equivalent vessels.

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ELECTROCHEMICAL TECHNIQUES for Onsite Surface Qualification

By Luis Henrique Guilherme, PhD, Assis Vicente Benedetti, PhD, Cecilio Sadao Fugivara, PhD, Peter Hammer, PhD, and Joey Kish, PhD

Pharmaceutical critical utilities are typically built of 316L stainless steel; nevertheless, surface degradation has been reported due to the occurrence of different phenomena. This article aims to explain how field electrochemical techniques using a portable tool can be an effective method for surface inspection, qualification, and monitoring. The surface finish assessment considered different average roughness, obtained by mechanical polishing and electropolishing, and whether the surface was chemically passivated or not, to generate distinct passive films. This was done to prove the sensitivity of the field electrochemical tool using corrosion techniques.

EXPLANATION OF THE TECHNIQUES USED

The corrosion techniques used included open circuit potential (OCP), cyclic potentiodynamic polarization (CPP), and electrochemical impedance spectroscopy (EIS). X-ray photoelectron spectroscopy (XPS) measurements were performed to characterize the oxide film properties. EIS and XPS demonstrated a close match in terms of oxide thickness determination ($R^2 > 0.90$), and it is worth highlighting the agreement between the chromium to iron (Cr:Fe) ratio and the polarization resistance quantified by XPS and EIS, respectively. In this article, the influences of surface finish techniques on passive film properties and corrosion performance are discussed.

PHARMACEUTICAL 316L STAINLESS STEEL USAGE

The fine chemical industries, such as pharmaceutical and food-grade aseptic sectors, are used to facing challenges related to the expectations of consumers, price constraints, and strict regulatory requirements. In this scenario, the corrosion and surface contamination of the processing plant equipment plays an important role, as it can compromise product quality and requires adequate selection of the materials, a proper surface finish process, and periodic maintenance [1].

Stainless steel is widely used in pharmaceutical and food-grade industries due to its resistance to corrosion and oxidation, advanced mechanical strength at high temperatures, weldability, and relatively low cost [2–5]. Critical process utilities normally are built using 316L stainless steel due to its excellent passivation properties [6], although it is not immune to corrosion phenomena [7, 8], rouge contamination [9], and biofilm adhesion [10–12] after long-term exposure to industrial processes.

The passivation efficiency of 316L stainless steel depends on its passive film characteristics such as microstructure, surface morphology, oxide layer thickness and uniformity, semiconducting properties, and passivity breakdown in the bioprocess [13–17]. These characteristics change according to the surface finish process; thus, critical utility equipment is designed to achieve a clean and smooth surface that provides high corrosion resistance.

The American Society of Mechanical Engineers: Bioprocessing Equipment (ASME BPE) [18] code specifies the process contact surface finish requirements and acceptance criterion, where the surface finish can be prepared by mechanical polishing or electropolishing. Moreover, a modified passive film by chemical passivation treatment is required according to this code for bioprocess utilities.

The passive film on the surface is a naturally formed 1–3 nanometer (nm) thick layer consisting of chromium-rich oxide/hydroxide phases, whose composition, thickness, and protective action changes dynamically with bioprocessing time [1, 12]. The passive film modified by chemical passivation treatment results in a more resistant surface oxide layer compared to the naturally formed passive film. Indeed, 316L stainless steel passivated surfaces are reported as Cr-rich oxide layers in the form of chromium oxide (Cr_2O_3), which are mainly responsible for the high passivation ability [14, 19–21].

The main concerns about the use of 316L stainless steel is corrosion damage and the release of metal ions into the processed fluids, which can be hazardous for the end users. Therefore, bioprocess equipment is required to have passivated surfaces instead of natural passive films [1, 18].

However, as there is no field tool and technique available to quantify and qualify the passive film properties, the industrial practices for chemical passivation treatment are not able to assess the efficacy of these treatments. In fact, the ASME BPE code describes electrochemical techniques such as EIS as an advanced

Table 1: Finishing methods of American Iron and Steel Institute (AISI) 316L.

Sample ID	Ra[1] (µm)	Latter Grind-Paper	Electropolished	Passivated
0.8 microns (µm) grinding	0.8	220	No	No
0.8 µm passivated	0.8	220	No	Yes
0.3 µm EP	0.3	220	Yes	No
0.3 µm EP passivated	0.3	220	Yes	Yes
0.2 µm grinding	0.2	600	No	No
0.2 µm passivated	0.2	600	No	Yes
0.05 µm EP	0.05	600	Yes	No
0.05 µm EP passivated	0.05	600	Yes	Yes

[1] Ra: roughness average.

tool to measure the passivation property and corrosion resistance of the passivated surface, though the technology is not yet ready for field use [18].

This article aims to elucidate how electrochemical techniques can be applied in field surface finish inspections as an advanced tool for the surface qualification and monitoring of 316L stainless steel tanks and pipelines. It is worth emphasizing that the field electrochemical techniques need to be sensitive enough to differentiate the properties of surface finishes and therefore OCP, CPP, and EIS have been applied. XPS was used to characterize the passive film in terms of oxide chemical composition, thickness, and Cr:Fe ratio.

METHODS TO QUALIFY INTERNAL SURFACE FINISH

Portable electrochemical minicells have been used to perform surface inspection inside 316L stainless steel tanks to qualify the internal surface finish through the application of electrochemical techniques [22]. The most common surface finish applied to stainless steel tanks was assessed by the portable electrochemical minicell, as shown in Table 1, to prove the tool sensitivity for surface inspection. Each surface finish has an individual Cr:Fe ratio and consequently a specific electrochemical response is expected.

The surface finishing was performed using mechanical polishing, chemical passivation treatment (American Society for Testing and Materials ASTM A380 [23]), electropolishing (EP) according to ASTM B912 [36], and a combination of passivation, as can be seen in Table 1. The XPS and electrochemical measurements were carried out using 1 cm^2 area of a mockup of the finished surface. Additionally, electrochemical tests were employed in practical field inspections of stainless steel tanks. The reproducibility of the electrochemical tests, comparing bench and field measurements, was validated in a previous work [22].

Electrochemical techniques are recognized as the most advanced methods of stainless steel surface characterization [18, 24–26]. Previous studies described the importance of assessing passivated surfaces applying OCP and CPP, Cr-depleted zones, and sensitization (especially for welds) via double-loop electrochemical potentiokinetic reactivation (DL-EPR) [7, 8, 12]. In this article, the field EIS as an onsite technique for passive film properties characterization is introduced.

The portable electrochemical minicell is a portable surface tester capable of quantifying the passive film properties and the corrosion resistance of 316L stainless steel tanks and pipelines. It works as a conventional three-electrodes minicell using a silver chloride electrode (Ag|AgCl|KCl[3] mol/L) as the reference electrode and platinum (Pt) wire as counter electrode that was designed to be used in onsite inspection services [22].

During inspection activities for tanks, the minicell enables multiple measurements in confined spaces to be obtained using a multichannel potentiostat/minicell system. A vacuum cup system was designed to attach the minicell in all positions on the steel surface with a 1.7 millimeter (mm) diameter capillary pair to the tank surface, which was used as the working electrode. Figure 1 shows the portable electrochemical minicell in a field inspection.

Using the portable electrochemical minicell tool in situ, EIS data were recorded in 3.5% mass by volume (m/v) sodium chloride (NaCl) solution at (30±2)°C. The impedance spectra were generated by applying a sinusoidal signal of amplitude 10 millivolt (mV) over the frequency range 0.01 hertz (Hz) to 100 kilohertz (kHz). The resultant spectra were analyzed using the PStrace 5.9 software.

CPP tests were carried out to measure the passivation level and the pitting corrosion resistance in 3.5% (m/v) NaCl solution at (30±2)°C. After stabilization of the open circuit potential (OCP), an anodic polarization scan was performed at a sweep rate of 2.0 mV s^{-1}. The anodic scan was reversed after it reached one of the criteria:

Figure 1: A: Portable electrochemical minicell tool for onsite stainless steel surface inspection. B: EIS data acquisition through Bluetooth connection.

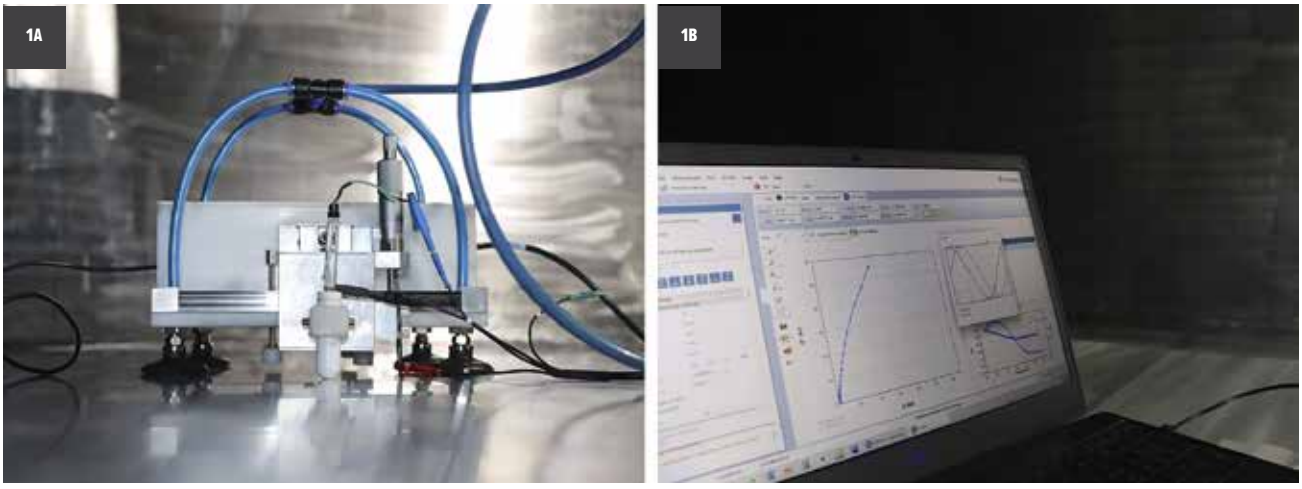


Table 2: Electrochemical techniques and respective acceptance criteria for 316L stainless steel.

Tank Conditions	Objective	Technique	Performance Parameters	Acceptance Criteria
Passivated surface in qualification	Passivation level	EIS	R_p, Q_{CPE}, η^1, C_{eff}	Passive film thickness (δ): 1 nm < δ < 3 nm
				$R_p \geq 2.0$ MΩ cm^2
		CPP	E_{corr}, E_{pit}, E_{prot} passivation level	E_{prot}-E_{corr} > 350 mV
In operation process	Early rouge and corrosion detection	Combining OCP and EIS	E_{corr}, R_p, Q_{CPE}, η^1, C_{eff}, EEC (equivalent electrical circuit)	OCP ≥ + 10 mV (Ag|AgCl|KCl 3 mol/L)
				$R_p \geq 0.5$ MΩ cm^2
				1 nm < δ < 3 nm

[1] Constant phase exponent.

(a) current density of 1 milliampere per square centimeter (mA cm^{-2}) or (b) potential of 1 volt (V). Then the inspected surfaces were scanned in the cathodic direction to a potential of –200 mV vs. OCP.

Table 2 summarizes the period of evaluation and its respective type of inspection, describing the inspection objective and electrochemical technique for surface inspection. The passivation properties and corrosion resistance of 316L stainless steel were based on literature to specify the acceptance criterion [7, 27].

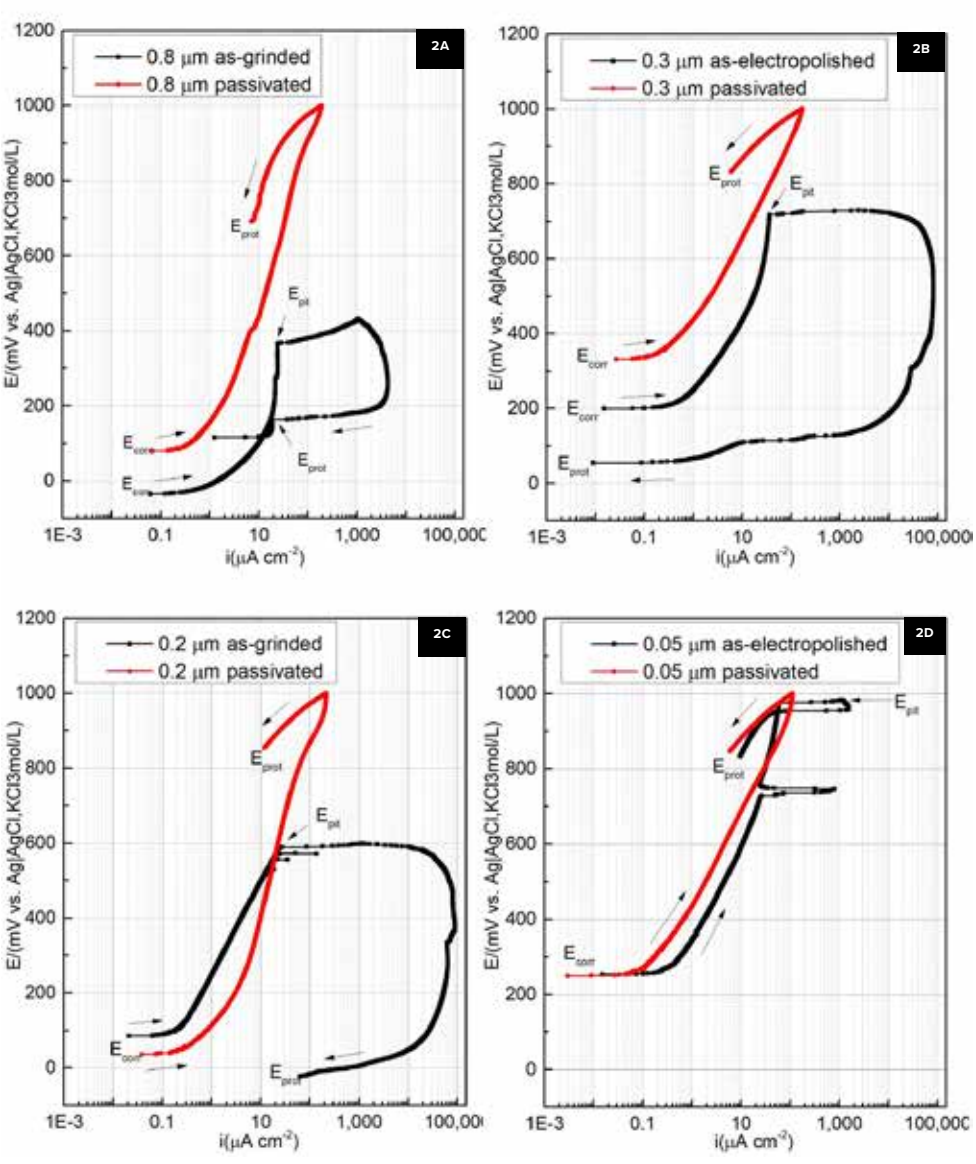
The surface elemental analysis of the samples with different surface treatment was carried out by XPS using a commercial spectrometer (UNI-SPECS UHV) at base pressure lower than 10^{-7} Pa.

RESULTS

Open circuit potential and CPP curves in 3.5% (m/v) NaCl solution at (30±2)°C were performed after reaching a stable OCP for all surface finishes and the performance parameters are presented in Figure 2. In Figure 2, each figure shows the CPP curves of the surfaces in the conditions as polished and passivated. All polarization curves showed a passive behavior during the anodic scan. The surface performance was quantified based on the CPP parameters shown in Table 3: corrosion potential (E_{corr}), pitting corrosion (E_{pit}), corrosion protection (E_{prot}), and passivation current density (i_{pass}).

It is worth analyzing what sort of hysteresis was observed during the positive or negative potential reversal. The hysteresis

Figure 2: Cyclic potentiodynamic polarization curves obtained for 316L stainless steel in 3.5% (m/v) NaCl, at (30 ± 2)°C, and 2.0 mV s^{-1} of A: 0.8 µm as-grinded and passivated surface; B: 0.3 µm as-electropolished and passivated surface; C: 0.2 µm as-grinded and passivated surface; and D: 0.05 µm as-electropolished and passivated surface.



behavior shows either pitting growth or surface repassivation, findings which have been discussed in a previous paper [7]. Based on the electrochemical parameters, it is safe to state that the mechanical polished surfaces generated inferior passivation properties, whereas the electropolished surface significantly decreases the passivation current density and increases the pitting resistance. Nevertheless, mechanical and electropolished surfaces have registered the pitting corrosion in a potential range of 300–600 mV and 600–900 mV, respectively. Furthermore, a positive hysteresis was observed after reversing the potential scan, indicating that the pitting continues to grow. In contrast, the passivated surfaces presented a higher corrosion resistance evidenced by the absence of pitting potential, reduced passivation current density, and negative hysteresis.

The passivation level (PL) represents the andic passivation range of the material (equation 1) based on the electrochemical parameters derived from the CPP curves: corrosion potential (E_{corr}) and corrosion protection potential (E_{prot}). If E_{prot} is nobler than E_{corr}, there is a potential range where the passive film is stable and localized corrosion such as pitting, crevice, or cracking will not develop or grow [24]. The acceptance criterion for the PL, according to equation 1, is 350 mV[7]. The corrosion resistance parameters

Table 3: PL assessment of studied surfaces obtained in 3.5% NaCl solution.

Surface Finish	$i_{pass\ @0.3V}$ ($\mu A\ cm^{-2}$)	E_{corr} (mV)	E_{prot} (mV)	E_{pit}[1] (mV)	PL (mV)
0.8 µm grinded	24.5	-35	+162	+365	+197
0.8 µm passivated	3.7	+90	+692	+1,000	+602
0.3 µm EP	2.1	+200	+54	+716	-146
0.3 µm EP passivated	0.02	+331	+831	+1,000	+500
0.2 µm grinded	1.6	+85	-23	+588	-108
0.2 µm passivated	6.3	+40	+854	+1,000	+814
0.05 µm EP	0.6	+253	+832	+975	+579
0.05 µm EP passivated	0.2	+250	+850	+1,000	+600

[1] E_{pit} = 1,000 mV indicates that stable pit nucleation and growth did not occur.

obtained from the OCP and CPP curves in 3.5% NaCl were performed after 12 months of reactor operation and are summarized in Table 3.

$$PL = E_{prot} - E_{corr} \quad (1)$$

Figure 3 shows optical micrographs for 316L stainless steel scanned surface area after CPP testing. It shows stable pits for grinded and electropolished surfaces (see Figure 3A and 3B), whereas the passivated surfaces remained pitting-free (see Figure 3C).

EIS spectra in the Nyquist representation recorded during immersion in the 3.5% (m/v) NaCl at (30±2)°C are reported in Figure 4. They are portions of depressed semicircles, that can be fitted with the simple EEC model for a compact film [1], as can be seen in Figure 4, where R_{el} is the electrolyte resistance, R_p is the polarization resistance and CPE is a constant phase element introduced to account for the heterogeneity of oxide layer which cannot be represented by a pure capacitance.

EIS spectra were fitted using an $R(R_{CPE})$ EEC. The passive film thickness was estimated according to the power law model [28] to be in the range of 1–3 nm, in agreement with previously reported values [1, 21]. The fitting parameters, reported in Table 4, suggest that RP was substantially increased in the case of passivation treatment for all surface finishes (mechanical and electropolished).

Furthermore, the best-fit exponent (n) of the constant phase element yields values < 1, as expected for passive films on stainless steel [1, 29]. As seen in equation 2, this behavior is explained by the formation of a passive film with a resistivity gradient going from the metal–oxide interface to the oxide–electrolyte interface, where Q vs. n can be described according to the power law model [30]:

$$Q = \frac{(\varepsilon\varepsilon_0)^n}{g\delta\rho_\delta^{1-n}} \quad (2)$$

where ε is the passive film dielectric constant, ε_0 is the vacuum permittivity (8.8542×10^{-14} F cm^{-1}), δ is the oxide layer thickness, ρ_δ is the resistivity of the oxide at the oxide–solution interface, and g is a numerical function given by [29]:

$$g = 1 + 2.88(1-n)^{2.375} \quad (3)$$

Considering that the CPE results from a dielectric response of the material, it allows us to determine the film thickness, d, in terms of an effective capacitance and dielectric constant, e, according to [28]:

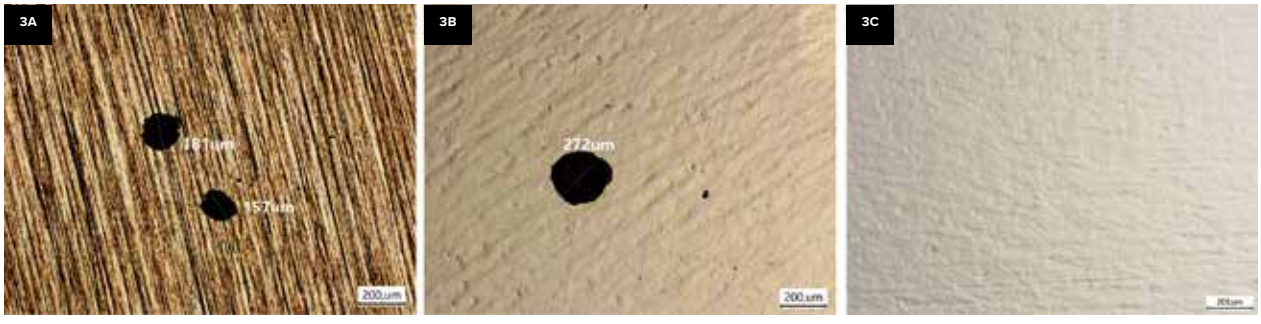
$$\delta = \frac{\varepsilon\varepsilon_0}{C_{eff}} \quad (4)$$

Combining equations 2 and 4 yields an expression for the effective capacitance as [30, 31]:

$$C_{eff} = gQ(\rho_\delta\varepsilon\varepsilon_0)^{1-n} \quad (5)$$

The passive film thickness estimated assuming a dielectric constant of chromium and iron oxide of 12 and ρ_δ = 500 Ω cm [1] is shown in Table 4.

Figure 3: Optical micrographs of 316L stainless steel scanned surface area after CPP measurements of A: Ra = 0.8 µm grinded surface with E_{pit} = +365 mV; B: Ra = 0.3 µm electropolished surface with E_{pit} = +716 mV; and C: Ra = 0.3 µm electropolished and passivated surface without E_{pit}. Electrolyte: 3.5% (m/v) NaCl.



The mechanical polished surface demonstrated a passive film thickness between 2.1–2.3 nm, whereas the values of the electropolished surface were thinner in the range of 1.5–2.1 nm. As a rule, all passivated surfaces were reported to have the thinnest passive film of about 0.9–1.4 nm, showing the highest passivation properties and corrosion resistance [19]. This is explained by the fact that the naturally formed passive film has a nonuniform Cr-rich layer and a thicker Fe-rich oxide and hydroxide, whereas the passive film modified by passivation treatment is composed of a thin, uniform, and compact Cr-rich oxide layer [6, 13, 14].

The obtained passive film thickness values were confirmed by XPS analysis resulting from the exponential attenuation of the metallic Fe $2p_{3/2}$ peak intensity. A comparison of the layer thicknesses in Table 4 obtained by both techniques shows a close match between the values, using two independent methods. To investigate the elemental composition and identify the phases that form the passive layer a quantitative analysis of the deconvoluted XPS spectra was performed. Table 5 displays the atomic percentages of the metallic elements for different treatment conditions, including the as-received alloy as reference and highlighting the Cr to Fe ratio.

DISCUSSION

Surface qualification of 316L stainless steel tanks using field electrochemical measurements via portable electrochemical minicell was applied as a promising tool to ensure high product quality. The bioprocessing tanks are required to be submitted to a surface qualification process before introducing them to the industrial process, and ASME BPE code describes the electrochemical techniques as an advanced inspection method, although this technology is not yet ready for field inspections. As a complementary technique, XPS measurements are allowed to characterize the passive film, supporting the efficacy of portable electrochemical minicells for field surface inspection.

Comparing the corrosion resistance performance of the different treatments, it is safe to state that the passivated surface reached the highest parameters for all conditions, highlighting an approved PL quite superior of the acceptance criterion of 350 mV. In addition, it is worth pointing out that the absence of pitting corrosion and the negative hysteresis running in a quite reduced passivation current density confirms that the passive film is composed by Cr-rich and uniform oxide [14, 15, 20, 24, 32-35]. On the other hand, an ASTM B912 [36]

Figure 4: EIS spectra in Nyquist representation recorded during immersion in 3.5% (m/v) NaCl for 316L stainless steel passive film with surface finish: A: 0.8 µm grinded and 0.8 µm grinded and passivated; B: 0.3 µm electropolished and 0.3 µm electropolished and passivated; C: 0.2 µm grinded and 0.2 µm grinded and passivated; and D: 0.05 µm electropolished and 0.05 µm electropolished and passivated.

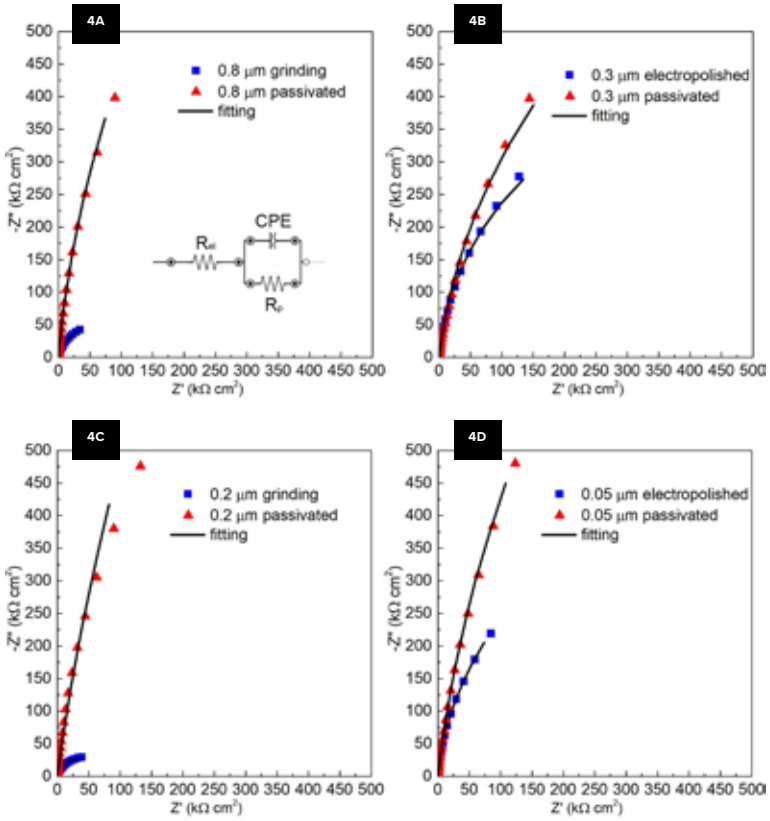


Table 4: XPS and EIS surface characterization.

Sample	R_{el} (W) cm^2	R_p (MW) cm^2	CPE Y_0 (mF cm^2)	n	$\chi^2/10^{-3}$	d_{EIS} (nm)	d_{XPS} (nm)
0.8 µm grinding	5.4	0.15	239	0.81	1.8	2.33	2.37
0.8 µm passivated	5.1	3.52	46	0.91	1.6	1.55	1.74
0.3 µm EP	5.1	0.86	50	0.91	1.6	1.44	1.50
0.3 µm EP passivated	5.4	1.72	54	0.92	0.8	1.12	1.02
0.2 µm grinding	4.7	0.07	208	0.82	2.7	2.14	2.80
0.2 µm passivated	4.3	8.14	54	0.91	4.5	1.36	1.31
0.05 µm EP	3.7	0.57	118	0.85	2.3	2.14	2.30
0.05 µm EP passivated	4.4	3.96	51	0.92	1.1	1.09	0.92

Table 5: Atomic composition of 316L stainless steel surfaces obtained by XPS.

Sample	Cr (at.%)	Fe (at.%)	Ni (at.%)	Molybdenum (Mo) (at.%)	Manganese (Mn) (at.%)	Cr:Fe Ratio
As received	23.9	65.2	5.7	3.0	2.2	0.4
0.8 µm grinding	29.7	62.1	2.1	5.1	1.0	0.6
0.8 µm passivated	52.6	34.9	5.6	5.6	1.3	1.5
0.3 µm EP	51.2	31.4	4.7	11.6	1.2	1.6
0.3 µm EP passivated	55.1	27.5	10.7	5.6	1.1	2.0
0.2 µm grinding	35.1	59.7	1.2	3.8	1.2	0.6
0.2 µm passivated	61.9	25.2	4.8	7.1	1.0	2.5
0.05 µm EP	34.0	50.6	6.8	7.8	0.8	0.7
0.05 µm EP passivated	57.4	28.5	7.2	5.1	1.8	2.1

Figure 5: Correlation between the XPS and EIS passive film thickness data.

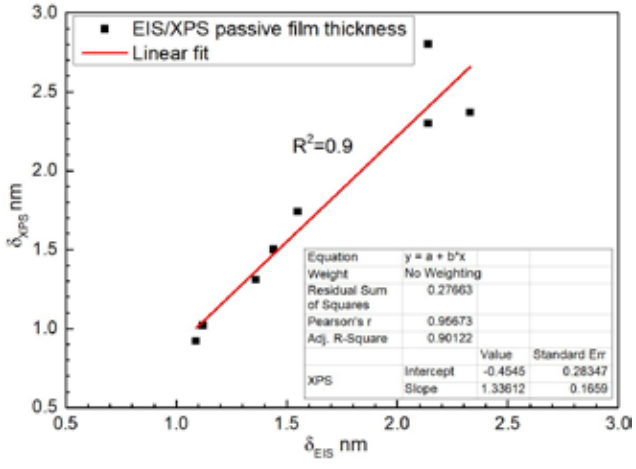
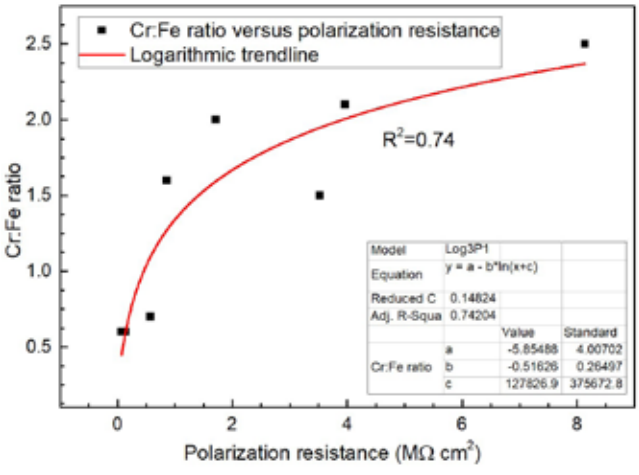


Figure 6: Parabolic relation between Cr:Fe ratio and polarization resistance.



electropolished surface did not perform as resistant as expected considering that ASME BPE specify that the electropolished surfaces are considered as passivated.

However, the maximum corrosion resistance was obtained when combining the electropolishing process with the chemical passivation treatment in sequence. The grinded surface finish is a concern due to the poor pitting potential, a nonacceptable PL, and a high passivation current density. On the other hand, electropolished surface and grinded surface finishes were improved in terms of corrosion resistance by the chemical passivation, achieving acceptable PL after the treatment.

XPS measurements demonstrated that the passive films on 316L austenitic stainless steel had a structure as previously described, which consists of an inner region composed of a Cr-rich oxide layer (Cr_2O_3) in contact with the metallic substrate, whereas the outermost layer is composed of $Cr(OH)_3$ and Fe-rich oxides and hydroxides: iron(II) oxide (FeO), iron(III) oxide (Fe_2O_3), iron(III) oxide-hydroxide (FeOOH).

Besides these iron species, magnetite (Fe_3O_4) and $Fe(OH)_2$ were also reported to compose this layer [14, 15, 38–41]. However, a closer look at the data obtained for different surface treatments revealed distinct features. On mechanical polished surfaces grew a natural passive film, with a thick oxide layer in a range of 2.4–2.8 nm, chemically characterized as Fe-rich oxides with a low Cr:Fe ratio of about 0.6 (see Tables 4 and 5).

When compared to the mechanical polished surfaces, the

Table 6: Conclusion matrix.

Criteria	Conclusion
Passive film thickness	A linear relation between the passive film thickness obtained by EIS and XPS measurements was found. The passive film thickness determined by EIS and XPS techniques were very close, with residual values varying within an interval of 0.2 nm. This means that it is safe to state that onsite electrochemical tests provide consistent data in terms of passive film properties.
Correlation of Cr:Fe ratio and Rp	The polarization resistance and the Cr:Fe ratio show parabolic power law dependence, allowing us to relate EIS field inspection results with those of XPS for the qualification of the passivation treatment procedure. This is important information for onsite measurements that allows for the estimation of the tank resting time after passivation treatment.
Sensitivity of the tool	The portable electrochemical minicell was able to differentiate the surface resistance of different surface finishes, where the distinguished value of Cr:Fe ratio was known. The most common surface finishes for pharmaceutical tanks were assessed and the portable electrochemical minicell was able to differentiate the surface resistance. Each surface finish had a specific Cr:Fe ratio, and it was measured distinguished polarization resistance, which proved the sensitivity of the tool.
Bottom line	Field electrochemical measurements applying EIS technique has proven to be accurate in determining passive film properties, and it can be a powerful tool for qualification and monitoring of the passivation properties of stainless steel surfaces.

electropolished surfaces grew a thinner (1.5–2.3 nm) and more Cr-rich passive film, resulting in a Cr:Fe ratio of 1.6–2.3 nm. The latter value highlights the 0.3µm-EP sample. Even though electropolished surfaces provided an improved passive oxide when compared to the mechanical polished surfaces, it is important to note that in both cases an Fe-rich and nonuniform passive film was formed on the surface, as indicated by the breakdown potential in cyclic polarization tests.

The main hypothesis taken into consideration is the fact that the mechanical and electropolishing processes promoted the growth of the Fe-rich layer [18, 20]. On the other hand, the passive film modified by chemical passivation treatment provided the highest passivation properties with the Cr:Fe ratio of up to 2.5 nm (see Table 5) due to the selective dissolution of iron. The layer consists mainly of Cr_2O_3 and $Cr(OH)_3$ phases, which are responsible for the high corrosion resistance [41] (see Table 4). These surfaces showed the thinnest passive film being in the range of 1.0–1.7 nm, containing a reduced quantity of Fe oxides, a small fraction of Mo oxides, and traces of nickel and Mn oxides.

Portable electrochemical minicell is a portable tool used to measure the passivation properties and corrosion resistance of stainless steel tank surfaces in field conditions. This work demonstrates that, using portable electrochemical inspection techniques, an accurate onsite tank surface performance can be determined in terms of corrosion resistance and passivation parameters.

The results are consistent with those obtained by XPS, confirming the passive film thickness values obtained by EIS, and associating the high corrosion resistance, obtained from the OCP and CPP curves, to the distinct structure of the thin passive layer. These notable results are shown in Figures 5 and 6. Figure 5 displays a linear trendline correlating the passive film thickness determined by both techniques with R-squared values > 0.90, which represents a good fit to the data.

Additionally, as can be seen in Figure 6, a parabolic relation between polarization resistance and Cr:Fe ratio was found in a preliminary assessment. This demonstrated the great potential of the portable electrochemical minicell technique for field surface qualification. However, further studies are needed to establish this method as the standard test for stainless steel tanks.

CONCLUSION

The portable electrochemical minicell's efficacy was tested through the inspection of different surface finishes of 316L stainless steel typically applied in tanks and facilities. Table 6 shows the conclusions according to the performance perspective of the portable tool. Field electrochemical measurements applying EIS technique has proven to be accurate in determining passive film properties, and it can be a powerful tool for qualification and monitoring of the passivation properties of stainless steel surfaces.

Acknowledgments

The authors would like to thank the São Paulo Research Foundation (FAPESP) for providing financial support for this research (Proc. no. 2021/11684-4).

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SELECTION CRITERIA
for Pharmaceutical Containment Equipment

By Morihiko Takeda

Pharmaceutical manufacturing facilities produce a variety of products, including highly potent products that require safety measures to prevent adverse health effects on patients and operators. To ensure safety, these facilities use containment equipment to minimize the risk of contamination. This article presents criteria for selecting containment equipment, considering both cross-contamination and industrial hygiene risks.

Planning safety in pharmaceutical manufacturing facilities requires a proper evaluation of the risk involved, such as the risk of cross-contamination between the target product and other drugs and the risk of industrial hygiene to operators. Based on this proper evaluation, the appropriate containment equipment should be selected for use in manufacturing facilities.

SELECTION CRITERIA OVERVIEW

The selection of containment equipment is often based on the degree of airborne exposure because inhalation or airborne transfer are the main routes of exposure for operators. This selection method has proven effective in reducing industrial hygiene risks to operators.

Containment equipment is also effective in preventing cross-contamination risk in pharmaceutical manufacturing. It is important to consider exposure through mechanical transfer, in addition to airborne transfer, when evaluating containment equipment. However, there has not been a system proposed for selecting containment equipment based on the degree of exposure through mechanical transfer.

Selection criteria are based on the evaluation of exposure routes through both airborne and mechanical transfer and are driven by advancements in engineering for highly active pharmaceuticals and exposure measurement. This criterion could also be applied to maintenance design of the accessories for pharmaceutical manufacturing equipment or containment equipment, such as changing the filters of dust collector or fluid bed dryers.

The containment equipment selected during the initial design phase may need to be reselected as a result of more detailed risk assessments conducted later in the design process, such as failure modes and effect analysis (FMEA), hazard and operability studies (HAZOP), or other similar methods. In particular, the source of both cross-contamination and industrial hygiene issues, which are often due to the changeover for each campaign manufacture, needs to be evaluated in terms of standard operating procedures (SOPs) and equipment design.

The keystone of this article is organized in the following section, which introduces the risk assessment method that forms the basis of this article, and in the section on the method for selecting containment equipment, which delves into the specific steps for selecting containment equipment.

RISK ASSESSMENT METHOD

In developing a method for selecting appropriate containment equipment considering both cross-contamination and industrial hygiene risks, it is important to clearly identify each risk scenario and the acceptable level of risk.

Risk Assessment for Cross-Contamination

Risk is a function of severity and probability:

$$\text{Risk} = f(\text{Severity, Probability})$$

In applying this function, the risk of cross-contamination can be defined as the combination of the amount of drug A entering into drug B (amount of exposure) and the potential toxicity (hazard) of drug A that causes health problems in patients administered with drug B. In other words, cross-contamination risk is a function of both hazard and exposure [1]:

$$\text{Cross-contamination Risk} = f(\text{Hazard, Exposure})$$

Note that although hazard is defined as "the potential source of harm (ISO/IEC Guide 51:2014)" in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals

for Human Use's (ICH's) Q9(R1) [2], in this article, we define it as the toxicological potential of a drug to cause adverse health effects (toxicity).

Cross-contamination risk assessment in multiproduct facilities, in accordance with the quality risk management process of ICH Q9, identifies whether the risk of cross-contamination in each manufacturing process is acceptable or not. This is accomplished by a) identifying exposure routes of cross-contamination and analyzing the amount of exposure caused by that route and b) using the potential toxicity of the drug (cross-contamination limit) as an index.

According to ICH Q9(R1) 4.3 Risk Assessment: "In some risk management tools, the ability to detect the harm (detectability) also factors in the estimation of risk" [2]. But detectability is often clarified during the detailed specification phase of containment equipment. Therefore, it was not considered in the stage of selecting the basic functionality of the containment device.

Identification of the cross-contamination exposure route

If cross-contamination of products occurs during the manufacturing process, patients who are administered that product will be exposed to the risk of adverse health effects caused by the other cross-contaminated drug. Identifying the cross-contamination route (risk factor) is identifying "a potential source of harm," as mentioned in ICH Q9(R1) [2].

There are four routes that cause cross-contamination risks—mix-up, retention, mechanical transfer, and airborne transfer—and the respective risks are identified [1, 3] in the following sections.

Mix-up

Mix-up is the use of the wrong active pharmaceutical ingredients (APIs), intermediates, or products and is mainly caused by human error. GMPs and related guidelines have proposed various requirements to prevent mix-up. To reduce the risk of cross-contamination through this exposure route, implementing monitoring systems and measures to prevent human error (e.g., appropriate SOPs and labeling, double-checking) is effective. Containment equipment does not contribute to this risk reduction.

Retention

Retention is defined as the carryover of material on product contact surfaces from one product to another in the same equipment used in a campaign manufacturing. The factors affecting retention relate to the effectiveness of the cleaning procedure [1]. That is, the cross-contamination risk due to retention has been accepted through cleaning validation. However, as specified in the 2015 revision of the PIC/S GMP Guide Annex 15 (Process Validation) [4], the acceptable residue limits need to be established based on toxicological health-based exposure limits. This differs from industry-proposed limits, such as 10 ppm (parts per million), 1/1000, and the visual detection limit that have been adopted by many pharmaceutical companies [5].If the equipment is designed so that powder loading into the equipment, discharge of intermediate products from the equipment, or changeover cleaning (clean-in-place [CIP] compliance) can be performed under completely closed conditions, then the risk of cross-contamination due to retention is acceptable through cleaning validation. However, any type of equipment, especially for solid dosage forms, cannot maintain a completely closed state (containment of exposure below acceptable limits) for such processes. Therefore, it is important to consider the exposure risk from other routes such as mechanical and airborne transfer.

> In developing a method for selecting appropriate containment equipment considering both cross-contamination and industrial hygiene risks, it is important to clearly identify each risk scenario and the acceptable level of risk.

Mechanical transfer

Mechanical transfer is an event in which a drug substance is transferred from a product contact surface to a nonproduct contact surface (e.g., the exterior surface of manufacturing equipment, facility walls and floors, operator's garment) and later is mixed with other products. There is no need to consider cross-contamination due to mechanical transfer if the products are not transferred to a nonproduct contact surface.

However, many mechanical transfers occur in the pharmaceutical manufacturing process and all routes by which material can be transferred from contaminated nonproduct surfaces into the product must be considered. This includes product contact surfaces contaminated by contact with contaminated surfaces, inadvertent or transient contact with other contaminated non-designated product contact areas, and direct contact of the product with such surfaces as operator apparel and gloves [1].

One example includes any solid dosage manufacturing equipment that handles powders, such as tableting machines. If the equipment cannot be cleaned to below acceptance level without disassembly, the disassembly of wet parts after wet in place, cleaning, and reassembly of that equipment presents a cross-contamination risk, due to the assumption that the drug substance would adhere to the operator's garment.

If tableting machines and other formulation equipment could be cleaned in a completely closed state without requiring disassembly, like in CIP systems, then the risk of the cross-contamination

caused by mechanical transfer would be acceptable. Physical containment of the product contact part, which is the source of contamination, is also effective in reducing the cross-contamination risk caused by mechanical transfer. The degree of cross-contamination risk varies depending on the robustness of the containment equipment.

Airborne transfer

Airborne transfer is an event in which the drug substance on the product contact surface becomes airborne and disperses in the form of aerosol or dust and carries over into another product. Physically segregating the product contact surface and containment by airflow is effective in reducing the cross-contamination risk by airborne transfer. The degree of cross-contamination risk varies depending on the selection of the containment equipment.

In other words, containment equipment cannot contribute to the reduction of cross-contamination through mix-up and retention, but it can be effective in reducing the risk of cross-contamination via mechanical transfer and airborne transfer.

Analysis of the cross-contamination limits

Cross-contamination shall be analyzed to determine whether the risk of cross-contamination of the manufacturing process is at an acceptable level by using the potential toxicity of a drug substance (cross-contamination limit) as an index. It is necessary to scientifically establish the cross-contamination limit based on toxicology or pharmacology.

A representative index of the health-based exposure limit is the permitted daily exposure (PDE)/acceptable daily exposure (ADE). ADE is defined as "a dose that is unlikely to cause an adverse effect if an individual is exposed, by any route, at or below this dose every day for a lifetime" [1]. The PDE is established by identifying a threshold without adverse health effects based on validated preclinical (animal) and clinical (human) data and incorporating appropriate safety factors.

Note that the terms used in Europe and the United States to express ADE is different as follows, but the definition is the same toxicologically. In Europe, PDE is used by the European Medicines Agency, ICH, and the PIC/S. In the US, ADE is used by the FDA and ISPE.

Risk evaluation of cross-contamination exposure routes

In pharmaceutical manufacturing, cross-contamination risk of each exposure route should be evaluated using the following method. This will ensure that the APIs of a product manufactured in a shared equipment for multiproduct facilities do not enter into a daily dose of another product above its PDE level:

- In many cases, risk of cross-contamination due to mix-up can be reduced by detection through a specification test.
- For the risk evaluation of cross-contamination due to retention, cleaning validation is effective. The critical limits of cleaning validation, however, should be toxicological-based limits.
- Risk of cross-contamination due to mechanical and airborne transfer has been considered acceptable if the nonproduct contact surfaces (operation rooms, exterior surfaces of equipment) are visually cleaned. However, in manufacturing processes where highly active drugs are handled, the risk evaluation of cross-contamination using conventional visual inspection cannot be regarded as a *risk evaluation based on scientific knowledge*.

Although these cross-contamination risks were considered detectable through the specification tests, they cannot be detected by the verification of a limited number of samples. This is because contamination of another drug via mechanical transfer and airborne transfer usually occurs locally and does not uniformly contaminate the whole batch.

It is necessary to evaluate the cross-contamination and industrial hygiene risk through mechanical transfer and airborne transfer by:

- Identifying the route of carryover into another product
- Identifying the amount of carryover caused by that route
- Evaluating the acceptability of that amount of contamination using an acceptable limit as an index

It is reasonable to consider the exposure route that represents an exposure scenario based on actual cases. Thus, we should focus on airborne exposure from the boundary surface of containment equipment and exposure to residues on surfaces that operators could contact. The acceptable level is applied to the risk assessment of cross-contamination due to mechanical or airborne transfer previously described. Cross-contamination is often caused by operators contacting surface residues; therefore, adopting wipe limits (surface exposure limits), an industrial hygiene index that shows how operators contact with the contaminated surface, is considered reasonable.

However, the airborne exposure measurement at some specified points is not always lower than that of the exposure measurement for operators. This means that it is not enough to assess the risk of cross-contamination by merely evaluating the operators' exposure. It is reasonable that the amount of the airborne exposure on the boundary of containment equipment can be considered the sum of the airborne exposures that could cause cross-contamination.

Risk Assessment for Industrial Hygiene

As one aspect of "industrial hygiene" as defined by OSHA [6], this article introduces the concept that to ensure operators' safety, the amount of residue on surfaces with which they may contact should remain below exposure limits. Operators are exposed to drug substances through a variety of routes during a manufacturing process, such as nasal and oral inhalation, dermal absorption, and mucosal absorption.

The definition of risk stated previously is also applicable to industrial hygiene risk. The industrial hygiene risk in this article can be defined as *the combination of the probability of occurrence of harm due to the drug substance which will come into*

contact with an operator and the health disorder raised by the drug substance extracted.

The same method used for cross-contamination risk evaluation can be applied to the industrial hygiene risk evaluation. So, the evaluation can be carried out as follows: a) identify the route of operator exposure to drug substances, b) analyze the amount of exposure through that exposure route, and c) determine the acceptability of industrial hygiene risk of the process using the potential toxicity of the drug as an index.

Identification of industrial hygiene exposure

The exposure of drug substances to the operators is limited to mechanical and airborne transfer. As mentioned previously, the use of containment equipment is effective in reducing the cross-contamination risk caused by both mechanical and airborne transfer. The selection of containment equipment also reduces industrial hygiene risks.

The use of personal protective equipment (PPE) is effective in reducing exposure to the operator, but it is considered a last resort or secondary protection [1]. It protects only operators, and it does not mean the environment where the operators' activity takes place has been controlled. In this article, the effectiveness of PPE is not considered in the selection of containment equipment.

Analysis and evaluation of exposure limits for industrial hygiene

Permissible exposure limits for industrial hygiene should be scientifically established based on toxicology or pharmacology. The limits are set for each route of exposure, but in principle, operators should not intake more than PDE/ADE of the drug substance from any route of exposure.

Permissible exposure limits for airborne transfer

Occupational exposure limits (OELs) set an acceptable airborne concentration at or below which no adverse health effects to operators are expected after a daily work shift of eight hours (one working day) where the target substance exists. It is calculated based on PDE, unless there is an excessive workload. It is often calculated with an assumption of OEL = PDE/10, according to the air intake volume (approximately 10 m^3) of an operator during the eight-hour working shift. If the bioavailability by inhalation has been verified, it should be considered.

Permissible exposure limits for mechanical transfer

The residues of drug substances on the surface where operators may touch should not exceed the wipe limits. Wipe limit is defined as PDE/100 cm^2 [3]. This is because 100 cm^2 is the mean value of the total number of palms area, or the number of human hands, that could touch the surface. The use of these limits was proposed because operators' palms are most likely to contact the substances handled by their hands.

In the establishment of these indices, there are arguments to strictly evaluate the bioavailability for dermal absorption, the number of times the operator touches the surface, and secondary (indirect) exposure. However, using the index method is beneficial to conveniently evaluate the residues on exterior surfaces of equipment and surfaces of facilities from the viewpoint of the operators' safety.

EQUIPMENT SELECTION METHOD

Selection Criteria Control Exposure Risk

As mentioned previously, the use of containment equipment is effective for reducing cross-contamination risk caused by mechanical and airborne transfer, but not caused by mix-up and retention. Both cross-contamination and industrial hygiene risks are caused by the transfer of drug substances from product contact surfaces to nonproduct contact surfaces through mechanical and airborne transfer. These risks depend on the following factors:

- Physical/chemical properties of the subject drug substance (e.g., state, volume)
- Characteristics of the process operation (e.g., operations that apply energy to the subject drug substance resulting in airborne transfer, such as milling, or operations that cover the exposed surface, such as coating)
- Performance of containment equipment or containment performance of manufacturing equipment

In pharmaceutical manufacturing, it is impractical to change the formulation, the physical and chemical properties of the drug substance, or the manufacturing process unless in the development stage of new drugs. Therefore, selecting appropriate containment equipment is practically effective to control the industrial hygiene and cross-contamination risks.

Equipment Selection Policy

Basic policy for the selection of containment equipment should be established with the following procedure:

- Set permissible exposure limits: Establish the exposure limit band for industrial hygiene/cross-contamination risks based on the hazardous properties of the subject drug substances.
- Set exposure level: Identify the predicted exposure (PE) band. The details are described in the following paragraphs for each process operation based on the physical/chemical properties of the drug substances and the characteristics of process operations.
- Select engineering control (EC) band: Select an EC band to reduce the exposure of each identified process operation to a level below a permissible exposure level and select an appropriate containment equipment.

Each procedure is detailed in the next section.

Equipment Selection Procedures

Setting permissible exposure limits

Classifying the subject drug substance according to its exposure limits and sharing this with the related personnel ensures they

Table 1: Exposure limit band.

Index \ Exposure limit band		1	2	3	4	5	6
ADEs/PDEs: Permitted daily exposure	/ Day	> 10 mg	> 1 mg ≦ 10 mg	> 100 µg ≦ 1 mg	> 10 µg ≦ 100 µg	> 1.5 µg ≦ 10 µg	≦ 1.5 µg
OELs: Occupational exposure limits (8-hour time-weighted average)	µg / m^3	> 1,000	> 100 ≦ 1,000	> 10 ≦ 100	> 1.0 ≦ 10	> 0.15 ≦ 1.0	≦ 0.15
Wipe limits: Acceptable surface limit	/ 100 cm^2	> 10 mg	> 1 mg ≦ 10 mg	> 100 µg ≦ 1 mg	> 10 µg ≦ 100 µg	> 1.5 µg ≦ 10 µg	≦ 1.5 µg

Note 1:

The criteria for setting exposure limit band are as follows:

- OEL: 10 µg/m^3 is the occupational exposure limit level that the physical segregation should consider
- PDE: 1.5 µg/day is the threshold of toxicological concern (TTC) value for mutagenic substance
- Wipe limits: 100 µg/100 cm^2 is the minimum visible detection limit
- OEL: 100–1,000 µg/m^3 is the range of visual detection limit for dust

Note 2:

When handling mutagens and anticancer drugs with genotoxicity, the most robust containment equipment for manufacturing equipment is used. Moreover, the ICH M7 guideline explains that the default value of PDE for the "compounds having direct effect on DNA, those are, mutagens and anticancer drugs with genotoxicity," is 1.5 µg/day. This is based on the TTC except for the aflatoxin-like compounds, N-nitroso compounds, and alkyl azoxy compounds, which are classified into a group of highly mutagenic carcinogens "Cohort of Concern" [7]. Therefore, a value of < 1.5 µg/day is set for the PDE of the most active category in the exposure limit band.

Table 2: Predicted exposure band.

Handling amount / Physical properties	Trace Amount A < 100 mg	Trace Amount B < 10 g	Small Amount A < 100 g	Small Amount B < 1 kg	Medium Amount < 10 kg	Large Amount > 10 kg
Low	PE0	PE0	PE0	PE1	PE1	PE2
Medium	PE0	PE0	PE1	PE1	PE2	PE3
High	PE0	PE1	PE1	PE2	PE3	PE3

Note: The units used for the classification of "amounts used" in COSHH Essentials are grams, kilograms, and tons, but these units are too large compared to the quantities handled in pharmaceutical manufacturing and are impractical. Thus, this article establishes handling amounts, such as trace amounts A/B and small amounts A/B, so that they can also be applied to laboratory and quality control room scales.

understand that the materials they handle are hazardous property. Table 1 summarizes classified exposure limits, which we call the exposure limit band.

Setting the exposure level

The subject material changes its physical form as the process operation proceeds and is exposed to a nonproduct contact surface from a product contact surface. The potential degree of exposure is predicted from the physical condition and the amount being handled, and a PE is determined based on the criteria described in Table 2.

Predicted exposure band

A PE band is used to classify the degree of exposure of a subject drug substance to nonproduct contact surface based on its physical form and daily handling amount. This index shares the same basic concept with the exposure predictor (EP) band proposed in Control of Substances Hazardous to Health Regulations (COSHH) Essentials.

In this article, however, airborne and the mechanical transfer are included when considering the *degree of exposure of the subject substance to the nonproduct contact parts*. In this respect, the PE band in this article is a different concept from EP in COSHH Essentials, and therefore the term PE is used.

Physical properties of the drug substance

Intermediate products change their physical properties as the process proceeds. The changes occur before and after each process. Therefore, physical properties of the substances handled in

each process are determined at the inlet of the intermediate product to the process, during process, and at the outlet of the intermediate product. When applying Table 2, the physical properties are classified in the following categories, which define the viewpoint of the degree of exposure in the representative physical form of the drug substance.

These are the physical properties of drug substances in the filling process:

- Low: Liquid/suspension, soft capsules after dedusting, and coated tablets
- Medium: Uncoated tablets, wet powders, wet pellets, soft capsules before dedusting, hard capsules that are difficult to dedust, and coated granules
- High: Micropowders, dry powders, powders, fine granules, granulated products, and freeze-dried products

The degree of exposure during filling operation should be evaluated for each risk scenario, such as exposure in the event of bottles accidentally toppling. This is because the degree of exposure during the filling of the drug substance into containers depends on unexpected (but possible) accidental events in the process operation. It should be noted that what is important is *evaluating the amount of daily exposure* and not *discussing the frequency of occurrence*.

Handling amount

The handling amount in Table 2 indicates the daily amount of subject drug substance handled in that containment equipment because permissible exposure limits are based on a unit of one day. If the API is diluted with excipients, such as intermediates for solid dosage, the apparent exposure limit band can be used. In this case, the exposure limit band can be relaxed in accordance with a dilution rate as long as the actual amount of the API in the airborne dust correlates to the dilution ratio.

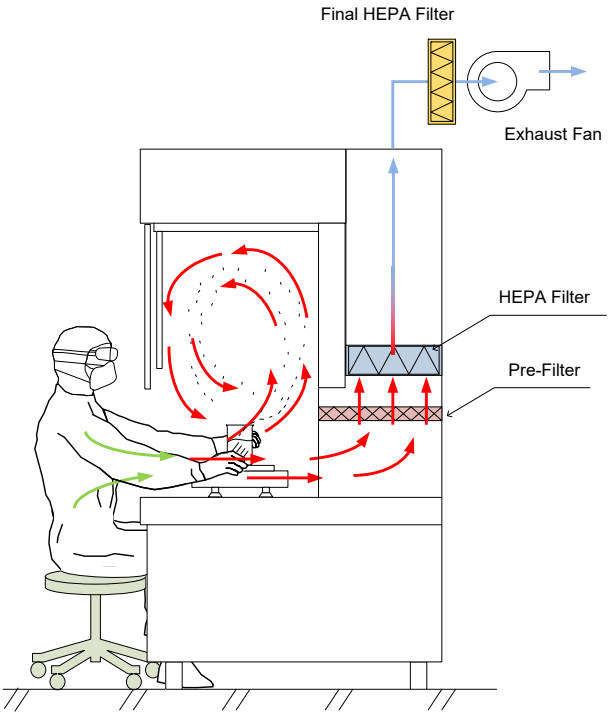
EC Band

Subject drugs should be handled at exposures below the permissible limit for each process operation. So, appropriate containment functions are required according to the physical properties and amounts handled and the exposure limits in the process. The containment function required is achieved by having equipment and facilities that control or limit transfer to nonproduct contact surfaces due to process operations.

The typical containment equipment used in the formulation process in the pharmaceutical industry can be classified into the following four EC band categories based on its containment performance during *process operation and decontamination of the drug substance residues*.

1. EC1: General ventilation (HVAC) facility.
2. EC2: Containment by air flow and local dedusting device. For example, local dust collection (external device), local dust collection (enclosed type, push-pull system), local dust collection (enclosed type, draft chamber type), closed restricted access barrier system.

Figure 1: Enclosed dust collection booth allocated to EC2.

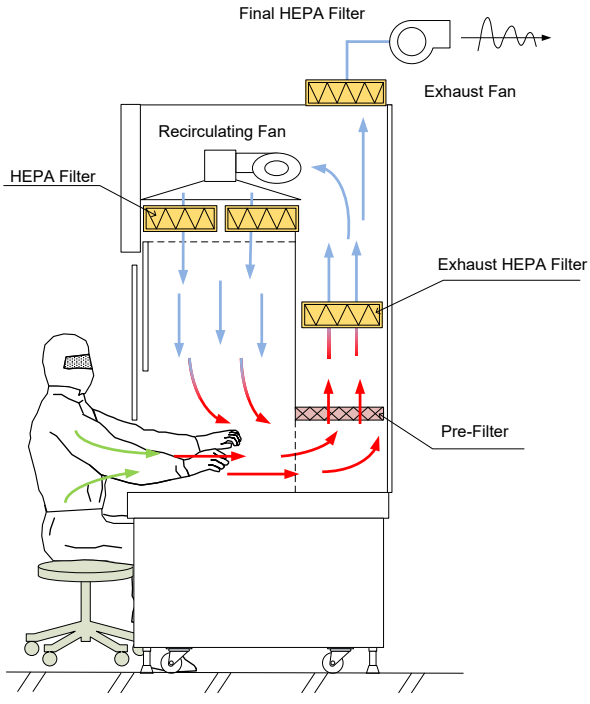


3. EC3: Physical isolation device, containment equipment using airflow that allows decontamination of the exposed area only by manual hand operation. For example, enclosed dust collection booth that allows in/out transfer of items and inside decontamination by hands, safety cabinet with unidirectional flow, negative pressurized isolator box with pass-through hatch or positive pressurized robust isolator, split valve, flexible (single use) isolator box.
4. EC4: Physical isolation device that allows in/out transfer of items and inside decontamination under closed condition: For example, negative pressurized glovebox or negative pressurized isolator with rapid transfer port (RTP).

The containment equipment cannot be considered robust if the drug substance or operator is exposed to the outside of the chamber by air when decontaminating the inside of the chamber or the drug substance is exposed to the outside of the chamber by mechanical transfer. This is true even if the equipment can control the containment by airflow.

For example, the equipment shown in Figure 1, which includes a structure to enclose the source of dust generation and controls exposure of openings for manual operation by airflow, may generate turbulence and vortex airflow in the chamber. The drug substance may be airborne to the area where the operator's hands cannot reach. So, the operator may put their upper body inside the

Figure 2: Enclosed dust collection booth allocated to EC3.



chamber to perform the decontamination work, and therefore, the EC band should be set to EC2.

On the other hand, in the airflow containment equipment shown in Figure 2, the airborne dust and adhesion of residues are limited because there is a laminar flow inside the chamber. The operator can decontaminate the chamber to a level below an acceptable residue limit by simply reaching out their hands into the chamber. When considering a series of process operations including decontamination, the containment performance is more robust than the above-mentioned equipment, and the EC band is set to EC3.

Selecting containment equipment

The exposure in each process operation is predicted and allocated into an appropriate EC band to control the exposure of a subject drug substance to the level below its acceptable limit. Table 3 is an EC band showing the containment categories determined based on the exposure levels and exposure limits predicted from the past exposure measurements. The EC band can be selected from the PE band for each process and exposure limit band. (A detailed explanation on how to create Table 3 is provided in the Appendix.)

Additional requirements for visual detection limits

Cross-contamination and industrial hygiene risks can be reduced if the degree of exposure can be visually detected. Visual detection limits are highly dependent on the characteristics of drug substance, the manufacturing process, and the internal surface specifications in the operation room.

The following requirements should be considered in the process validation and verification. In the case where the drug or intermediate is classified as 3–4 in the exposure limit band and the PDE/100 cm^2 or under cannot be confirmed visually, identify the area where there is a potential for exposure in the actual manufacturing process or in the process simulation test using the surrogate powders. If necessary (e.g., if the exposure level exceeds 1/10 of the acceptable limit), the residuals should be verified on a periodic basis.

In the case where the drug or intermediate is classified as 4–6 in the exposure limit band, identify the area where there is a potential for exposure in the actual manufacturing process or in the process simulation test using the surrogate powders. If necessary (e.g., if the exposure level exceeds 1/10 of the acceptable limit), secondary exposure prevention measures should be considered, and the residues should be verified periodically. If the decontamination operation is performed manually, the residues inside the containment equipment (primary barrier) should be verified for every lot (or every campaign).

CONCLUSION

This article introduces a methodology for selecting containment equipment in the early stages of design for pharmaceutical facilities. Selecting containment equipment does not mean that the cross-contamination or industrial hygiene risks of pharmaceutical manufacturing facilities are now acceptable. There are some pharmaceutical processes where adequate containment equipment cannot be applied.

In addition, the containment equipment is only a primary barrier, and a secondary barrier should be considered in case of primary barrier failures. Such comprehensive risk assessment should be defined and implemented as cross-contamination or industrial hygiene risk management based on ICH Q9 or a contamination control strategy.

In the risk assessment of containment equipment, it is also necessary to consider the following issues:

1. Risk assessment of containment equipment specifications
2. Risk assessment of secondary barriers, such as specification of facilities such as heating, ventilation, and air-conditioning (HVAC) systems and specification of the operation room (capabilities of containment, washing, decontamination)
3. Risk assessment in case of containment equipment failure where PPE or emergency mist/shower would be needed
4. Risk assessment in cases where containment equipment cannot be applied and technical/organized measures of a robust secondary barrier system would be needed

It is equally important to define their risk assessment methods, which may be introduced in a separate article if the opportunity arises.

Table 3: EC band.

Predicted exposure band / Exposure limit band	PE0	PE1	PE2	PE3
1	EC1	EC1	EC1	EC1
2	EC1	EC1	EC2	EC2
3	EC1	EC2	EC2	EC3
4	EC2	EC2	EC3	EC3
5	EC2	EC3	EC3	EC4
6	EC3	EC3	EC4	EC4

Adjustment for the dust emission property of the process operation:

When assuming the degree of exposure for processes that amplify the energy for powders to become airborne, such as milling, it is not possible to select the appropriate containment equipment if the exposure band is set based on the physical property of the drug substance in Table 2. For such processes, therefore, the EC category selected based on the Table 3 EC band should be raised to one higher category.

This article includes major technical suggestions that can be selected and applied when establishing a quality management system (QMS) based on ICH Q9(R1). However, when incorporating these suggestions into an ICH Q9–based QMS, appropriate selection and adjustments may be required to reflect the actual situation of each manufacturing site.

APPENDIX: METHOD FOR CREATING TABLE 3

Table 3.1

First, we prepared Table 3.1 from approximately 100 data points of our actual exposure measurements and actual exposure measurements shown in the published literature.

Data

The data in Table 3.1 included:

- Airborne exposure measurement data at operator's mouth, which is shown as "operator's airborne exposure."
- Airborne exposure measurement data at fixed points around the containment equipment, which is shown as "maximum airborne exposure at stationary point."
- Mechanical transfer measurement data remaining on operator's chest in the form of residues, which is shown as "residue on operator."
- Mechanical transfer measurement data remaining at fixed points around the containment equipment in the form of residues, which is shown as "maximum residue at stationary point."

Columns

- The containment equipment column shows the EC band, which represents the required containment performance for each process.

- The PE band column shows:
  - The handling amount when measuring exposure
  - The state of material to be handled
  - The PE band selected from Table 2

- The airborne transfer data column shows:
  - The operation time, operator's airborne exposure, and OEL given by OEL = (operation time) × (operator's airborne exposure) / (480 minutes)
  - The maximum airborne exposure at stationary point and 8-hour time weight average given by: 8-hour time weight average = (operation time) × (maximum airborne exposure at stationary point) / (480 minutes)
  - The actual exposure limit band (airborne), which is obtained by applying the largest value of OEL and 8-hour time weight average to Table 1

- The mechanical transfer data column shows:
  - The residue on the operator, which is measured on the operator's chest and maximum residue at stationary point
  - The actual exposure limit band, which is obtained by applying the largest value of residue on operator and maximum residue at stationary point to Table 1

Table 3.1: List of characteristics of exposure measurement data (excerpted version).

NO.	Process	Containment Equipment		Predicted Exposure Band			Airborn Transfer Data						Mechanical Transfer Data		
		Type	EC	Amount (g/batch)	Properties	Predicted Exposure Band (PE)	Operation (min)	Operator's Airborne Exposure ($\mu g/m^3$)	OEL ($\mu g/m^3$)	Maximum Airborne Exposure at Stationary Point ($\mu g/m^3$)	8-Hour Time Weighted Average ($\mu g/m^3$)	Actual Exposure Limit Band (airborne)	Residue on Operator ($\mu g/100cm^2$)	Maximum Residue at stationary point ($\mu g/100cm^2$)	Actual Exposure Limit Band (residue)
1	Dispensing/Cleaning	LE	EC2	17,700	Powder	PE3	24	1667	83.35	160	8	3	440.48	174.24	3
2	Charging	LE	EC2	17,700	Powder	PE3	7	667	9.73	1191	17.37	3	117.6	33.77	3
3	Dispensing/Cleaning	LE	EC2	1,150	Powder	PE3	32	67	4.47	131	8.73	4	86.72	84	4
4	Dispensing/Washing	GB+PB	EC3	5,000	Powder	PE3	17	112	6	-	<1.0	4	5.75	0.91	5
5	Charging	SV	EC3	5,000	Powder	PE3	9	-	<1.0	92	1.7	4	5.75	-	5
6	Dispensing/Milling/ Washing	PP on the table	EC3	5,000	Powder	PE3	75	33	5	5.1	0.8	4	110	450	3
7	Milling	FH	EC2	150	Powder	PE2	134	0.52	0.15	0.88	0.26	5	126	97.5	3
8	Dispensing/Charging/Was hing	GB+PB	EC3	440	Powder	PE2	30	-	<0.006	-	<0.006	6	<0.008	0.3	6
9	Dispensing/Charging	GB+BO	EC3	20,000	Powder	PE3	168	0.424	0.08	-	<0.003	6	0.512	0.66	6
10	Dispensing	GB+BO	EC3	5,400	Powder	PE3	117	-	<0.229	-	<0.229	6	<0.22	<0.22	6
11	Dispensing	PP (operator within the booth)	EC2	8,000	Powder	PE3	29	394.5	23.8	25.8	1.558	3	2.6	24.3	4
12	Charging	SV	EC3	8,000	Powder	PE3	18	0.093	0.0035	7.7	0.29	5	2.7	26.9	4
13	Dispensing	GB+PB+BO	EC3	3,500	Powder	PE3	77	-	<0.003	-	<0.003	6	0.16	202.3	3
14	Granulation/Sizing/ Charging into the Container	Closed system with pneumatic conveyer and SV for charging	EC3	20,000	Powder	PE3	241	0.079	0.039	0.078	0.04	6	3.436	0.194	5
15	Tabletting	GB SV for charging BO for sampling	EC3	20,000	Granulated Product	PE3	225	0.408	0.19	0.48	0.224	5	2.491	7.942	5
16	WIP/Parts Disassembly by Operator	LV	EC2	Small-B	Wet Powder	PE1	388	0.396	0.323	0.799	0.646	5	41.137	208.116	3
17	Tabletting	GB SV for granule charging BO for sampling	EC3	20,000	Granulated Product	PE3	126	0.16	0.04	0.7	0.16	5	–	38.42	4
18	WIP/Parts Disassembly by Operator	LV	EC2	Small-B	Wet Powder	PE1	222	0.74	0.34	0.11	0.051	5	0.22	124.54	3
19	Charging and Discharging to/from Coating Chamber	GB (no-glove) SV for granule charging BO for sampling	EC3	20,000	Uncoated Tablet	PE2	189	0.325	0.124	0.244	0.096	6	14.508	9.288	4

Abbreviations: BO: bag-out; DB: down-flow booth; EC: engineering control; FH: fume hood (draft chamber); GB: glovebox and isolator; HF: half-suit; LE: local exhaust; LV: local ventilation; OEL: occupational exposure limit; PB: pass box; PE: predicted exposure; PP: push-pull booth; SC: safety cabinet; SV: split valve; WIP: wet-in-place.

Tables 3.2 and 3.3

Second, we prepared Table 3.2 and Table 3.3.

Table 3.2 is created for airborne exposure with exposure limit band and EC band as the vertical axis and PE band as the horizontal axis. The number in each cell is the number of exposure measurement cases listed in Table 3.1, which is counted as one case per row.

Similarly, Table 3.3 is created for exposure by mechanical transfer with exposure limit band and EC band as the vertical axis and PE band as the horizontal axis, and the number in each cell is the number of exposure measurement cases listed in Table 3.1, which is counted as one case per row.

For example, the dispensing/cleaning process in the first row of Table 3.1 shows a dispensing/cleaning operation that assumes an exposure equivalent to PE3 for a containment equipment equivalent to EC2. From the airborne exposure at that time, we obtained the measurement result that we can handle substances up to exposure limit band 3. This example corresponds to the column of exposure limit band 3, EC = 2, and PE = 3 in Table 3.2.

Similarly, from the exposure by mechanical transfer, we obtained the measurement results that the materials up to exposure limit band 3 can be handled. In other words, this case corresponds to the column of exposure limit band = 3, EC = 2, and PE = 3 in Table 3.3.

In this example, the exposure limit band of the material handled in the dispensing/cleaning process is the same for airborne exposure and mechanical transfer. However, in other measurement data, the exposure limit band may differ depending on the exposure route. This indicates that the selection of containment equipment based solely on conventional airborne exposure is insufficient.

To indicate which column of Table 3.2 or 3.3 corresponds to which number of the data listed in Table 3.1, the data numbers are listed as circled numbers. In the same way, about 100 measurement cases were applied to Table 3.2/3.3.

For each exposure limit band (1-6) and PE band (PE0-PE3), selecting the EC band (EC1-4) corresponding to the shaded cell or the cell below it would result in the risk of cross-contamination and industrial hygiene to be accepted.

Table 3

Table 3 was established by summarizing the exposure limit band/ EC/PE combinations corresponding to the masked cells. The data

Table 3.2: Results of airborne exposure around containment equipment.

Exposure Limits Band	Engineering Control Band	Airborne Predicted Exposure Band			
		PE0	PE1	PE2	PE3
1	EC1				
	EC2				
	EC3				
	EC4				
2	EC1				4
	EC2				②
	EC3				
	EC4				
3	EC1				3
	EC2		1		①⑪
	EC3				
	EC4				
4	EC1			2	1
	EC2		1	1	③
	EC3				④⑤⑥
	EC4				
5	EC1			1	
	EC2		⑯⑱	⑦	2
	EC3		1		⑫⑮⑰
	EC4				1
6	EC1				
	EC2		7	9	5
	EC3	12	3	⑧⑲	⑨⑩⑬⑭
	EC4				7

Table 3.3: Results of residue in, on, and around containment equipment.

Exposure Limits Band	Engineering Control Band	Residue Predicted Exposure Band			
		PE0	PE1	PE2	PE3
1	EC1				
	EC2				
	EC3				
	EC4				
2	EC1				
	EC2				1
	EC3				
	EC4				
3	EC1				3
	EC2		⑯⑱	⑦	①②
	EC3				⑥⑬
	EC4				
4	EC1			3	3
	EC2		1		③⑪
	EC3			⑲	⑫⑰
	EC4				
5	EC1				
	EC2		2		
	EC3		2	1	④⑤⑭⑮
	EC4				1
6	EC1				
	EC2				1
	EC3	6	2	⑧	⑨⑩
	EC4				2

were not sufficient to fill all cells for the matrix, so Table 3 was created on the premise that cells with no exposure data available can be filled by interpolating from the existing exposure data. The exposure data in Table 3.2 and Table 3.3 indicate that containment to a level below acceptable exposure may be achieved even with containment equipment which has less performance than defined in Table 3. This means that Table 3 may be rather conservative. This table will be developed to be more precise and rational as future exposure data will be accumulated.

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A SUSTAINABLE APPROACH
to Steam Quality Management

By James Heseltine, FRSC, Nicholas Haycocks, and Robert J E Bowen, DipArch ARB

The world is beginning to grasp the huge challenge of achieving net-zero carbon emissions, or carbon neutrality, by 2050. Many countries have committed to achieving this ambitious goal. As a major global industry, the pharmaceutical sector has a significant role to play. For thermal energy–intensive industries, such as pharmaceutical manufacturing, the long-term future options to maintain current manufacturing processes are few and look to significantly increase energy costs. Optimizing current systems and considering new strategies is necessary.

UNDERSTANDING THE CHALLENGE AHEAD

Net zero is defined as when the amount of carbon dioxide we add is no more than the amount taken away. Whether electrification, hydrogen, biofuel, or even synthetic fuels are considered, each will require significant investment in production, distribution, and infrastructure at a national, local, and individual site level to make the necessary changes.

The journey to achieve net zero must therefore include our focused and deliberate efforts to minimize infrastructure investment cost and timeline to delivery. This can be done by treating energy as a highly valuable resource and establishing best practices in energy efficiency, eliminating waste, and recovering and reusing waste heat from existing processes.

Categorization of Greenhouse Gas (GHG) Emissions

GHG emissions are categorized into three groups or "scopes" by the most widely used international accounting tool, the Greenhouse Gas Protocol [1]. Scopes 1, 2, and 3 are a way of categorizing the different kinds of carbon emissions a company creates within its own operations, and across its wider value chain (see Figure 1).

It is possible to think of scopes in terms of three categories of emissions—scope 1, 2, and 3—and key themes emerge when considering the scopes.

Scopes 1 and 2

Scope 1 covers the GHG emissions that a company makes directly; for example, while running its boilers (including steam), manufacturing utilities, vehicles, etc. Scope 2 covers emissions a company produces indirectly or emissions produced on the company's behalf. These include emissions from electricity, steam, and energy purchased for heating/heat transfer, cooling buildings, and manufacturing utilities.

Scope 1 and 2 emissions are usually within an organization's control. It is highly likely that an organization will have access to the source data needed to convert direct purchases of gas, steam, and electricity into a value in tons of GHGs. This information may be captured and managed by procurement, finance, estates management, utilities, or facilities management departments, or in a sustainability function.

In some cases, solutions currently exist to deliver net zero for scope 1 and 2 emissions. For example, an organization can source renewable electricity, gas, and steam; electrify the source of its energy transfer/heat demand (or use another suitable renewable option); and transition to electric vehicles.

Scope 3

This scope covers all of the emissions that the organization is indirectly responsible for, both up and down its value chain. For example, an organization is indirectly responsible for the emissions produced from purchasing products from its suppliers and from its products when customers use them. Scope 3 emissions are a highly impactful concern.

Scope 3 emissions tend to have the most negative impact and are more challenging to address. For many businesses, scope 3 emissions will account for more than 70% of their carbon footprint. For example, for an organization that manufactures products, there will often be significant carbon emissions resulting from the extraction, manufacture, processing, and distribution of the raw materials and finished goods.

Organizations may also have less control on how scope 3 emissions are addressed. Businesses can offer to collaborate on solutions to reduce emissions with current suppliers or consider changes to their own supply chain. However, in most areas, businesses' current suppliers will have considerable influence on how emissions are reduced through their own purchasing decisions and product design.

Figure 1: GHG emissions created by various company operations are categorized into scopes 1, 2, and 3 [1].

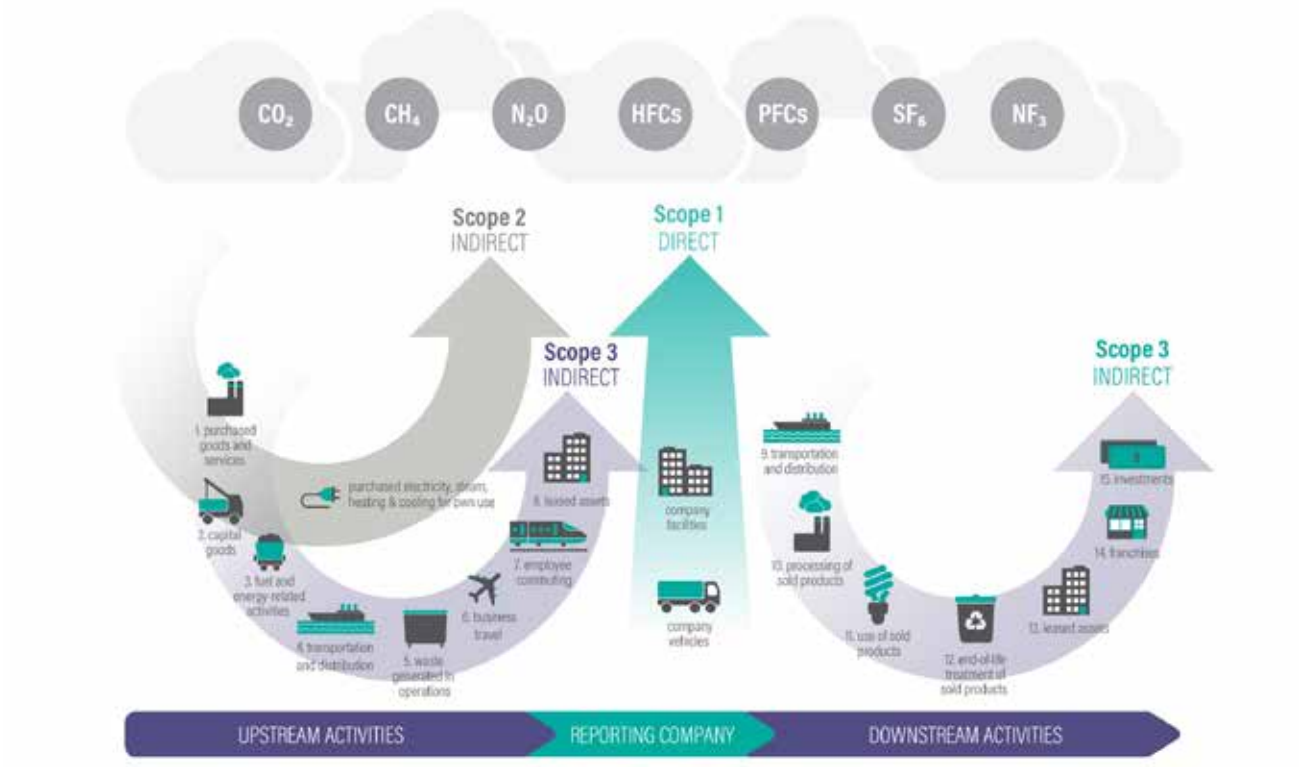

Figure 2: Steam system optimization, now and in the future, building sustainability by design.

Committing to reach net zero will involve significant focus on scope 3 emissions. Definitions for what constitutes net zero ambition are evolving, but businesses looking to adopt best practices will commit to focusing on scope 3 emissions as part of their plans. Mapping a company's emissions footprint by scale, and how much control a company will have over the source of such emissions, will be an effective way to start addressing them. It will also bring the emissions hotspots within reach to effect change.

WHY THE PHARMACEUTICAL INDUSTRY USES STEAM

It is prudent to specifically address the pharmaceutical industry's need to raise, distribute, and bring steam of the correct quality and quantity to each plant and process point of use (POU). It is the intent of the authors that the following discussion may be considered as an example of how such steps could be taken when considering scope 1 and 2 emissions within the pharmaceutical industry. Equally, it may be considered that such principles and examples may be applied to other industries that currently use steam as part of their manufacturing requirements. Together, we have significant opportunity to optimize existing steam systems and innovate new ones, building sustainability by design now and in the future (see Figure 2).

In discussing the use of steam in the pharmaceutical industry, we should first ask, "Why is steam used in pharmaceutical manufacturing across plant and process (critical) utilities?" The answer

is simple, but offers a very compelling and insightful outcome. Steam is powerful, and it has capabilities that other fluids will find hard to match. The high-energy density of steam enables efficient and effective thermal energy transfer with precise temperature control (through steam's pressure/temperature relationship).

There are two important factors to consider as we continue to explore steam's role in pharmaceutical manufacturing: First, it is necessary to ensure existing steam systems operate as efficiently as possible for the energy employed. Second, it is necessary to ensure steam of the correct quality and quantity arrives at each plant and process POU, thus enabling a safe, compliant, and energy-efficient system, or sustainability by design.

Steam is widely recognized as a powerful and highly efficient thermal energy transfer fluid. Steam itself is a natural fluid and environmentally benign; when all of the available heat from steam is used, only water remains in the form of condensate, which can be reused through the steam and condensate loop. However, the current general method used to raise steam is burning fossil fuels, which means steam generation is a significant source of carbon intensity.

Steam Quality Management Enables Energy-Efficient Systems

From the boiler through distribution to plant and process POU, it is critical to achieve a stable, mechanically correct, and appropriately maintained steam system by adhering to steam system engineering best practices. This will ensure steam of the correct quality and quantity is raised, distributed, and provided to each POU (plant and process/critical utilities).

Then, one can consider further optimization of the system. In short, each POU is 100% reliant on steam of the correct quality and quantity to ensure efficient and appropriate energy transfer to the manufacturing process.

One such example is heating, ventilation, and air conditioning (HVAC) systems. HVAC systems have always been an integral part of pharmaceutical manufacturing across comfort and current Good Manufacturing Processing (cGMP) areas. Many large pharmaceutical multinational companies estimate that HVAC demands account for 60%–70% of total operational energy consumption. In fact, operating costs of cGMP HVAC in cleanrooms are often 20–100 times larger than those employed in typical comfort areas, such as offices.

With such large numbers in mind, it is understandable that reducing overall consumption and improving efficiency is an area of importance for utilities and facilities management teams. Indeed, there has been considerable focus on demand reduction, and the complete steam system represents a compelling area where efficiencies may be identified and implemented.

Therefore, it is critical for organizations to embed stepwise and pragmatic sustainability initiatives into day-to-day improvement operations, as well as the overall business model. This will enable positive and impactful change, which can be felt across the entire pharmaceutical community.

Steam itself is a natural fluid and environmentally benign. However, the current general method used to raise steam is burning fossil fuels, which means steam generation is a significant source of carbon intensity.

BACKGROUND ON STEAM QUALITY MANAGEMENT

At this point, it may be helpful to frame steam quality as the measure of steam's thermal energy transfer attributes and the relevance of the globally recognized EN 285 standard and methodology [2]. First, we discuss the different steam types and their manufacturing purpose and suitability.

Steam Types

Pharmaceutical steam may be classified into two types based on their respective sources:

- Plant steam, raised from a utility boiler: A universally used steam grade for efficient thermal energy transfer
- Process steam, generated from a nonutility dedicated source:
  - Chemical-free steam: A nonproduct contact grade used in nonsterile manufacturing
  - Pure steam (clean steam): A direct product contact grade used in sterile manufacturing

Plant steam

Plant steam is normally produced using conventional steam boilers, typically of steel construction, and potable water, with chemical additives to raise the pH to 9.5–10.5 to protect carbon steel equipment from scale and corrosion. These scale and corrosion inhibitors may include substances, such as amines (that cannot be removed through filtration) that may not be acceptable in steam used in pharmaceutical processes (e.g., form a contaminant, which may cause an undesired reaction in the drug product). Hence, plant steam is used in applications that do not involve direct contact between the steam and the product or product contact equipment.

Plant steam is raised at relatively high pressure with the potential of generating superheat during expansion. Superheated steam is produced by heating the steam beyond saturation temperature or by generating the steam at higher pressure in a boiler

and then reducing the pressure through a regulating valve. Superheat may be dissipated downstream of the regulating valve due to heat loss in distribution pipework.

The presence of superheat makes steam more difficult to condense, as a portion of the heat exchange surface will be used to remove the sensible heat before a phase change can occur. The presence of superheat may be beneficial when considering steam distribution, but problematic when considering efficient thermal energy transfer points of use, such as heat exchangers and sterilization processes.

Plant steam is used as a heat source for noncritical and cGMP heat exchangers for heating (frost protection) coils in HVAC applications, as well as in critical applications such as water for injection (WFI) production via sanitary (double tube sheet) heat exchangers. Plant steam can also be used for biological destruction of nonproduct contact equipment or of solid or liquid wastes in equipment, sometimes known as kill tanks.

Chemical-free steam

Chemical-free steam is a noncontact steam grade. It is produced by a steam generator from pretreated water with nonvolatile additives that meet the FDA Generally Recognized as Safe (GRAS) listed additives or an equivalent international standard, where applicable. It is primarily reserved for humidification and nonsterile product sanitization or bioburden control.

Chemical-free steam is also used for noncritical steps in the manufacture of active pharmaceutical ingredients (APIs) without product contact and humidification for HVAC pharmaceutical systems (usually provided prior to the system's high efficiency particulate air [HEPA] filter). The bioburden control of early-stage manufacturing equipment both fall into this category. Chemical-free steam provides an acceptable level of purity because any added impurities will be removed in subsequent procedures.

Pure steam

Pure steam is a direct contact steam grade produced by a steam generator. When condensed, the steam condensate meets the requirements of relevant compendial standards (e.g., US Pharmacopeia [USP], European Pharmacopoeia [Ph. Eur.]) for WFI, except for microbial content (steam purity in chemical and biological composition).

Pure steam is predominantly used for sterilization. Steam used for sterilization in autoclaves for international manufacturing also should meet the requirements of the EN 285 standard and methodology. This will ensure steam's thermal energy transfer attributes (i.e., dryness, superheat, and noncondensable gases), all of which negatively impact the efficient thermal energy transfer properties of steam, are rigorously maintained.

When considering pure steam, guidance documents from regulatory agencies include various definitions. The commonly used terms are "pure steam" and "clean steam." In this article, we use the term "pure steam," as referenced in USP 1231 "Water for Pharmaceutical Purposes" [3].

Pure steam is generated from treated water that meets applicable drinking water regulations and is free of volatile additives, such as amines and hydrazines (which can react with pharmaceutical products). It is used for sterilization processes and is considered especially important to mitigate contamination risk from injectable drug products.

Pure steam is characterized as having no additives or buffer and limited generated superheat except when the generated pressure is significantly higher than the use pressure of the steam. The condensate of pure steam should meet the requirements of relevant compendial standards (e.g., USP and Ph. Eur.) for WFI (except for microbial content), and should not contain additives or buffer, with a relatively low pH compared to that of plant steam.

The user has the ultimate responsibility for system design and performance and for ensuring that the proper type of steam is used for a given POU/process. The USP provides guidance as to the generation, quality attributes, and uses of pure steam [3]. The pure steam section of the USP monograph provides direction for the feed water source, added substances, and testing of condensable attributes. Pure steam dryness and noncondensable gases, however, should be determined by the user based on the intended POU, guided by the globally recognized EN 285 standard and methodology.

The parameters used for confirming the quality of pure steam used for sterilization can also be used to measure the quality of other steam types. The test results can be interpreted based on the use of the steam at that point. The parameters to be considered are dryness, superheat, and noncondensable gases.

Further discussion on these parameters and their potential impact is included in the *Pharmaceutical Engineering*® article "Introduction to Steam Quality and Testing" [4]. The EN 285 standard provides guidance on the test methods for these attributes, with specialist companies offering internationally recognized vocational qualification in these testing parameters (e.g., City & Guilds).

Steam Management Industry Practices

Steam for sterilization

When steam or the resulting condensed water comes into direct or indirect contact with the drug product, the purity (i.e., the correct grade of steam) should be equivalent to the water purity acceptable for the manufacture of the drug product (i.e., purified water and WFI).

It should be noted that a continuous supply of dry saturated steam at the POU is considered necessary for efficient steam sterilization. As discussed previously, water carried by steam in suspension may reduce heat transfer. Superheated steam is considerably less effective than saturated steam when used for sterilization, or any other POU where efficient thermal energy transfer is required. Noncondensable gases, if contained in the steam, act as an insulating barrier to efficient thermal energy transfer and may prevent the attainment of sterilization conditions in parts of the sterilization load.

Table 1: Typical steam points of use, and method of steam generation or steam grade (adapted from [5]).

Steam POU	Method of Steam Generation or Steam Grade
Sterile dosage form applications where steam may be in direct drug product contact with product/product contact surfaces	Pure steam generator or multiple-effect still
Critical step in the manufacture of APIs used for sterile drug product that may be in direct drug product contact with the API/API contact surfaces	Pure steam generator or multiple-effect still
Humidification of cleanrooms systems, where the drug substance/product/primary container is not directly exposed to room atmosphere or where steam is injected pre-HEPA filter	Chemical-free steam generator (fed with potable or softened potable water)
Humidification of cleanrooms systems, where the drug substance/product/primary container is exposed to room atmosphere and steam is injected post HEPA filter	Pure steam generator or multiple-effect still
Heat sources for noncritical (nonproduct contact) and cGMP heat exchangers	Plant steam
Deactivation of solid or liquid biological process waste (i.e., kill tanks)	Plant steam in a dedicated deactivation vessel: The use of a pure steam generator may be required if kill is performed within a process vessel
Bioburden control of direct product contact production equipment, process vessels, and containers	Chemical-free steam generator (fed with potable or softened potable water)
Sterilization of direct product contact production equipment, process vessels, containers, and packaged product	Pure steam generator or multiple-effect still

Steam for humidification

When steam is used for indirect humidification, such as injection into HVAC air streams prior to final air filtration, the steam grade does not need to be purer than the entrainment air and suitable plant steam. It should be noted that chemical-free steam, produced from a generator fed with pretreated water and without buffers or corrosion inhibitors, is suitable for some HVAC humidification applications (i.e., nonsterile manufacturing).

When humidifying process areas, however, the potential level of impurities including amines and hydrazines should be evaluated to ascertain the impact on the final drug product. This is particularly important in areas where open processing takes place, such as aseptic filling suites and formulation areas. If the diluted water vapor is found to contribute to the contamination of the drug, a purer grade of steam should be selected.

STEAM'S THERMAL ENERGY TRANSFER ATTRIBUTES

From boiler to distribution and to each plant and process POU, a complete steam system audit will address the many areas that pharmaceutical facilities management teams may consider when looking to improve steam system efficiency. Some of these steps can be very simple.

For example, steam quality testing (which allows for understanding of steam's thermal energy transfer attributes at critical test points) and steam trap surveys (which establish a complete inventory of all plant and process steam traps) are both steps that may improve steam system efficiency. Such information enables stepwise and pragmatic recommendations to be made based on steam system engineering best practice. This ensures a safe, compliant, and energy-efficient system that meets local legislation.

It should be noted that isolating dead legs (sections or components of a steam pipework system that have minimal or zero flow which can lead to stagnation, contamination, and corrosion of the fluid and the pipe) or pipework to processes that are not in use for a long period of time is considered good practice. Keeping distribution lines hot when not needed (e.g., steam lines to frost coils in summer) wastes energy both in terms of steam production and often again in the HVAC system when removing such heat from the production environment. If isolation valves are located at height or in a technical space, making it difficult for access, thought should be given to the use of actuated valves that can be operated remotely or as part of the building management system.

Steam pipe insulation condition has a significant role in reducing energy loss and reducing condensate levels in distribution piping. Often after a maintenance period, insulation and insulation jackets are removed for access and then are not replaced. This results in energy loss and excess condensate forming.

Note that poor insulation, dead legs, and suboptimal steam trap performance can result in the formation of additional condensate, which can affect the dryness measurement component at critical points. Therefore, steam quality testing at critical points can serve as a good qualitative measure of system performance and diagnostic indicator for thermal efficiency.

THE NET ZERO TRANSITION AND CHANGES TO BOILER ROOMS

Boiler rooms are responsible for large amounts of pharmaceutical emissions, and adjustments to boiler room operations will be necessary to reach net-zero goals.

Reduced Fuel Consumption

Fortunately, the boiler room presents several opportunities to reduce fuel consumption, such as by controlling a boiler's total dissolved solids and using an associated heat recovery system. Another way to reduce boiler room fuel consumption is to capture thermal energy in the boiler flue gases using an economizer, which is typically used to preheat feed water going into the boiler.

Flash recovery from the condensate blowdown vessel can also be used to preheat water and reduce energy consumption. Fuel savings from each of these examples, which lower emissions while improving efficiency, can typically be between 3%–5%.

Electric Boilers and Energy Storage

Boiler manufacturers are already diversifying and offering both electric and hydrogen-fueled boilers. And as energy supplies become less flexible, energy storage will be key in providing uninterrupted process heat.

Electrically generated steam is 15%–20% more efficient than steam from conventional natural gas boilers and with zero flue gas emissions. Combining electrical heating within a boiler or steam generator and subsequent accumulator allows thermal energy, in the form of steam, to be stored when electricity is available or when it is available at low cost when there is oversupply in the grid. This allows for the system to store and discharge steam, as required by the users. It is also possible to charge and discharge at the same time, allowing the use of a smaller generation source with a system that is capable of meeting high peak demands that exceed the generator capacity, thus providing greater flexibility.

Another advantage is that such energy accumulation can be placed closer to the POU, reducing pipeline losses and maintaining steam quality. Furthermore, such technology lends itself perfectly to plant steam indirect heating/thermal energy transfer applications, using a standard accumulator vessel, as well as chemical-free steam used in nonsterile pharmaceutical manufacturing processes, using a suitable stainless steel accumulator vessel.

Such technology is important to demonstrate strong commitment to sustainable energy. It supports the pharmaceutical industry as it strives to reduce steam system carbon intensity, and it ultimately provides a zero-carbon energy source as the grid receives more sustainable energy from renewable sources such as solar, wind, hydrogen, and even nuclear.

Other Emission Reductions

Other possible options for emissions reductions in boiler rooms include generating steam from the combustion of organic waste materials, such as olive pulp, rice husks, and palm kernel shells created from various manufacturing processes. Biomass can be used to generate electrical energy as well as heat when used in a combined heat and power system.

The reduction of organic waste and the use of biomass helps improve environmental sustainability and lower energy bills. In addition, wood chip boilers are already used in the US, eliminating fossil fuels and enabling renewable resource usage. Flues are also controlled for stack emissions.

SUSTAINABILITY THROUGH ENERGY MONITORING SYSTEMS

Sustainability improvements are available with the use of energy monitoring systems. Such technology is invaluable to establish service demand and consumption patterns, enabling key stakeholders to know where, when, and how action should be taken.

Those responsible for energy use across the complete plant and process steam system often use burner efficiency to track overall efficiency, but this method does not consider all aspects of the boiler operation. Factors such as fouled heat transfer surfaces, carryover, radiation losses, and excessive boiler blowdown rates all impact overall boiler room efficiency. This, in turn, may lead to an overestimation of actual boiler room efficiency. It is critical to remember that plant steam quality has a direct impact upon process steam quality, due to the thermal energy transfer attributes of steam at critical heat exchange points, such as a sanitary heat exchanger prior to a pure steam generator or a WFI system.

Using dedicated methods and technology, a complete overview of the plant and process steam system is possible, allowing measurement of overall boiler room efficiency, distribution efficiency, and POU quality. This will help target improvements and associated savings. The utilities and facilities management team may consider using measured inputs from fuel, feed water, steam output, condensate return, and blowdown to build a true picture, helping yield energy reductions and increasing overall efficiency.

Some key considerations of measured inputs:

- Remote monitoring and control of steam systems will play a key role in sustainability.
- Over and above inefficient reactive responses to everyday problems, digitalization brings early alerts, predictability, and rapid problem-solving with new levels of control.
- Greater efficiency is built-in; problems are detected and acted upon immediately, before more severe consequences present.
- Early problem detection means smarter maintenance and repairs.
- Optimized steam systems yield a significant reduction of carbon intensity as energy emissions are reduced.
- Rigorous steam quality management across the complete system will enable improved process productivity through efficient thermal energy transfer.

A COMPLETE STEAM SYSTEM AUDIT APPROACH

Pharmaceutical utilities and facilities management teams may continue to make considerable progress with some of the steps mentioned previously. However, there will certainly be times when these teams will need to engage with specialists outside of their organization. Knowledge partners are available to provide expert advice through the deployment of steam system engineering best practice to ensure complete steam quality management through a complete steam system audit approach.

Steam system audits are vital tools to understand the health and wellbeing of the complete plant and process steam system.

The audit assessment helps identify recommended improvements based on steam system engineering best practice and steam quality management. These changes ensure a safe, compliant, and energy-efficient system, while meeting stringent local legislation.

Steam System Audit Steps

The steps for the steam system audit follow. In addition, it should be noted while respecting the challenges of COVID-19 and social distancing, it is possible to conduct remote steam system audit capabilities with the use of digital technology (e.g., sensor data, video, and images) to identify areas for improvement.

Initial assessment

- Deploy steam quality testing capabilities (the authors suggest adopting EN 285 tests and methodology) to understand steam's thermal energy transfer attributes at critical test points.
- Deploy steam trap survey capabilities to establish a complete inventory of plant and process steam traps, considering status, condition, maintenance record, and supporting validation/compliance documentation.

Comprehensive assessment

- Conduct a complete steam system overview, from boiler through distribution to each plant and process POU to identify energy-saving possibilities and optimization solutions.
- The initial assessment and comprehensive assessment will focus on achieving a stable, mechanically correct, and appropriately maintained plant and process steam system, otherwise known as sustainability by design.

Thermal energy assessment

- Conduct detailed steam and condensate loop thermal energy mapping to discover plant and process optimization possibilities and to understand and address thermal energy demand reduction possibilities across the complete steam and condensate system.
- A thermal energy assessment approach is taken on a case-by-case basis, as the scope of such an assessment is often very broad with multiple variables and site-specific details.

Steam System Engineering Best Practice

Training onsite staff and optimizing their skillsets, focusing on steam system efficiency, can also contribute to a more sustainable operation. Seeking out training centers that provide accredited courses, such as the Combustion Engineering Association's Guidance on Safe Operation of Steam Boilers (BG01) course, ensures safe working.

It also equips key personnel with the skills and knowledge, such as steam quality testing or EN 285 standard and methodology, required to maximize the efficiency and performance of the steam system. Again, as we adapt to a changing work environment, remote training and webinars are an increasingly effective way of ensuring that personal development can continue.

More industries and organizations are recognizing that steam, as a highly efficient thermal energy transfer fluid, integrates with their sustainability initiatives.

THE TRANSITION TO GREENER STEAM TECHNOLOGIES

More industries and organizations are recognizing that steam, as a highly efficient thermal energy transfer fluid, integrates with their sustainability initiatives. Adopting greener steam generation, distribution, and POU methods is a simple way to reduce GHG emissions. With new steam generation technologies, we are on a path toward carbon-free steam generation.

The current focus on climate change has brought into sharp focus the desire to invest in greener steam technology, as the world's demand for heat continues to grow. Raising the efficiency of steam generation will make a significant sustainability impact in the long term, and electric steam generation systems, mentioned earlier in this article, would be one such example. Furthermore, the immediate sustainability impact will be realized through the attainment of stable, mechanically correct, and appropriately maintained existing steam systems, through the rigorous deployment of steam system engineering best practice and steam quality management.

Sustainable Solutions Are Available

Industrial-scale solutions are already in operation to generate, distribute, and deliver steam of the correct quality and quantity to POU in cleaner, more sustainable ways. Renewable, electric steam is carbon-free, emission-free, and 100% renewable steam.

- Higher-capacity users in the pharmaceutical sector can decarbonize their steam generation today, thanks to electric systems. Such systems align well with the portfolio of solutions driving progressive companies toward a truly sustainable business.
- When coupled with 100% renewable power sources (such as hydroelectric, PV solar, and wind), electric steam generators are capable of steam production without emission or carbon generation.

CONCLUSION

As pharmaceutical manufacturers continue to deploy global

sustainability initiatives to reduce their carbon footprint, the focus on energy-saving solutions is greater than ever. With particular focus on steam systems critical to manufacturing processes, steam users in the pharmaceutical sector should be reassured that there are various ways to lower emissions.

This can be done while improving efficiency, maximizing the impact of existing steam infrastructure, and working in a safe, smart, and sustainable manner. In working to lower emissions, pharmaceutical manufacturers will address the two considerations for steam's role in pharmaceutical manufacturing:

- To ensure existing steam systems operate as efficiently as possible for the energy employed
- To ensure steam of the correct quality and quantity arrives at each plant and process POU, thus enabling a safe, compliant, and energy-efficient system

Taking this into account, a complete steam system audit approach to steam quality management, as previously mentioned, will enable pharmaceutical utilities and facilities leaders to meet sustainability goals. It will allow them to improve efficiency through the deployment of steam system engineering best practice and steam quality management. This will ensure maximum system performance for the energy employed and that steam of the correct quality and quantity arrives at each plant and process POU.

Steam is natural and part of everyday life. This extraordinary fluid is a highly efficient, mission-critical tool for diverse and important industries, such as pharmaceuticals, and is increasingly relevant as part of our sustainable future. Existing steam systems can be significantly optimized to perform far more efficiently than they currently do, and a complete steam system audit approach to steam quality management will enable a stable, mechanically correct, and appropriately maintained steam system to be achieved—the very foundation of sustainability.

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CONCLUDING COMPLIANCE CHALLENGES with Validation 4.0

By Sambit Mohapatra

As the pharma industry moves to an ambitious Validation 4.0 paradigm, computerized systems play a pivotal role in enabling the rapid transition. Innovation and agility in computerized system validation (CSV) received a strong push in the second half of 2022 with the publication of the FDA draft guidance on "Computer Software Assurance for Production and Quality System Software" [1] and the *ISPE GAMP® 5 Guide: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)* [2].

Within ISPE, there has been further discussions on a model for Validation 4.0 as an integrated process with articles like "Industry Perspective: Validation 4.0 - Shifting Paradigms" [3]. Furthermore, there have been discussions on moving away from legacy maintenance of massive documentation to digital artifacts and tools to provide a real-time view of compliance and control [4]. This article aims to provide a high-level perspective on seven key pillars for a Validation 4.0 approach with reference to some subtle variance from the legacy CSV approach.

PROGRESS TOWARD VALIDATION 4.0

The methodology in pharmaceutical companies is evolving to keep pace with draft industry guidance and changing validation expectations, which introduces challenges and opportunities typical of any radical transformation. Information technology (IT) quality division, IT managers, and consultants who have been used to a rigorous documentation and testing approach are suddenly exposed to the possibility of a much more lenient way of working.

This has introduced questions about practical implementation and potential risks with the sudden downgrade. Business owners who, in the new approach, now have a greater onus for accurately defining the risks at a more granular level are also trying to adjust their understanding, availability, and collaboration approach to rise to the occasion.

Table 1: The seven key pillars of Validation 4.0.

Key Pillars of Validation 4.0
1.Process and data flows as foundation for validation activities
2.Digital-tool-based artifacts for system documentation
3.Critical-thinking-based risk approach for assurance activities
4.Optimizing test scripting rigor
5.Automated and pragmatic test execution approach
6.Integrating efforts with cybersecurity and other regulatory units
7.Continuous control and cognitive compliance

PROCESS AND DATA FLOWS FOR VALIDATION ACTIVITIES

Validation 4.0 envisages a validation model that incorporates the process and key data early in design to get a head start on defining the associated risk and needed controls [4]. There is also a possibility of completely replacing user requirements specifications. In the context of CSV, although traditional user requirements specifications are replaceable, individual user requirement statements linked to parent process or data flows may still be necessary as a unique source of traceability.

It is important to take process and data flows as a foundation for understanding the business process for definition of risks and all linked downstream activities. This is also key to understanding any data integrity flaws introduced with manual interventions and the need for additional control points in the process flow to mitigate these risks.

An important aspect here is also the possibility of deriving requirements directly from the process and data flow diagrams. Traditionally, these flow diagrams have been considered a purely business topic and have been created, maintained, and referred to by business organization only—with CSV activities starting only at the user requirements level. User requirements could be derived directly from data flow diagrams if marked appropriately as a supported system rather than duplicating the efforts to write user requirements again.

Using the actual process flows employed by business organizations as starting points for scaling CSV efforts also drives consistent process nomenclature and better collaboration between business and IT organizations. Some existing tools (e.g., business process model and notation) may already be supporting this functionality. Effort could be made to fine-tune it to efficiently derive requirements where possible from process and data flow diagrams or to link newly created requirements to flow diagrams entities.

DIGITAL-TOOL-BASED ARTIFACTS FOR SYSTEM DOCUMENTATION

There has been a lot of discussion around paperless validation, and pharma companies are in different stages of adaption. Industry-standard application life cycle management tools have come in handy. The move to agile ways of working has also accelerated this process because agile approaches necessitate the use of tools to manage the scrum deliverables.

Some items in the validation life cycle have been easily automated: for example, test management and execution and requirements management with multiple commercially available options. There are still practical challenges to integration or completely moving all validation deliverables to tools. This is due to the lack of capability of any single tool to provide flexibility, like Microsoft Office Suite products do, to produce diagrams, tables, annotations, flow charts, and technical details. It has been further complicated with the need for compliance with 21 CFR Part 11 requirements [10].

An important constraint in innovation for these supporting tools has been the confusion around electronic signature/approval and data integrity requirements. Most industry-standard software tools supporting agile delivery are easy to use but have limited functionality for capturing multiple electronic signatures.

To meet the varying needs of diverse stakeholders, organizations must use the best product available for capturing a particular activity and collate and approve that information in a single repository for completion of validation process. This has also led to cases where the best tools are used for ease, but information is extracted and approved in another validated document management system, leading to overhead efforts. Usage of different tools also leads to different naming conventions and redundancies in managing traceability.

VALIDATION 4.0 GOALS

The Validation 4.0 model should aim to accomplish the following goals.

Encourage Use of Digital Documentation and Metadata

One of the key extrinsic values of using digital documentation is that it transforms information into knowledge quickly [5]. Extensive use of metadata (i.e., data about data) directly in the tool makes searching, filtering, and reporting easier. This metadata can include country and site codes, traceability, keywords, system impacted, change requests, etc.

Digital documentation also helps achieve principles for attributable, legible, contemporaneous, original, and accurate (ALCOA) with detailed audit trails. For example, a Microsoft Word–based document may need to enable track changes but would not have a track change history retained for all approved versions. However, a digital version can be configured to keep mandatory detailed change tracking starting from the first approved version.

Minimize Validation Expectation for Software Tools

As per *GAMP® 5 Second Edition*, "tools and systems supporting system life cycles, IT processes and infrastructure should not be subject to specific validation, but rather managed by routine company assessment and assurance practices and good IT practices" within industry standard frameworks like ITIL [Information Technology Infrastructure Library] as they do not directly support GxP-regulated business processes or GxP records and data [2]. To buttress this point, the GAMP guidance has categorized these tools as GAMP Category 1.

Furthermore, the full scale of data integrity controls and electronic signatures would also not apply. Regulated companies should explore how best to use a standard audit trail and simple approval functionalities of these tools to provide reasonable assurance of review and acceptance. Locking the documentation objects after approval and other version control aspects also may need to be considered.

Avoid Redundancy in Tool Usage

With reduced expectation for e-signature controls, the need for extracting requirements or testing done with best available tools, and reapproving in a validated document management system as

consolidated documents, also becomes unnecessary. Reports and logs extracted from these tools can be used to achieve pragmatic reviews in a consolidated view. They can also be used as supporting documents for providing baseline status for requirements, test reports, traceability matrix, etc.

Employ a Holistic Document Management System

The system should fulfill the needs and flexibility of different stakeholders and documentation types. It should preferably use agile tools, a basic approval workflow, audit trails, and version control functionalities. These should be supported by some key dedicated modules covering:

- Business modeling that is customizable for easily defining business process flows and roles
- Requirement description (extractable/derived from business process modeling) and additional new individual requirements (nonfunctional, controls, etc.) with option to define requirement types
- An integrated functional specification, design, and configuration specification module with the potential to add interface description and flows, descriptive attachments, etc.
- Test scripting and execution, supporting easy defect management and reporting
- Validation and project management, offering flexibilities in line with Microsoft Word and Excel

CRITICAL-THINKING-BASED RISK APPROACH FOR ASSURANCE ACTIVITIES

The FDA draft guidance defines Computer Software Assurance (CSA) as "a risk-based approach for establishing and maintaining confidence that software is fit for its intended use" [1]. Risk-based approaches have always been used in pharmaceutical IT, but they have primarily been a checklist activity, with the majority of the outcome focused on a scripted testing type for every GxP functionality. The new approach for Validation 4.0 should enable the shift in focus and effort for all stakeholders from testing to accurate risk assessments to determine holistic assurance activities with application of critical thinking.

The *ISPE GAMP® Good Practice Guide: Enabling Innovation* illustrates critical thinking as "proactive adoption of a risk-based approach suitable for the intended use of the computerized system that takes into account the multiple layers of assurance provided by the business process" [6]. Note that as part of a comprehensive assurance approach, and as described in *GAMP® 5 Second Edition* and ICH Q9, the primary objective of quality risk management is to identify and assess GxP risks [2, 7]. This is so that appropriate controls may be applied to protect product quality and patient safety, and not just to support the use of risk scoring to optimize testing approaches.

This shift needs to be more organic and requires a transition at different levels. Some transitions are outlined next.

Comprehensive Assurance Approach

The new approach would require understanding assurance as a full spectrum of activity, combining process, design, and manual controls with testing as a final step of assurance. Key examples include improving the process or system design, understanding four-eye and review checks by quality personnel in the business process, increasing the level of detail of specification, design reviews, etc.

Binary Risk Definition and Patient Safety Focus

An important enabler for all stakeholders in accurate assessment of risks would be to keep the definitions at a binary level only. Traditionally, regulated companies tend to categorize risks with multiple values for each risk, e.g., high, medium, low. This is problematic, especially for practitioners when trying to fit between these values with subjective judgements. Binary values can make decision-making easier and faster.

The FDA draft guidance noted the importance of outlining binary risks and limiting the definition of risks to only be based on the impact to patient safety. This is compared to the traditional approach of considering patient safety, product quality, and data integrity. The new approach also considers product quality as reference but ultimately checks how the risk to product quality impacts patient safety. A single-minded focus would help stakeholders clearly understand the impact.

Use Identification and Traceability at the Appropriate Level

As per the FDA draft guidance on CSA, software may have multiple intended uses depending on the features, functions, and operations [1]. It may also present different risks with different levels of validation efforts required. The current approach of functional risk assessment may not always be suitable to capture the level of details required to ringfence risks. The risk assurance approach should have an enabler, and a traceability approach can be a good fit.

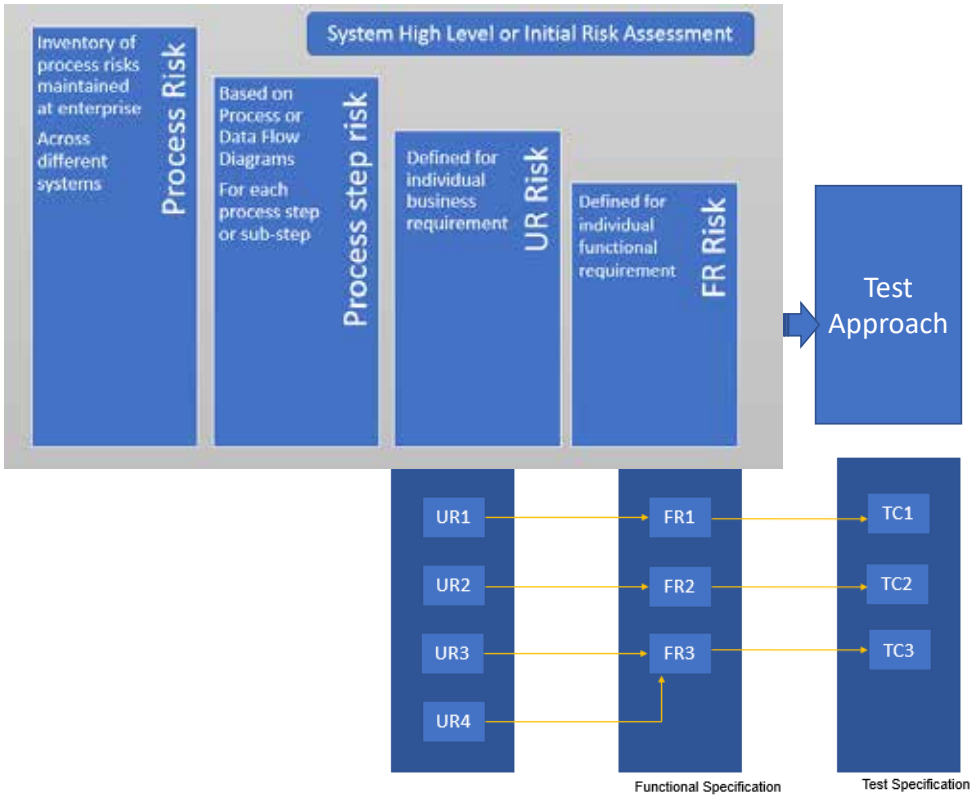
There have been different approaches used to manage traceability—from a generic document level to an atomic level. A Validation 4.0 approach would need traceability at a more atomic level. That is, each user requirement would need to be linked to a unique functional requirement (that can represent a specific feature fulfilled by the system rather than a functionality), which is in turn linked to a unique test case (rather than a generic test script). This would also be an enabler for inheritance of risks, as described in Figure 1.

Risk Inheritance Concept

It can often become tedious to define GxP risk for every feature or requirement, and a concept of inheritance may be considered to optimize risk assignment. *GAMP® 5 Second Edition* encourages the use of a hierarchical approach to help simplify risk assessment, and it also hints at the use of major and subsidiary functions or requirements to group similar entities [2].

A good starting point for this hierarchical approach can be a process risk assessment. As per *GAMP® 5 Second Edition*, "a process risk assessment (also known as business process risk

Figure 1: The concept of risk inheritance supported with traceability.



assessment) is a non-system-specific high-level assessment of the business process or data flow, which may occur before system-specific QRM [quality risk management] activities" [2]. The initial risk defined at the process level would be inherited across process steps, process sub-steps, associated user requirements, and functional requirements.

The need for the number of levels of hierarchy can be based on system and process complexity. For example, a user requirement can also be generic and linked to multiple user requirements with more specific details or directly linked to multiple detailed functional requirements. Having a baseline risk would help stakeholders only downgrade it at a subsidiary level, when necessary, without having to start the risk assessment process from scratch for every requirement. Figure 1 demonstrates the concept of risk inheritance supported with traceability.

Inherited risks vs. final risks

Inherited risks give us a good baseline risk. For any low-risk process steps or substeps, the risk assessment process may end at that level. The final risk score may still need to reassess for individual requirements for some cases.

Downgrade from inherited risks

Risks at any level classified as high may need to be revaluated at a subsidiary level to see if any subitems have a lesser risk than the overarching entity. Downgrades may be necessary in such cases and a simple principle that the substep or a subsidiary entity cannot have risk higher that the overarching process area risk can be used.

Upgrade from inherited risks

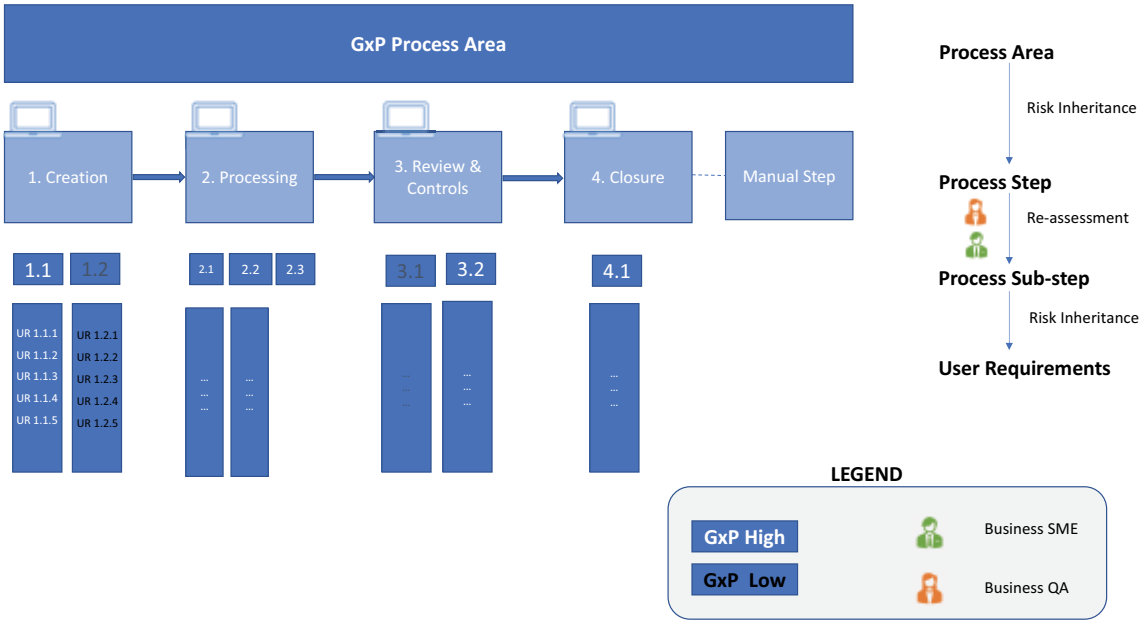
Upgrade from inherited GxP risk should seldom be used. It is important here to note that although additional flexibility is being introduced with GxP risks, other factors (including business risks and other compliance and legal considerations) should not be overlooked. Upgrade for the overall risk for the entity based on these factors may still be necessary to have a holistic control strategy.

Risk definition and inheritance process

A simple example to examine the process for risk definition and inheritance is given here and shown in Figure 2. A GxP process area can be at a high-level process (manufacturing execution, quality and batch management, etc.) or represent data like the material master.

To ensure end-to-end traceability, the traceability marker starts with a unique numbering system from each process step (simplified as 1, 2, 3, etc.). This includes a simplified model for creation/input, processing/execution, review, controls, and closure/output for a GxP master data.

Figure 2: An illustration of a risk inheritance model.



The numbering marker is inherited by all respective downstream objects like process substep (1.1, 1.2, 2.1, 2.2, etc.), user requirements (UR 1.1.1, UR 1.2.1, etc.), functional requirements (FR 1.1.1.a, FR 1.1.1.b, etc.), and test cases (TC 1.1.1.a, etc.). For example, if a process step is classified as GxP high, all of its linked objects will inherit the same GxP classification.

Inherited risks priority classification moves as is from process area to process step and is examined for reclassification at the process substep level. For example, substep 1.1 continues to have GxP high risk, but 1.2 is reclassified as GxP low risk. Any linked user requirements within substeps 1.2 are also classified as GxP low and no further GxP assessment is required at the item level. For substep 1.1, further assessments happen and require the GxP risk to downgrade to low.

Scenario 1.1

To illustrate this further, substep 1.1 (GxP high) is considered as scenario 1.1 in Figure 3. Most of the linked requirements within this step continue to be high risk and only one user requirement (UR 1.1.2) is re-assessed as low risk. The primary consideration was that there is low GxP risk for this requirement, and secondary considerations (regulatory, downstream controls, overall business risk) were also considered by key stakeholders to conclude that the final risk for this requirement is low indeed.

Scenario 1.2

Similarly, substep 1.2 (GxP low) is considered as scenario 1.2 in the Figure 3. Here, all requirements continue as low risk with GxP. Two of these linked requirements (UR 1.2.4 and UR 1.2.5) are classified as high risk considering other factors (e.g., UR 1.2.4 was considered high due to high business risk and UR 1.2.5 due to privacy risk). The final user requirement risks are then considered to be inherited to functional requirements.

OPTIMIZING TEST SCRIPTING RIGOR

Once appropriate risks are defined and other assurance activities are in place, any items with residual risks need to be tested. The shift in focus is from providing detailed documentation regarding completion of a testing phase to improving defect detection. One of the key aspects introduced with the FDA draft computer software assurance approach and *GAMP® 5 Second Edition* is the use of a different unscripted testing approach for low GxP risk functionalities [1, 2].

To derive the final test rigor, the functional requirement (inherited risk) is combined with the IT risk for that functional requirement as defined by the IT subject matter expert (or a group of IT experts with functional, technical, domain architecture knowledge, etc.). This is illustrated in Figure 4. Again, a critical thinking approach could be used to define IT risks. Risk is considered high for custom developments, new technologies, or systems provided by new suppliers with improvement areas during supplier evaluation. Only scenario 1.1 from the previous risk section is considered in the following description (see Figure 4).

It is very clear that only TC 1.1.5.a would now require a robust scripted testing that is optimized. This is compared to the legacy

Figure 3: Classification of risks in scenario 1.1 and scenario 1.2.

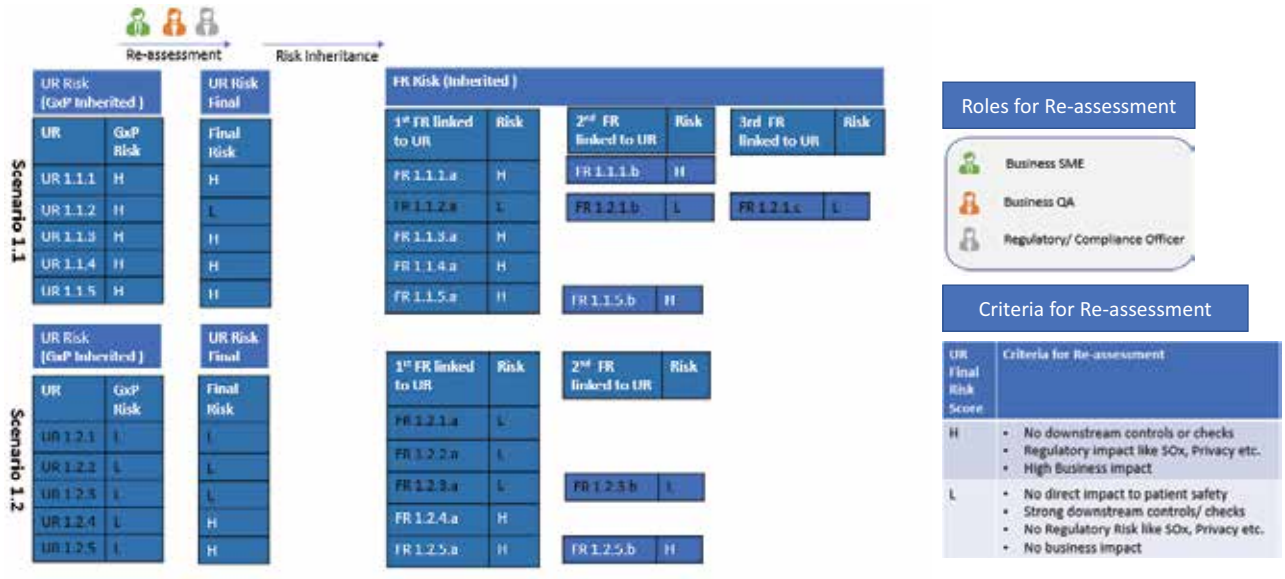
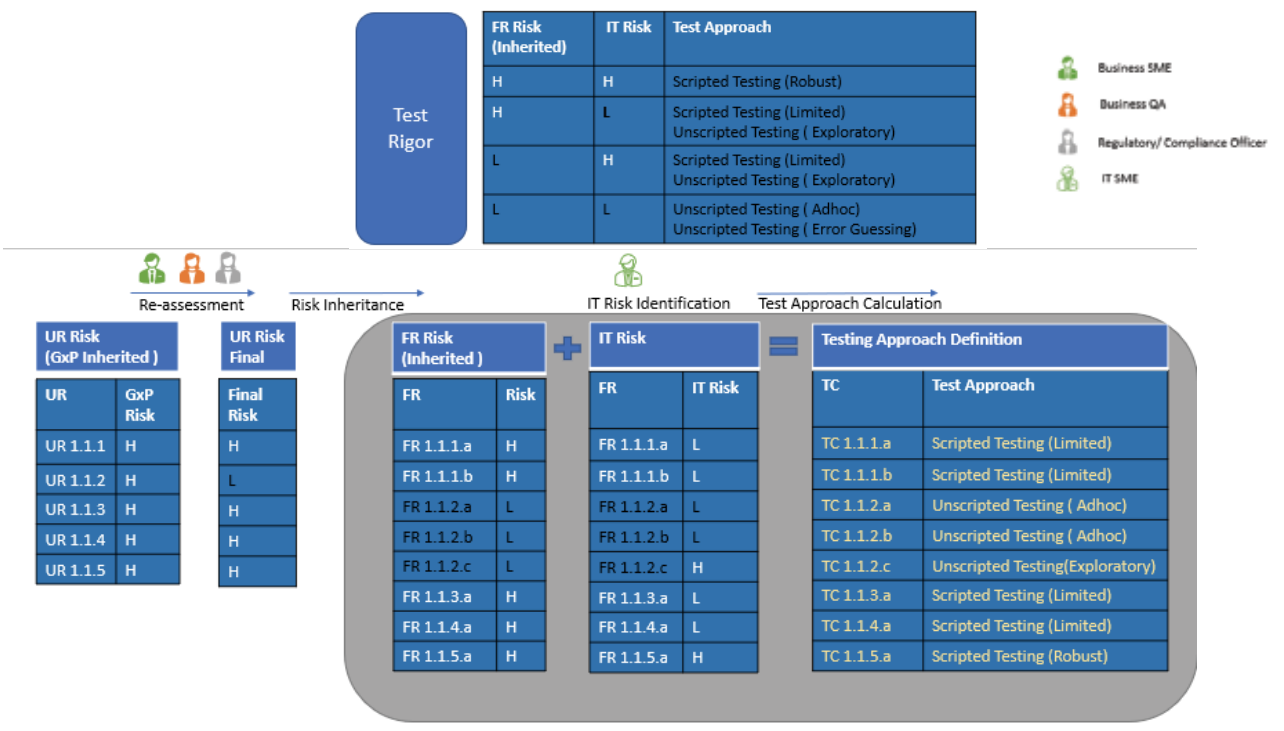


Figure 4: The inherited risk is combined with the IT risk to determine the testing approach definition.



approach where each of eight GxP impacted functionalities would have been tested with a robust scripting approach.

The test approach outcome here is primarily used to define the functional (operational qualification) or integration testing to be done by an IT team. The requirement for user acceptance testing (UAT, or performance qualification) is based on the process step risk. The UAT is driven by a process step risk with a simplistic approach of robust scripted testing for GxP high and scripted testing (limited) or unscripted (exploratory) testing for GxP low.

It may not always be possible to define risks at a particular level for UAT because they tend to run end-to-end scenarios covering multiple process steps. Most importantly, critical thinking should also be used to define UAT scripting approach based on parameters like experience of planned business testers, novelty of the system, etc.

A key risk to highlight here is the temptation to downgrade a custom development test approach to exploratory or ad hoc testing. This should be taken up only in a pilot and phased manner as irrespective of the GxP risk criticality, custom development brings in new exposures and effort should be made to use limited scripted testing.

This would be useful during the project phase and the operations/maintenance phase as custom developments need to be verified with different scenarios. Additionally, this is problematic when maintenance support is provided by a different vendor or team than those involved in system development phase. Critical thinking approach can be applied and simple custom developments (e.g., simple reports) can use leaner testing approaches.

AUTOMATED AND PRAGMATIC TEST EXECUTION APPROACH

Automated test execution is the best option to minimize manual overhead and is suitable for simple and integrated software suites that require multiple iterations. There is still some time before industry moves to complete automation, and where that's not possible, pragmatic approaches to manual test execution can be applied to achieve greater efficiency.

GxP good documentation practices have heavily relied on robust test scripting as a basis for test execution with verbatim response to each test script step. A shift to a simpler scripting level approach throws new challenges into execution expectation. In the absence of a script expectation, the source of truth would move back directly to requirements and the level of detail at which they are written.

For example, a GxP low risk failure error message in the system should be exactly as aligned by business representatives, and hard coding in script would have easily detected deviations, if any were present. The error message would now need to be checked with requirement and specification documents, and this can be facilitated by taking the respective requirement ID or specification ID as an input parameter during execution.

A decrease in scripting robustness would also require an increase in robustness for writing unique testable user and functional requirement statements, supported by solid functional and quality reviews to ensure the business expectations are clearly enumerated and met. Additionally, the focus would be back on a more robust and extended UAT phase with additional time after the UAT phase for fixing any new defects.

Automated test execution is the best option to minimize manual overhead and is suitable for simple and integrated software suites that require multiple iterations. There is still some time before industry moves to complete automation, and where that's not possible, pragmatic approaches to manual test execution can be applied to achieve greater efficiency.

Another risk associated with the usage of unscripted testing is the availability of experienced functional users for testing. Due to the volume of activity during the testing phase, junior resources are often onboarded in testing phases to follow the scripted test manual and execute tests. Care must be taken to only use experienced testers who are part of the functional design process, to achieve the expected benefits from unscripted testing approaches. In cases where this is not possible, robust training should be considered before assigning unexperienced users for unscripted testing.

It is also paramount to use pragmatism to adjust the expectation for capturing test execution. A few key areas of improvement include the following.

Recording Detailed Observed Results

Traditionally, GxP good documentation practices required actual observed test results for each step to be written in detail as per the expected evidence. A more pragmatic approach is described in *GAMP® 5 Second Edition* where "a simple 'pass'" can be recorded when the system response matches the expected result and detailed statements are provided only for "failed" steps, adding additional notes for root cause analysis [2].

Recording Observed Results Contemporaneously

Good GxP and data integrity practices expect results to be recorded contemporaneously. This is sometimes abused with the

expectation of recording the observed result in the same minute of taking the screenshot. Although digitization of testing has helped capture the exact time stamp of the execution, some leniency in line with a paper execution could still be provided.

In a traditional paper-based wet ink execution, a tester might execute testing in the morning, take screenshots, and write the observed results sometime later the same day. A pragmatic approach can be adapted in cases where the tester missed attaching a screenshot or did not take screenshots out of the testing tool at the exact minute and second. This would also allow the tester to provide delayed additional screenshots without a full re-execution on the same day.

Screenshot Expectation

Legacy testing has heavily focused on print screen attachments as the basis for objective evidence provided for quality review. As per *GAMP® 5 Second Edition*, "prolific screen shots do not add value and are unnecessary" and "test evidence is only collected for proving steps that are not inherently covered by evidence from another step" [2].

INTEGRATING EFFORTS WITH CYBERSECURITY AND OTHER REGULATORY UNITS

With the Pharma 4.0™ focus on having a smart factory and extensive usage of innovative tools, cloud, and the Internet of Things, there are evolving cybersecurity challenges. As per *GAMP® 5 Second Edition*, for GxP computerized systems, "it is usually the case that risk from cybersecurity threats directly correlate to the data integrity considerations of GxP risk" [2]. There is considerable equivalence of requirements between cybersecurity controls like ISO 27001 [8], NIST SP 800-53 [9] (with embedded privacy controls in Revision 5), and pharma regulations like 21 CFR Part 11 [10] and Annex 11 [11]. This equivalence is expected because they are derivatives from the ITIL framework.

This brings good potential for synergy between an information security management unit (responsible for the confidentiality, integrity, and availability of systems) and a quality assurance compliance unit across multiple scenarios. This includes audit trails, security, data exchange, infrastructure, etc., as enumerated in a recent iSpeak blog [12]. The Validation 4.0 model must integrate cybersecurity and leverage activities of the information security organization to reduce redundant checks and achieve faster compliance. Combining risk assessment efforts with other compliance units achieves a holistic risk baseline for a comprehensive assurance effort required.

CONTINUOUS CONTROL AND COGNITIVE COMPLIANCE

The usage of tools and artifacts supports creation of real-time traceability and test reports, which are readily available for self-assessments. According to a 2021 *Pharmaceutical Engineering®* article, "instead of relying on difficult to maintain silos of documentation, we look toward digital artifacts managed with appropriate tools that can instantaneously provide reporting and notifications on the state of control" [4]. Carefully configured validation checks can highlight discrepancies in the updating of linked objects. For example, if a functional specification is updated without updating the linked design specification, it will be flagged as an issue item for consideration.

Key quality metrics can be defined and compliance dashboards can be created, with the option of filtering and reporting. Parameters can be set based on the number of red flags highlighted, and a group of objects or a project may be zeroed down as a potential audit candidate that will feed into audit plans. Continuous process verification (CPV) is considered key for Validation 4.0 [4]. The same principle should be applicable for CSV to ensure key validation documents and that the metadata and traceability is in a continuous state of control.

Other Pharma 4.0™ priorities like the usage of artificial intelligence (AI) can also be used to gain insights that were not possible before [5]. Although document content reviews may still be done manually, there is a lot of potential with advent of AI. Simple good documentation practice checks (e.g., usage of templates, filling of all subsections, expected metadata values in some fields, blank spaces, date format, and other specific checks based on document types) can be easily automated. This will help quality reviewers to validate in conjunction with manual review.

With ChatGPT having revolutionized all industry areas, a similar AI tool can also be used in validation context. Typical inputs for this tool can be a high-level project documentation with project context and answers to some key questions with the output as a project documentation list. This should set the context for the minimum required deliverables for a lean validation approach with any additional documents only added in scope with appropriate justification.

HOW THE SEVEN PILLARS SUPPORT THE PHARMA 4.0™ OPERATING MODEL

It is important to note how these pillars support the key themes of the Pharma 4.0™ operating model.

Holistic Control Strategy

As noted in a previous *Pharmaceutical Engineering®* article, "the validation strategy must be part of the holistic control strategy, and stakeholders must use critical thinking to ensure lean and robust risk assessment" [3]. Furthermore, this article also notes that holistic control strategy enables data-based decision on all aspects of the pharmaceutical product life cycle. The same holistic approach can be extrapolated to the computerized system life cycle with data derived from software tools as the key drivers for real-time dashboards and continuous audits.

Another aspect for holistic control strategy and integrating efforts is leveraging efforts between different compliance groups within the pharma organization—GxP compliance, cybersecurity managers, and other regulatory compliance officers to avoid redundancy of checks and duplication of efforts.

Data Integrity by Design

Process and data flows form a key part of ensuring data integrity by design because clear understanding of the flow can help to detect any integrity flaws and mitigate them. Prospective data integrity is a key feature of Pharma 4.0™ [13], and usage of software tools and digital documentation ensures data integrity for validation documentation is foolproof and detailed. Tool-based digital documentation data is legible, attributable from the time it's recorded, contemporaneously recorded with real-time version history, stored in the original format, and contains validation checks for accuracy.

Digital Maturity

Moving to predictive capability and adaptability can be achieved through real-time dashboards. In terms of computer system validation tools, maturity needs to move from Level 2 and Level 3 to Level 4. A shift from Pharma 3.0 (until Level 2) to Pharma 4.0 (Level 3 onward) is a business imperative for companies moving to niche products or advanced therapy medicinal product needs [13]. Some pharmaceutical companies are already at Level 3 to some extent, but a complete transition needs to happen.

Moving to the new approach would require validation managers to develop the skillset of techno-functional business analysis in challenging the risk assessments more confidently. This would allow them to set the baseline for a risk-based testing effort and to become champions to facilitate the critical thinking approach.

The critical thinking approach in this article has only been discussed in a limited context, but the use of a rational and a well-reasoned approach adds value across all aspects of CSA [6]. Yet another key enabler could be the close involvement of reviewers in training and setting the right expectation before the start of the activity. This would ensure document definitions are correct from the beginning, with iterative reviews happening to avoid rework. There are other enablers in terms of management support and regulatory feedback, and publication of the final CSA guidance will hopefully provide a definitive conclusion to this conundrum.

CONCLUSION

CSV has been interpreted and used in myriad ways in the pharmaceutical industry, with stringent organization-specific conventions and practices sometimes exceeding regulatory mandates. This has burdened delivery teams with unrealistic checklist-based expectations. *GAMP® 5 Second Edition* made a key contribution in this regard by highlighting practices that are overhead tasks and not truly required to fulfill regulatory expectation [2].

One of the main objectives of Industry 4.0 is to build a lean digital core, and a primary value of the Validation 4.0 approach would enable a lean validation approach, supporting establishment of this lean digital core. The key pillars highlighted support early identification of risks. This enables ringfencing of high-risk individual items and the required assurance activities without impacting full related functionality.

Furthermore, the industry's focus is shifting to extensive defect detection without producing piles of documentation to demonstrate compliance. Some challenges will remain, especially with respect to the acceptance and adoption of the new approach, the organizational change management, and the cost of tools and integration.

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Sambit Mohapatra is currently working as a Consultant at Infosys Ltd. He has over 11 years of experience providing services to multiple top pharmaceutical clients. He began his career as a Business Analyst for clinical applications and has now moved into CSV and IT audit roles. Sambit's current interest areas include achieving GxP compliance in merger and acquisition scenarios; integrating efforts between GxP, cybersecurity, and other regulatory areas; and championing lean validation. Sambit holds a bachelor's degree in biotechnology from Vellore Institute of Technology, Vellore, and a postgraduate diploma in management from the International Management Institute, New Delhi.

COMPUTER SOFTWARE ASSURANCE and the Critical Thinking Approach

By Gaurav Walia and Danilo Neri, PhD

In 2022, the US Food and Drug Administration (FDA) issued their draft guidance "Computer Software Assurance for Production and Quality System Software" [1] to enhance the computer validation process required by predicate rules, either in the pharmaceutical or medical device space. The critical thinking approach was introduced by ISPE GAMP® Guides and emphasizes a focus on clear thinking through a plan, then creating documentation from a process perspective. These methods combined create the optimal replacement for computer system validation (CSV).

New FDA draft guidance marked a transition to computer software assurance (CSA) in 2022 [1]. Historically, CSV practices unfortunately focused on generating great amounts of paper-based testing records, and it was believed that the larger the stack of documentation, the better the quality and effort when validating a computerized system and eventually presenting it to the FDA.

The reality is that a mountain of paperwork did not equate to proper CSV, which resulted in a failure to fully ensure the product quality, data integrity, or patient safety. Critical thinking is a term that was introduced by GAMP guidance (initially in *ISPE GAMP® Good Practice Guide: Enabling Innovation* [2] and then more recently in *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)* [3]), and it focuses on those critical considerations missed by CSV.

When applied, this critical thinking approach potentially results in the conclusion that a tremendous amount of documentation cannot possibly represent quality, especially when inspectors continue to identify a multitude of issues during inspections. These issues stem from items including, but not limited to, segregation of duties, data integrity potential violations, and whether the system works as intended after testing.

The FDA draft guidance states [1]: "Computer software assurance is a risk-based approach for establishing and maintaining confidence that software is fit for its intended use. This approach considers the risk of compromised safety and/or quality of the device (should the software fail to perform as intended) to determine the level of assurance effort and activities appropriate to establish confidence in the software. Because the computer software assurance effort is risk-based, it follows a least-burdensome approach, where the burden of validation is no more than necessary to address the risk. Such an approach supports the efficient use of resources, in turn promoting product quality."

UTILIZATION OF THE CRITICAL THINKING APPROACH

The critical thinking approach can be used in potentially limiting testing evidence for low-risk functionalities through the following use of innovative testing approaches: unscripted and scripted testing.

Unscripted Testing

This is dynamic testing in which the tester's actions are not prescribed by written instructions in a test case. This can include:

- Ad hoc testing: A concept derived from unscripted practice that focuses primarily on performing testing that does not rely on large amounts of documentation (e.g., test procedures) to execute
- Error-guessing: A test design technique in which test cases are derived on the basis of the tester's knowledge of past failures or general knowledge of failure modes
- Exploratory testing: Experience-based testing in which the tester spontaneously designs and executes tests based on the tester's existing relevant knowledge, prior exploration of the test item (including results from previous tests), and heuristic logical rules regarding common software behaviors and types of failure

Scripted Testing

This is dynamic testing in which the tester's actions are prescribed by written instructions in a test case. It includes:

- Robust scripted testing: Scripted testing efforts in which the risk of the computer system or automation includes evidence of repeatability, traceability to requirements, and auditability
- Limited scripted testing: A hybrid approach of scripted and unscripted testing that is appropriately scaled according to the

risk of the computer system or automation. These test methods require that the tester, through training and/or experience, has the knowledge to devise appropriate tests

WHY SOFTWARE ASSURANCE IS CRITICAL

Software assurance saves time and money. Software quality assurance ensures that developers find bugs and errors at the early stages of software development when less amount of time and money is required to fix them. The CSA approach provides flexibility and agility in helping ensure that the software is maintained in a validated state.

In determining the risk-based approach for software systems, the main intent is to use a risk-based methodology to ensure targeted and focused validation. This confirms that the computerized system is functioning for its prescribed, intended use, focusing (i.e., limiting a larger amount of documented evidence) on those functionalities that may directly impact patient safety and product quality.

For example, a software feature, function, or operation might pose a high process risk when its failure to perform as intended may result in a quality problem that foreseeably could compromise patient safety. In addition, software features and functions may maintain process parameters—such as temperature, pressure, or humidity—that affect the physical properties of product or manufacturing processes which are identified as essential to product safety and quality.

THE CSA RISK FRAMEWORK

The CSA risk framework is a risk-based approach intended to help manufacturers establish and maintain the reliability and safety of computer software throughout the life cycle, reducing the testing effort. Several steps must be taken to ensure the successful implementation of the CSA approach.

Identifying the Intended Use

Manufacturers must first determine whether the software is intended for use as part of production or the quality system. In general, software is either used directly as part of production or the quality system, or it supports production or the quality system.

Software that is used directly as part of production or the quality system includes software intended for automating production processes, inspection, testing, or the collection and processing of production data. It also includes software intended for automating quality system processes, collection, and the processing of quality system data, or maintaining a quality record established under the quality system regulation.

Manufacturers must validate software with these intended uses to ensure that it is reliable and functions as intended according to the associated risk. This is critical for both the pharmaceutical and biopharmaceutical industries, as well as medical device manufacturers.

Determining the Risk-Based Approach

The CSA risk framework provides guidance on identifying and mitigating the risks associated with software validation and includes examples of applying the framework to various CSA situations. Once it has been determined that a software feature, function, or operation is intended for use as part of production or the quality system, a risk-based approach should be used to determine the appropriate assurance activities.

The CSA risk framework is a risk-based approach intended to help manufacturers establish and maintain the reliability and safety of computer software throughout the life cycle, reducing the testing effort. Several steps must be taken to ensure the successful implementation of the CSA approach.

This approach involves identifying historical software failures, determining whether such a failure poses a high process risk, and systematically selecting and performing assurance activities commensurate with the medical device or process risk. The risk-based analysis for production or quality system software should consider which failures are historically known (as opposed to likely) and the risks resulting from each such failure.

Process risks refer to the potential to compromise production or the quality system, whereas direct system risks refer to the potential for a device to harm the patient or user. In CSA, the risk determination is therefore a key element to be carefully designed and executed to focus validation testing on the functionalities oriented to manage high-risk processes.

Determining the Appropriate Assurance Activities

Different types of assurance activities should be considered, corresponding with the system risk or process risk. For software features, functions, or operations that pose a high process risk, assurance activities should be considered higher corresponding with the system risk. Conversely, for software features, functions, or operations that do not pose a high process risk, appropriate assurance activities should be considered lower corresponding to the risk identified.

Table 1: Comparison of CSV to CSA (part 1).

CURRENT VALIDATION	CSA
Focus on creating documents/records for compliance and securing evidence for auditors (paper mountain effect)	Focuses on critical thinking and testing to achieve higher confidence in the quality of the system
Risk is based on failure mode effects analysis (FMEA) business risk and meeting regulatory requirement	**Risk is based on the impact on patient safety, product quality (intended purpose), and data integrity**
Validation involves testing all functionality (e.g., focus on COTS vs. potentially missing the higher-risk areas)	Validation is based on applying the right amount of diligence to a given level of risk to patient safety, product quality, and data integrity
Ignores previous assurance activity or related risk controls (e.g., one example is COTS functionalities)	**Leveraging prior assurance activity, risk controls, and any documentation that exists with the vendor and others** (e.g., build a good vendor risk management/vendor audit program that can be used to justify reduced COTS function testing)
All testing is scripted	Uses unscripted and ad-hoc testing in addition to scripted testing and employs the least burdensome approach to documentation
80% of time spent on documentation / 20% of time spent on testing	20% of time spent on documentation / 80% of time spent on testing

CSA AND REQUIRED RECORDS

CSA enforces the need for regulated companies to establish the appropriate record. When establishing the record, the manufacturer should capture sufficient objective evidence to demonstrate that the software feature, function, or operation was assessed and performs as intended. In general, the record should include:

- The intended use of the software feature, function, or operation
- The determination of risk of the software feature, function, or operation
- Documentation of the assurance activities conducted
- The date of testing activities and the name of the person conducting them
- Establishing review and approval, when appropriate

The documentation of assurance activities should not include more evidence than necessary. However, it should retain sufficient details to serve as a baseline for improvements or as a reference point if issues occur. To reduce the need for manual or paper-based documentation, the FDA recommends that manufacturers "leverage automated traceability, testing, and the electronic capture of work performed to document the results. As a least burdensome method, FDA recommends the use of electronic records, such as system logs, audit trails, and other data generated by the software…in establishing the record associated with assurance activities" [1].

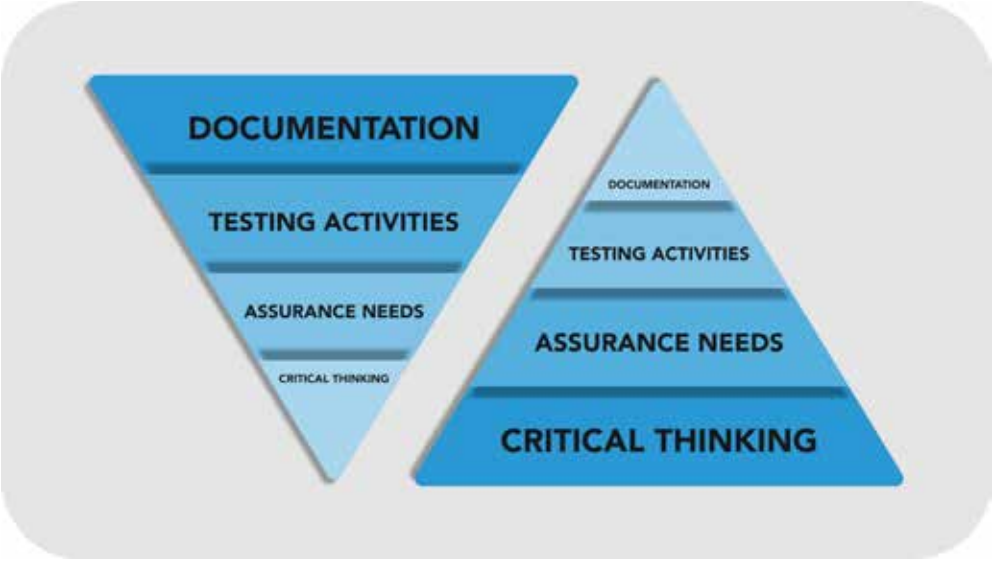
THE DIFFERENCE BETWEEN CSV AND CSA

CSA is a new way of looking at the traditional CSV approach through consideration of risk whereby the focus is on what matters—patient safety, product quality, and data integrity. A comparison of the two approaches for assurance activities and records is shown in Table 1.

The focus of CSV is a decision to carry out excessive and unnecessary tasks/testing, which creates excessive documentation, and too much time is spent on testing on all system functionalities. In comparison, when using CSA, the primary focus allows manufacturers to leverage principles such as risk-based testing, unscripted testing, continuous performance monitoring, and data monitoring, as well as validation activities performed by other entities (e.g., developers, suppliers). The CSA approach provides flexibility and agility in helping assure that the software maintains a validated state. This allows for assurance that the data provided is accurate, compliant, and more efficient.

In Figure 1, the left triangle represents the CSV approach, and the right triangle shows the differences that occur with CSA. As shown, in CSV, the decision to carry out excessive and unnecessary tasks/testing with documentation is the primary function, whereas critical thinking comes last. Issues and potential enhancements are identified in the last stages of the processes, resulting in a need for reworking and a waste of resources.

Figure 1: Comparison of CSV to CSA (part 2).



Current thinking with respect to *GAMP® 5 Second Edition* promotes a risk-based approach to ensure fitness of the system for its intended use [3]. In many instances of validation strategy, people do not apply critical thinking to ensure that the approach they are taking is customized and proportionate to the needs of the specific system they are validating: for example, when implementing the 21 CFR Part 11 requirement of segregation of duties (SOD), where roles and privileges are properly defined, configured, and followed [4, 5].

Using critical thinking (instead of having general training on the system regarding SOD), a customized/tailored approach to system training around the routine tasks of the different system user types should be followed. This will ensure that each user type is given training centered on their specific tasks and responsibilities so that SOD is clearly defined and followed.

Critical thinking is the most advantageous process for companies and manufacturers. It ensures that issues and enhancements are determined in the first stages, thereby focusing proper efforts toward assurance needs. Thus, it results in better-defined testing activities to ultimately ensure proper intended use and working functionality of the computerized system.

TRANSITIONING FROM CSV TO CSA

Organizations that want to pivot from a CSV to a CSA approach need to properly invest in activities and apply critical thinking to how software assurance will be performed and to how time and efforts will be allocated to achieve these tasks. For example, if a firm is implementing a new laboratory or manufacturing software/computerized system, the firm should apply critical thinking to assess the system and functional requirements risks as well as the intended use of the system, instead of spending significant time on excessive testing or documentation. This is because risk determination is the CSA core process.

The computerized system should be explored for what its intended use will be, what the key functions are, and what risks lie with its functionalities. Its potential impact on product quality and patient safety, historical issues, data integrity, and potential violations should also be assessed. This is necessary to properly outline the strategy of assurance and testing activities before the true efforts on documentation begin.

In addition, after the initial critical thinking phase of the process, teams should decide the key software assurance activities that must be performed to determine what needs to be tested and how testing should be documented. This will determine the amount of testing and evidence required to prove that the test function is working as intended.

The culmination of the activities previously mentioned should then be combined with a proper vendor risk management inspection program—especially for information technology service providers and technology vendors—that should include equipment and software-computerized systems.

Vendor risk management, audits, and inspection programs currently represent significant industry gaps. Performing these activities and having vendors' quality systems assessed, when in good standing and documented, can potentially be further leveraged. This is especially true with commercial-off-the-shelf (COTS) and software as a service (SaaS) platforms when leveraging these vendor audits/inspections to minimize out-of-the-box functionality testing or excessive service testing/verification.

The activities previously mentioned are a recommended way of pivoting from CSV to CSA in practice—and from a CSA perspective. It is equally important to shift and develop an organization's mindset and culture to change from CSV to a CSA approach with critical thinking.

Having a proper quality system with a good foundation that establishes a vendor risk management or vendor audit program is a necessity.

The risk-based analysis for production or quality system software considers factors that may impact or prevent the software from performing as intended, such as proper system configuration and management, security of the system, data storage, data transfer, or operation error. Thus, a risk-based analysis for production or quality system software should consider which failures are reasonably foreseeable (as opposed to likely) and the risks resulting from each such failure.

Pivoting from CSV to CSA and using critical thinking can help the industry become more compliant and drive processes to be more agile while also ensuring better data integrity, product quality, and patient safety. It will also concurrently ensure that a stronger focus on validation of computerized systems will come with a more focused risk-based approach. Industry examples of CSA implementation while demonstrating new strategies with effective critical thinking can help ensure that the new paradigm will result in also using a risk-based approach to work smarter and not harder.

KEY STRATEGIES FOR CSA IMPLEMENTATION

Key strategies for effective implementation of better computerized systems with more efficient and agile processes and less work can produce more targeted efficiency with improved outcomes for product quality, patient safety, and data integrity.

As an example, COTS spreadsheet software may be composed of various functions with different intended uses. Based on FDA guidance on CSA, when using the basic input functions of the COTS spreadsheet software for the intended use of documenting the time and temperature readings for a curing process, a manufacturer may not need to perform additional assurance activities beyond those conducted by the COTS software developer and initial installation and configuration [1].

The intended use of the software—documenting readings—only supports maintaining the quality system record and poses a low process risk. As such, initial activities such as the vendor assessment and software installation and configuration may be sufficient to establish that the software is fit for its intended use and is maintained in a validated state.

However, if a manufacturer uses built-in functions of the COTS spreadsheet to create custom formulas that are directly used in production or the quality system, then additional risks may be present. For example, if a custom formula automatically calculates time and temperature statistics to monitor the performance and suitability of the curing process, then additional validation by the manufacturer might be necessary. Therefore, having a proper quality system with a good foundation that establishes a vendor risk management or vendor audit program is a necessity.

Using the SaaS Model

The increased utilization of SaaS solutions with cloud computing combined with proper and actual vendor audits (i.e., focused to verify the current practices of the vendor and not limited to high-level verifications) and a third-party vendor risk management program produces benefits. It allows for leveraging within the CSA approach (with SaaS solutions that have a good audit history) and for a reduction of the overall scope of SaaS solution and COTS functionality validation testing.

Manufacturers are responsible for determining the appropriate assurance activities to ensure the software features, functions, or operations are in a validated state. Some possible assurance activities and considerations (such as leveraging vendor risk management programs or third-party vendor audits, e.g., in SaaS or cloud computing vendors) reduce the amount of testing while leveraging any of the aforementioned activities. This is potentially combined with historical vendor testing data, COTS functionality, and overall historical data/experience with the software or vendor.

Benefits of the SaaS model

The SaaS model of selling software has become increasingly popular over the years due to its many advantages. The SaaS model allows customers to pay for only the services they use, eliminating upfront costs associated with purchasing and maintaining physical infrastructure or exhaustively upgrading on-premise versions.

Advantages of cloud technologies

The benefits of cloud computing for pharmaceutical companies are numerous, and include faster time to market, scalability, flexibility, cost savings, better collaboration, advanced security, and data loss prevention. In addition, new instances can be implemented, or old instances can be retired in seconds, allowing developers to accelerate development with quicker deployments.

Cloud computing enables the pharmaceutical community to innovate rapidly, manage changes effortlessly, and deliver new medicines to the market faster. Cloud-based infrastructure offers secure storage for sizable and sensitive information. It also supports data security, integrity, and compliance with regulatory entities.

Key Metrics for Success

An important step to determine successful implementation and delivery of a CSA approach is to ensure proper formulation and monitoring of key metrics or key performance indicators (KPIs). Examples include:

- Return on investment: Cost savings for overall reduction in the duration needed to ensure the software is working as intended
- Writing: Significant reduction in the writing of test scripts and protocols
- Execution: Significant reduction in the execution and testing of test scripts and protocols
- Review of key deliverables: Significant reduction in the review of key deliverables
- Approval of key deliverables: Significant reduction in the approval of key deliverables

The overall benefits include a shorter duration for testing with quicker approval times and less production issues. This also potentially produces fewer issues during an audit or inspection where the system can be shown to be tested properly to ensure it is functioning correctly. Thus, it also potentially reduces risk in data integrity, product quality, and patient safety.

GAMP® 5 Second Edition provides further detailed guidance on how to apply CSA and critical thinking. The opportunities and concepts discussed in the FDA draft guidance on scope of testing and the use of the most appropriate types of testing can readily be adopted and implemented within the system life cycle approach described in *GAMP® 5 Second Edition*.

CONCLUSION

Critical thinking emphasizes a focus on, first, clearly thinking through a plan and then creating documentation from a process perspective. Although this critical thinking theory started with medical devices, it can apply to any pharmaceutical or biotechnology product. Instead of companies generating mountains of paperwork that "say" the product is safe, CSA can reduce the amount of testing and documentation. It offers greater efficiency, creates fewer steps, and ensures safer products, and, therefore, better patient outcomes.

Digital systems are increasingly being proliferated by industry, and manufacturers must eventually become up to date with technology. Electronic data can be more readily accessible, retrieved, analyzed, and presented with more efficiency, especially during an audit or inspection. This is another benefit of a CSA approach.

CSA, with GAMP in mind, starts with critical thinking instead of first developing the documentation; this can work for paper documents as well as computer system digital formats. The focus is on quality aspects—assurance means more focus on patient safety and data integrity, which is where the most risk lies. Documentation should then be created accordingly. Rather than focusing on paper-based exercises, which can create problems, the focus should be on thought. This means thinking through a plan, testing to minimize risks (ensuring the software and its functions are working as intended), focusing on quality, and then creating documentation from a process perspective.

However, pharmaceutical companies should be careful to consider that FDA guidance is still a draft when deciding how to apply it: It may change before the issue is in its final version. Furthermore, at this stage, it is unclear how many other different national authorities around the world will accept the CSA draft guidance. Pharmaceutical facilities that must concurrently comply with US FDA and other national authorities will need to balance to what extent they apply the CSA draft guidance. This will ensure that they do not inadvertently fail to adhere to the mix of different regulatory expectations that are applicable to their facilities.

The current draft of the FDA guidance applies to the medical device and biologics space, although the governing principles are expected to be agreed on and recommended by regulatory agencies also in the pharmaceutical space. Meanwhile, a number of regulated companies of all the previously mentioned regulated spaces have initiated the process of switching from a CSV repetitive strategy (where persons are used just to re-execute the validation approach established in the past) to a critical thinking approach. This transition should be carefully planned and deployed because it requires a substantial change in the mindset of all actors involved in the assurance activities related to a computer system.

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INDEX

COPA-DATA	Back Cover
Elettracqua Srl	9
Endress+Hauser Group Services AG	5
Fluor Corporation	Inside Front Cover
Intelligen, Inc.	7
IPS-Integrated Project Services, LLC	1
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Siemens AG	3

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