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PIC/S IN LATIN AMERICA: Harmonization of cGMP Procedures

Global Collaborative Review: Understanding Overall Control Strategy and Patient Benefit-Risk

Industry Perspectives on Practical Application of Platform Analytical Procedures

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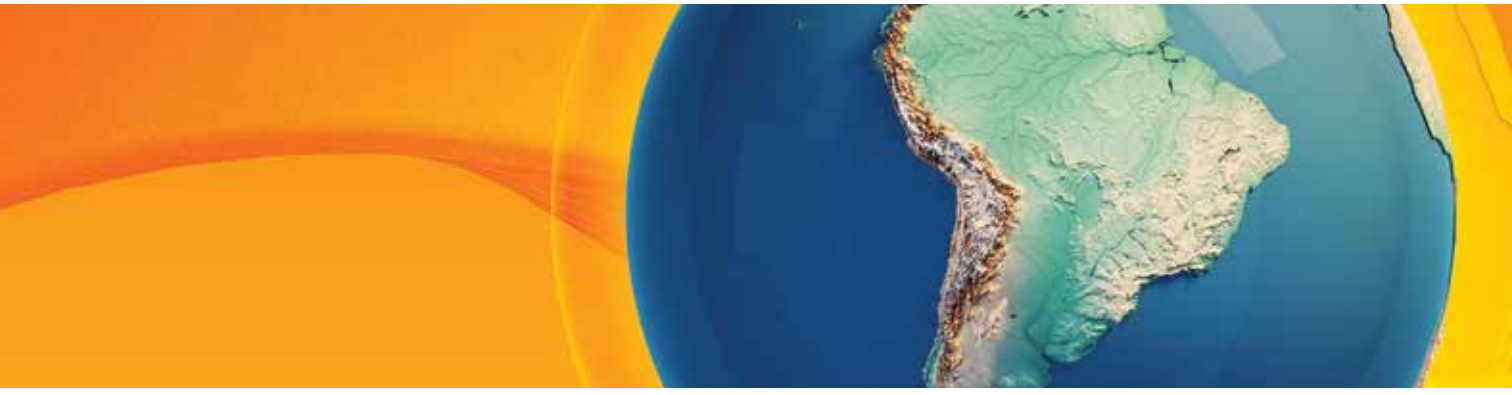

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By Scott W. Billman


Scott W. Billman

A Look at ISPE Activities: Summer to Fall

I hope everyone had the opportunity to enjoy the summer. The ISPE International Board of Directors and ISPE staff have kept busy through the summer months, launching two new Communities of Practice: Sustainability and Artificial Intelligence.

Both subjects are important and impactful to industry. The leadership for these groups will start to bring together industry leaders in these spaces to discuss the engagement and impact of their respective topics with the pharmaceutical and biotechnology industries. ISPE will look to bring together the experts in these spaces to share knowledge and develop programs for our membership. If you are interested in these areas, reach out and get engaged.

The International Board of Directors had our annual strategic discussion meeting where we reviewed ISPE's progress against the 2023–2025 Strategic Plan and started to discuss what 2025–2028 could look like for our industry. We focused the discussion on the global aspect of the industry and where ISPE can, and should, play a crucial role. We discussed the current industry trends and the needs in the areas of guidance documents and training.

We also completed the election process and have established the membership for the International Board of Directors that will be installed at the 2024 ISPE Annual Meeting & Expo. Thank you to the members that took the time to evaluate the amazing slate of candidates and cast a vote.

I hope you will take advantage of the various events, topics, and speakers at the 2024 ISPE Annual Meeting & Expo in Orlando, Florida, this year. I invite everyone to attend our ISPE Membership Meeting & Awards Lunch while you are there. I will be recapping the last year of ISPE activities, and you will hear from other ISPE leaders and colleagues

Thank you to the members that took the time to evaluate the amazing slate of candidates for the ISPE International Board of Directors and cast a vote.

about advances in our industry. We will also be celebrating our dedicated volunteers during the Annual Honor Awards ceremony during the membership lunch. The conference will end on Wednesday, but stick around and join us for the Annual ISPE Foundation charitable golf tournament that afternoon.

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Join us at the 2024 ISPE Annual Meeting & Expo in Orlando, Florida, 13–16 October.

This issue of *Pharmaceutical Engineering®* is focused on the regulatory and quality aspects of the industry. ISPE has an extensive portfolio of regulatory initiatives and interactions with global health authorities in areas such as quality management maturity (QMM), the practical application of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) quality guidelines, and drug shortage prevention. Our Regulatory team also published the results of the *Enabling Pharmaceutical Innovation: Delivering for Patients - A Report on the Barriers to Innovation Survey* this summer.

This issue includes an overview of the regulatory Q&A from the Aseptic Conference. A full transcript of the Q&A is available online at ISPE.org. You will also find articles around harmonization efforts in Latin America and a summary of the ISPE survey on harmonization. We have articles from across many of the ISPE volunteer groups. Members of the Regulatory Quality Harmonization Committee, Product Quality Lifecycle Implementation® Committee, Process Validation Team, Regulatory Steering Council, GAMP® CoP, and Combination Products CoP all contributed to the articles. I am continually impressed with the quality and content of the articles and technical trainings that these volunteer teams produce. It is a true testament to the dedication of the ISPE membership and their deep industry knowledge.

I look forward to engaging with the membership at the Annual Meeting & Expo in Orlando, Florida. I hope to see you there.

Scott W. Billman is Corporate Vice President of Global Engineering, Real Estate, and Facilities Services at Solventum and the 2023–2024 ISPE International Board Chair. He has been an ISPE member since 1996.

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By Miriam Kremer-van der Kamp


Miriam Kremer-van der Kamp

EMPOWERING WOMEN IN REGULATORY AFFAIRS

In the dynamic realm of regulatory affairs, a significant transformation is unfolding—a movement that empowers women to assume pivotal roles in decision-making, policy formulation, and leadership.

Historically dominated by men, regulatory agencies are now evolving into inclusive and diverse entities, where women are making remarkable strides.

Women are reshaping regulatory policies, offering invaluable perspectives, and challenging long-standing norms. Central to this advocacy is the urgent call for greater representation of women in clinical trials. Women have been notably underrepresented in these critical research studies, leading to significant gaps in our understanding of treatment efficacy and safety, particularly across diverse genders and backgrounds.

The imperative for diverse representation is fundamental to ensuring that medical interventions are tailored to meet the needs of all patients. The COVID-19 pandemic starkly highlighted the critical necessity of including pregnant and breastfeeding women in medical research. Acknowledging the pivotal role women play in discerning the safety and effectiveness of treatments, stakeholders are uniting to bridge the gender gap in research studies. Esteemed regulatory bodies, such as the US Food and Drug Administration (FDA), are actively collaborating with industry partners to champion the inclusion of these vulnerable populations in clinical trials. Through concerted efforts, steps are being taken to rectify the historical exclusion of these groups, ensuring their safety and well-being through evidence-based treatments.

Despite persistent challenges, such as the gender pay gap and unconscious biases, the momentum for change is palpable. A new generation of unyielding women is propelling us toward a future where diversity is the bedrock of progress. Embracing initiatives like Women in Pharma®, we stand as advocates for gender equality within regulatory agencies. We are optimistic about the transformative journey ahead, one where diverse voices resonate, policies are shaped inclusively, and innovation thrives.

Recent insights from the "Women in the Workplace" report [1] shed light on the evolving corporate landscapes of America and Canada. Though women's representation in executive positions has seen progress, the mid-tier pipeline remains a bottleneck, especially for women of color. The report dispels myths about women's ambition, revealing that post-pandemic flexibility has fueled a resurgence of drive among women professionals.

Drawing from the report's recommendations, companies can proactively bolster women's representation. Tracking outcomes, empowering managers, addressing microaggressions, and fixing the "broken rung" hindering women's advancement are pivotal actions for inclusive and equitable workplaces, where all talents can flourish.

The pharmaceutical industry, particularly within the Germany/Austria/Switzerland (D/A/CH) region, has witnessed a remarkable evolution. Robust investments in research and development, coupled with collaborative efforts between industry and academia, have propelled advancements. The region's well-established regulatory, exemplified by the Swiss Therapeutic Products Act of 2019 [2], ensure meticulous testing of medications before reaching patients, which fosters trust and growth.

Acknowledging the value women bring to the workplace, governments in the D/A/CH region have spearheaded initiatives to foster diversity and inclusion. Gender quotas on boards of directors and funding for programs supporting women professionals have raised awareness of gender equality. As a result, companies actively seek female talent, acknowledging the undeniable benefits of a diverse workforce.

The evolving landscape of the pharmaceutical industry heralds the dawn of a new paradigm: The workforce of the future. This paradigm encompasses the evolving nature of work, emphasizing attributes like digital literacy, lifelong learning, adaptability, and emotional intelligence.

In the vibrant landscape of regulatory affairs, women are at the forefront of transformative change. Their stories of resilience, advocacy, and empowerment serve as beacons for a new era of inclusivity. As we collectively forge ahead, guided by the principles of diversity and equity, we pave the way for a brighter, more inclusive future for healthcare and beyond. It is a future where women, empowered and supported, lead the charge toward progress, innovation, and lasting change.

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Miriam Kremer-van der Kamp is a Business Developer for VILS Switzerland GmbH. She is the Emerging Leader Liaison of the Women in Pharma International Steering Committee. She joined ISPE in 2022.

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By Monique L. Sprueill


Monique L. Sprueill

OPPORTUNITIES FOR EMERGING LEADERS AND STUDENTS

We are excited about the 2024 ISPE Annual Meeting & Expo in Orlando, Florida! A special thank you to the sponsors and planning committee for the Hackathon. We appreciate your commitment to ensuring that recent graduates and college students will benefit from this challenging and educational experience.

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Congratulations to the recipients of the ISPE Foundation Travel Grants! Many of the grant recipients are also participating in the Hackathon. We welcome all participants to this year's competition. Thank you for partnering with your teammates, leads, and mentors to work through your case study. We are confident that you will gain valuable experience and make meaningful connections during this event.

This edition of *Pharmaceutical Engineering®* focuses on the quality and regulatory landscapes. They are becoming more complex as workers are expected to perform multiple activities with streamlined resources. The roles of artificial intelligence (AI) and machine learning (ML) continue to increase, impacting how we execute projects, lead functional areas, and deliver for our patients. They can be used to simplify data collection and cleaning, perform administrative tasks, schedule audits, and assist in report generation. Increased capabilities to process, organize, and transform data lead to better decision-making and improved outcomes for patients.

There are many opportunities for Emerging Leaders and student members to use AI and ML to help companies manage, display, and optimize the use of information. Your innovative ideas, unique perspectives, and technical skills are needed to help companies continue to evolve and increase capabilities. Full-time, internship, and co-op open roles may be viewed at jobs.ispe.org

As an ISPE member, you have access to industry professionals, potential mentors, *Pharmaceutical Engineering®*, and networking events. These—as well as guidance documents, webinars, and blogs—are tools that can inspire you and assist in professional development.

Are you interested in being a member of a group that supports your career advancement? Join ISPE as a student member or Emerging Leader. Build your network, develop skills, and take your career to the next level.

Keep track of what is going on at your local Chapter or Affiliate. Find out which committees are in search of new members. Volunteer to gain more exposure. Actively participate in program planning to ensure that topics of interest are offered.

Key advantages of joining ISPE as an Emerging Leader or student include:

- Professional development
- Access to ISPE Good Practice Guides and educational resources
- Opportunities to establish and grow your network
- Exposure to thought leadership events
- Participation in Hackathons
- Career solutions to promote advancement
- Access to Emerging Leader and student member-only resources

We invite ISPE members to:

- Actively participate in Emerging Leader and student activities in your local Affiliate or Chapter
- Join Communities of Practice and connect with other industry professionals
- Add content, ask questions, and post your ideas
- Write a blog or article
- Talk with your manager and colleagues about presenting your project at a conference or local program

If you are not a member of ISPE, visit www.ispe.org to join today.

Monique L. Sprueill, CQA, CMQ/OE, PMP, is a Quality Risk Management Leader and the 2023–2024 International Emerging Leaders Chair. She has been an ISPE member since 2002.

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ISPE REGULATORY OPERATIONS

ISPE's regulatory initiatives and programs bring visibility and solutions to significant regulatory and quality challenges faced by the industry, facilitate the flow of information between ISPE members and global health authorities to find solutions, and promote interaction between regulatory bodies in the interests of harmonization.

ISPE members are the backbone of ISPE's regulatory operations. They progress the work of standing committees, limited duration working groups, and high-profile initiatives. Composed of ISPE volunteers and supported by ISPE staff and advisors, these groups ensure ISPE members have access to the latest regulatory developments and expectations.

Standing Committees

Regulatory Steering Council (RSC)

The RSC establishes ISPE's global regulatory priorities and strategy in alignment with the direction of the ISPE Strategic Plan. These members guide ISPE's interactions with regulators and health authorities to ensure the singularity of regulatory and compliance positions. They also act as an advisory council on regulatory issues and respond to emerging regulatory opportunities.

Regulatory Quality Harmonization Committee (RQHC)

The RQHC anticipates regulatory, quality, and compliance developments and the potential for ISPE's involvement or response (e.g., commentary, publication, educational presentation) to benefit the ISPE membership. The RQHC coordinates ISPE's organizational responses to new or draft regulations and guidance and it ensures the responses are of high quality and representative of the ISPE membership.

The management body of RQHC, referred to as "RQHC Global," provides direction and oversight to the RQH Regional Focus Groups. The regional groups provide ISPE with intelligence and identify opportunities for ISPE to provide input, guidance, and scientific and technical support on evolving regulatory issues and concerns for the specific region. The current Regional Focus Groups are Asia-Pacific, Europe/Middle East/Africa, and North America/South America.

Initiative Teams

Advancing Pharmaceutical Quality (APQ)

ISPE's APQ program is an industry-led quality management maturity assessment and benchmarking program that provides a practical set of tools and systematic approaches for organizations to advance the effectiveness of their pharmaceutical quality system. The program aligns with international initiatives that promote quality excellence and with the FDA's focus on quality management maturity and rating the maturity of manufacturing facilities.

Drug Shortages

For more than a decade, ISPE has been instrumental in facilitating communication between the different sectors of the pharmaceutical industry and global health authorities related to drug shortages. The Drug Shortages Team provides guidance, tools, and education to assist companies and support regulatory collaboration in preventing and mitigating drug shortages and works toward harmonizing expectations. The team's publications and tools have been cited in the FDA's *Drug Shortages: Root Causes and Potential Solutions Report* and the *EMA/HMA Good Practices for Industry for the Prevention of Human Medicinal Product Shortages.*

Product Quality Lifecycle Implementation (PQLI®)

ISPE's PQLI® initiative was created to provide guidance on the practical implementation of the concepts described in ICH guidelines, focusing on ICH Q8, Q9, Q10, Q11, and Q12 to help ensure product quality throughout a product life cycle, leading to continuous product improvement. The original project produced the ISPE PQLI® Guide Series. Today, PQLI Technical Teams are developing solutions in emerging regulatory and scientific topics related to chemistry, manufacturing, and controls (CMC) and GMP approaches to ensuring product quality. The current PQLI Teams are Accelerated Development & Manufacturing, Analytical Methods (ICHQ2/Q14), Continuous Manufacturing (ICH Q13), ICH Q12 Implementation, Patient Centric Specifications, Stability (ICH Q1, Q5C), and Transportable/Point of Care Manufacturing.

RECENT WORK DEVELOPED BY CROSS-GROUP REGULATORY VOLUNTEERS

A team of ISPE subject matter experts produced the *Increasing Domestic Resiliency in the Supply of Essential Active Pharmaceutical Ingredients* report in response to a request from a US federal agency. The report lays out technical, regulatory, and workforce changes that stakeholders in any country or region could consider to reduce the risks of API shortages to meet demands for essential medicines at any time, but particularly in pandemics and other emergencies.

ISPE also worked with McKinsey & Company to provide technical and CMC information on two workstreams to inform the European Commission Directorate-General, Health Emergency Preparedness and Response Authority (DG HERA).

For more information, visit ISPE.org/initiatives/regulatory

Carol Winfield is Senior Director of Regulatory Operations for ISPE.

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PIC/S IN LATIN AMERICA: Harmonization of cGMP Procedures

By Flávia C. Firmino, Juliana Perlow, Ania Vargas, and Maria Amaya, PhD

This article offers an overview of the benefits of Pharmaceutical Inspection Co-operation Scheme (PIC/S) membership for regulatory authorities and industry. It also highlights Latin American regulators' current perspectives on PIC/S membership to increase awareness and encourage open dialogue about harmonization, recognition agreements, and potential increase for export facilitation, all which will help increase the access of high-quality medicines to patients. Given that only three countries are PIC/S members in the Latin America region, this represents a huge opportunity for cGMP inspection.

In 1995, the PIC/S was established as an extension to the Pharmaceutical Inspection Convention (PIC) of 1970 as a non-binding, informal cooperative arrangement between regulatory authorities in the field of current good manufacturing practices (cGMP) of medicinal products for human or veterinary use [1].

PIC/S aims to harmonize inspection procedures worldwide by developing common standards in the field of cGMP and by providing training opportunities to inspectors. It also aims to facilitate cooperation and networking between regional and international organizations and competent authorities, thus increasing mutual confidence. This is reflected in the PIC/S mission statement: "To lead the international development, implementation, and maintenance of harmonized cGMP standards and quality systems of inspectorates in the field of medicinal products" [1].

The fact that PIC/S is non-binding allows participating authorities to cooperate and share information informally while keeping complete control over imported medicinal products. This was noted as a key advantage over a mutual recognition procedure by Margaret Hamberg, PhD, former US Food and Drug Administration (FDA) Commissioner [2]. PIC/S is open to any authority having a comparable cGMP inspection system.

Table 1: Candidates for PIC/S membership (January 2023) [2].

Applicants (Up to 6 Years)	Pre-Applicants and Former Pre-Applicants (Gap Analysis Only)	Interested
Armenia	Azerbaijan	India
Bulgaria	China	Bangladesh
Russian Federation		Sri Lanka
Jordan		Vietnam
Saudi Arabia		Philippines

PIC/S IN LATIN AMERICA

As of 1 July 2023, PIC/S comprises 56 participating authorities from all over the world—Europe, Africa, America, Asia, and Australia—as shown in Figure 1. Latin America comprises 33 countries, with the Caribbean Islands. However, of these, only three countries are members of PIC/S: Argentina, through the Argentina Health Authority, National Administration of Drugs, Food and Medical Technology (ANMAT); Mexico, through the Federal Commission for Protection against Health Risks (COFEPRIS); and Brazil, through the Brazilian Health Regulatory Agency (ANVISA).

As indicated in Table 1, the candidates for PIC/S membership are growing; nevertheless, there are no new candidates from Latin America. There is a great opportunity for cGMP inspection in the Latin America region seeing that only three countries are PIC/S members.

MEMBERSHIP TO PIC/S

An essential prerequisite to become a member of PIC/S is that the applicant authority must have a fully functional quality

Figure 1: PIC/S participating authorities [1].

management system (QMS). This is also the main difference from a cGMP perspective between PIC/S and the World Health Organization (WHO). The WHO includes countries with developing quality systems and cGMP programs and hence has a broad list of countries. The PIC/S requires the QMS to cover the systems and procedures of the inspectorate: cGMP inspection procedures, manufacturer licensing procedures, document control procedures, complaint and recall handling procedures, a program for the training of inspectors, code of ethics for inspectors, and more [3].

Before an authority is accepted by PIC/S, a detailed assessment is undertaken to determine whether the authority can apply an inspection system comparable to that of current PIC/S authorities. This assessment, called the accession process, is a 12-step process. In theory, this process can be completed in 18 months, but for most applicants it takes three to five years.

The accession process involves an examination of the authority's cGMP inspection and licensing system (or equivalent), quality system, legislative requirements, inspector training, etc. It is followed by a visit by a PIC/S delegation to observe inspectors carrying out routine cGMP inspections and includes a visit to the government analytical laboratories. During the process, changes and improvements might be recommended by the PIC/S Committee and where necessary, follow-up visits are undertaken to verify the suitability of corrective actions [4].

A PIC/S pre-accession process was introduced to better prepare potentially interested authorities for PIC/S accession. The main advantage of the pre-accession procedure consists in the carrying out of a pre-assessment by an auditor. This includes a gap analysis conducted by the applicant and monitoring by PIC/S-appointed rapporteur(s) to determine areas of noncompliance with PIC/S requirements. The pre-accession process also enables a regulator to determine whether they are ready to engage in a full application.

PIC/S Activities

The main activities of PIC/S are:

- Experience: Appropriate training for new and established members of the cGMP inspectorate
- Seminars: PIC/S meetings and training seminars are not open to industry
- Joint Visits program and coached inspectors: Inspectors from three different countries are teamed up to observe cGMP inspections to compare inspection procedures and techniques and to harmonize cGMP interpretation
- Expert circles: Discuss and exchange information on specific technical areas of cGMP, develop draft guidance documents, and provide training opportunities in their field of expertise
- Guidance documents: Development and promotion of harmonized cGMP standards and guidance documents
- Exchange of information: This scheme relies on the exchange of information on cGMP inspections on a purely voluntary basis; there is no obligation whatsoever to accept inspection results [4]

PIC/S Benefits

The benefits for members include:

- Access to an approved reference for pharmaceuticals manufacturing facilities inspection

The authors prepared a survey with the goal of increasing awareness of PIC/S in other Latin America countries, to encourage an open dialogue about harmonization and reliance, and to highlight the benefits for the Latin America region.

- Enhanced efficiency and quality of manufacturing practices of local factories
- Harmonized and standardized inspection procedures at the level of Member States in GMP
- A rapid alert system at the level of Member States
- Efficiency of the inspectors and training opportunities
- Recognition of exporters that comply with international cGMP standards
- Community adoption of international cGMP standards
- A more effective use of inspection resources through the voluntary sharing of cGMP inspection reports

Additional benefits of PIC/S membership for cGMP regulatory authorities include:

- An internationally recognized system of cGMP controls, including a quality system for the cGMP Inspectorate
- Inspection reliance: the 56 member authorities of PIC/S rely on each other's inspections and inspection reports, as they help avoid duplicate and same scope inspections
- Training opportunities for inspectors, including annual training seminars of specific topics, expert circle on technical topics, annual training seminars for new inspectors, joint inspector training, coached inspections, and access to the PIC/S Inspectorates' Academy for online training
- Opportunities for networking and information sharing among all inspectors of the PIC/S member authorities, particularly during the training events
- The opportunity to participate in the development of internationally recognized cGMP guides and guideline documents
- Involvement in a non-political forum for cGMP regulators

HISTORY OF PIC/S IN LATIN AMERICA

Argentina, ANMAT

ANMAT acceded to PIC/S in January 2008 [5], after a meticulous evaluation process that determined that the body has an inspection system equivalent to that of the high surveillance regulatory authorities belonging to PIC/S.

In line with the Joint Reassessment Programme, ANMAT was reevaluated by PIC/S in November 2018. Members of the PIC/S audit team reassessed the standards of GMP and quality systems of ANMAT's inspectorate. The delegation—made up of officials from the regulatory authorities of France, the Netherlands, Spain, and Israel—met with professionals from the General Coordination of the Inspectorate and the National Institute of Medicines to analyze the regulatory systems and inspection procedures for drug plants. The evaluation included a visit to various pharmaceutical plants in the country [6].

In April 2019, at the 47th PIC/S Meeting, the Compliance Subcommittee (SCC) informed ANMAT that they complied with the good practices standards and quality systems of their inspections for medicines. In doing so, ANMAT also successfully obtained full membership of the PIC/S regime [7].

Mexico, COFEPRIS

COFEPRIS acceded to PIC/S in January 2018 [5]. The process followed by COFEPRIS to enter PIC/S corresponds to the relevance of being part of this international cooperation initiative that facilitates, strengthens, and maintains mutual trust among its members in the field of inspections of GMP for pharmaceutical products.

COFEPRIS assumed the commitment to align the regulatory processes related to the standards established by PIC/S. This was done through intense institutional work for the development, implementation, and maintenance of actions that would allow the agency to effectively comply with international guidelines. As a result of this process, regulatory capacities in drug inspections have been strengthened with a view to optimize decision-making and the strategic development of inspections carried out by COFEPRIS.

In the context of increasing globalization of the pharmaceutical industry and advances in health sciences, it is essential to have a robust regulatory system. This system should ensure the supply of quality pharmaceutical products that are safe, effective, and economically accessible to the population.

The entry of COFEPRIS into PIC/S recognized the agency's implementation of health regulation tasks with the following main benefits [8]: international harmonization of cGMP allowing participation in the development/update of international guidelines; training opportunities (e.g., seminars, joint inspection visits); the exchange of information and fast alert system among participating agencies; and the facilitation of the negotiation of instruments for recognition of cGMP certification between the member agencies.

Brazil, ANVISA

In 2014, ANVISA formalized its interest in becoming a member of PIC/S. This meant that the agency was willing to start efforts to modernize its regulatory framework, invest in the qualification of inspectors working in the National Drug Inspection System, and harmonize inspection procedures for GMP in all Brazilian states.

The decisive year to boost the process of joining PIC/S was 2019. In that year, director Fernando Mendes and deputy director Meiruze Freitas adopted the process of joining ANVISA to PIC/S as a priority project. A major effort to modernize regulatory instruments and work processes was therefore initiated.

In 2019, the regulatory frameworks related to GMP for medicines and public health laboratories were widely discussed and duly updated. The audit work of state and municipal health surveillance was also intensified. In October 2019, the country received PIC/S inspectors from members of health agencies in the UK, Portugal, Malta, and Hong Kong (who audited ANVISA), the State Health Surveillance of Minas Gerais, and the Municipal Health Surveillance of São Paulo.

Additionally, the Ezequiel Dias Foundation (Funed) in Minas Gerais and private pharmaceutical laboratories were also audited. All this took place for the certification, by foreign health authorities, to ensure that the Brazilian inspection process is equivalent to that of the other countries that are part of PIC/S.

The decision for ANVISA's PIC/S membership was expected for the first meeting of the PIC/S Committee of 2020, held annually in April. However, due to the pandemic, the decision was postponed until a committee meeting was held on 15 October 2020. On 30 November 2020, ANVISA was formally notified of the approval of its membership. Membership began in January 2021 and ANVISA become the 54th member of PIC/S.

Technical Cooperation in cGMP

Reliance may take many forms, including full recognition of an inspection decision of a reference national regulatory agency (NRA). This allows for the use of minimal documentation to make a subsequent decision by another PIC/S member. Members may also use full, unredacted assessment reports and/or additional information to make an independent decision. The extent of reliance applied, and documentation required, is up to each national health authority agency to determine in line with their capacity capability and legal frameworks [9]. Latin America PIC/S members are taking steps toward formalizing regulatory cGMP inspection cooperation agreements in the region.

To that end, ANVISA and ANMAT agreed to exchange inspection certificates issued by both agencies with a view to issuing the cGMP certificates. This was done within the framework of MERCOSUR. MERCOSUR, the Southern Common Market, is a regional integration process, initially established by Argentina, Brazil, Paraguay, and Uruguay, and subsequently joined by Venezuela and Bolivia.

This cooperation agreement was signed in 2006, in the city of São Paulo, where both agencies also agreed that the cGMP certificates issued by them must be related to the historical data of the companies and products, in accordance with national regulation. The exchange of an inspection report is currently still required for each agency to conduct their local verification [10].

Recently, during the meeting of the national regulatory authorities of regional reference of the Pan American Health Organization (NRAr/PAHO) in July 2023, the alternatives to strengthening regulatory convergence and reliance in the region were discussed. As a concrete example, officials from Mexico (COFEPRIS) and Brazil (ANVISA) announced that they are working toward regulatory convergence and recognition of inspections and good manufacturing practice certification through PIC/S.

This step indicates an expansion of scope of existing cooperation agreement in place between the agencies. When implemented, it would help realize benefits for both countries, under the auspices of PIC/S, around joint inspection visits to standardize the surveillance processes while ensuring safe and effective health supplies are available in both countries. To advance in this direction would require the confirmation of legal frameworks [11, 12].

PERSPECTIVES ON PIC/S MEMBERSHIP: SURVEY RESULTS

The authors prepared a survey to obtain the current perspectives of the Latin America regulators on PIC/S membership. This was done with the goal of increasing awareness of PIC/S in other Latin America countries, to encourage an open dialogue about harmonization and reliance, and to highlight the benefits for the Latin America region. Key learnings from the survey responses provided by ANVISA are presented in the following section.

Application Process

Pre-accession process

The pre-accession process provides an effective tool for understanding the audit criteria. Through self-assessment, each agency can identify its gaps, understand its current status in relation to PIC/S requirements, and prepare the necessary action plans for the accession process.

Accession process

PIC/S auditors are trained and perform their functions within what is determined and required by the PIC/S audit checklist. Applicants with a positive pre-accession process, and those that have made the necessary improvements, will not have difficulties in relation to the expectations from PIC/S.

Advice for new applicants

Dig deeper into the pre-accession process. Be sure to thoroughly understand each criterion set out in the PIC/S questionnaire and audit checklist during this step. The audit checklist interpretation guide provided by PIC/S [13] is a useful tool for adjusting expectations between the auditee and the auditor.

MEMBER BENEFITS: EXPERIENCE FOR COUNTRIES

As a pre-applicant, countries already have partial access to training events, networking, harmonization, and information exchange. With the accession, countries have access to the PIC/S Inspectorates' Academy, with its vast technical bibliography and training courses available online. The pre-accession process itself leads to harmonization to meet the audit criteria according to PIC/S expectations.

BENEFITS FOR OTHER COUNTRIES IN THE REGION: RELIANCE

Some PIC/S member countries rely on ANVISA inspection reports. Each authority has autonomy and a strategy for dealing with reports issued by partner authorities. ANVISA accepted reports issued by all health authorities that are members of PIC/S during the COVID-19 pandemic (contingency and exceptional measure). The experience was positive, with no increased public health risk. The experience triggered ANVISA to accelerate actions in relation to the creation of a mutual recognition agreement.

INDUSTRY PERSPECTIVES

There are also related benefits to local industries within Latin America when their relevant regulatory authority becomes a member of PIC/S. These benefits may include the following [1]:

- Reduced duplication of inspections, especially since the introduction of the PIC/S Inspection Reliance Initiative
- Export facilitation (including export to non-PIC/S countries)
- cGMP control of imported medicines (a level playing field for local industry)
- Improved competitive standing internationally
- Enhanced market access
- Enhanced reputation of local industry
- Transparent inspection standards
- Consistency of cGMP inspections
- Reliable quality medicines available locally and internationally

When a regulatory authority becomes a member of PIC/S, it shows commitment to reliance and harmonization efforts, optimizing the use of inspection resources and increasing confidence and the reputation of the local industry while strengthening the reliable quality of medicines available locally and internationally.

The "Annual Regulatory GMP/GDP Inspection Survey 2022 Data" published by European Federation of Pharmaceutical Industries and Associations (EFPIA) confirms the PIC/S benefits to industry [14]. The survey was conducted to monitor trends and new focus areas while promoting the use of inspection resources to materialize the benefits of PIC/S membership. In summary, the survey shows that inspectors are back at manufacturing sites with numbers similar to 2019, after a reduction observed during 2020–2021 influenced by the COVID-19 pandemic.

Additionally, a much higher on-site presence for domestic inspections (about 95%) was found compared to foreign inspections (50%). The survey results demonstrated that routine domestic inspections performed by trusted inspectorates (such as PIC/S member states) are most efficient and demonstrate control of the QMS process. The survey also provided visibility to the inspection practice and the varying degree of acceptance for using electronic files, and requests from industry for regulators to continue cGMP/GDP inspections based on regulatory guidance rather than for-profit standards, which are developed by experts and may have conflict of interest.

A MORE EFFECTIVE USE OF RESOURCES

PIC/S membership allows a more effective use of inspection resources. The following inspection processes are encouraged for an efficient management of inspection workload: recognition of inspection reports; adoption of flexible inspection modes (on-site, remote, or hybrid); and a risk-based approach to adapt the scope, length, and frequency of inspections.

The establishment of a legal framework to allow acceptance for inspection from PIC/S participating authorities—along with the continuous skill-building and exchange of information—can play an important role in accelerating manufacturing sites' cGMP certifications. This will also help accelerate access to important medicines to patients.

PIC/S IMPROVEMENTS

Although limited, some positive improvements have been made between PIC/S participating authorities in the Latin America region. Of note is the long-lasting cooperation agreement between ANVISA and ANMAT. This was established in 2006, prior to either agency becoming a PIC/S member, to exchange inspection certificates issued by both agencies. Most recently, on 11 July 2023, the heads of COFEPRIS and ANVISA pledged to design a work plan for regulatory convergence, the recognition of inspection visit reports, and cGMP certificates and to harmonize inspection procedures in both countries [10, 11].

The ANVISA-ANMAT collaboration agreement, and potentially the future ANVISA-COFEPRIS collaboration agreement, mark an important step toward the adoption of reliance procedures for regulatory inspections in the Latin America region. Further benefits could be achieved by leveraging full or partial inspection reliance, and ultimately mutual recognition agreements between authorities. Advancing in this direction would make the best use of available resources and expertise, preventing duplication of regulatory assessments. It would also improve and expedite the regulatory inspections while enabling access of quality-assured, effective, and safe medical products to patients.

CONCLUSION

PIC/S offers a variety of advantages for both participating authorities and industry. However, the full benefits have not yet been achieved in the Latin America region. Only 3 out of the 33 countries are PIC/S members, which represents an excellent opportunity for the non-PIC/S participating authorities in the region. Furthermore, the implementation of formal inspection cooperation agreements and mutual recognition agreements in the region are in the early stages, and there is opportunity to develop and shape this sphere.

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GLOBAL COLLABORATIVE REVIEW: Understanding Overall Control Strategy and Patient Benefit-Risk

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The pharmaceutical industry faces considerable challenges throughout the development, manufacturing, and supply of medicines, largely due to the intricate and divergent global regulatory landscape. The adoption of structured data standards and utilization of cloud-based platforms offer immense potential to overcome these challenges by facilitating faster and more efficient global collaborations between health authorities and industry. This potentially can be achieved by using a visual roadmap of the overall control strategy to help understand patient benefit-risk more effectively.

Worldwide, industry has many regulations to comply with and compliance to these regulations can be challenging [1]. The process of preparing, submitting, and maintaining regulatory documents for product approval is a lengthy and expensive endeavor.

For many organizations, it is currently a manual process due to limited utilization of software tools to assist with these processes [2]. Another challenge that industry faces is managing postapproval changes. This is a vital and complicated part of pharmaceutical manufacturing and regulatory compliance, which requires a thorough understanding of regulatory requirements, effective risk management, and careful planning.

These changes may take years before they are approved by regulatory agencies [1]. In addition, the pharmaceutical industry must comply with inspections of manufacturing facilities by regulatory agencies to ensure alignment with GMP standards. The challenge is that preparing for inspections can be resource intensive, especially when multiple regulatory bodies conduct inspections at different times.

However, the burden of inspections can potentially be minimized by creating a standardized structure for the presentation of the marketing application dossier content. This standardized structure facilitates easier dossier navigation, helping the inspector quickly find the information and link to the underlying supporting data.

Another complicating factor arises from the varying rates at which new International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) members adopt ICH guidelines, as well as the interpretation of those guidelines by regulators from different countries. Additionally, there is a significant gap in the level of regulatory maturity from an innovation standpoint.

The complexity arises when reviewing innovative products, as there may be challenges in understanding the scientific principles behind the innovation, as well as the legal and regulatory requirements associated with them. These complexities can lead to differing perspectives on assessing risk, ultimately resulting in country-specific control strategies for new technologies.

A recent study conducted by the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) Control Strategy Global Harmonization Working Group examined 112 marketing applications encompassing both new synthetic and biological products from 11 companies [3]. The study aimed to evaluate industry's experience with divergences, raise awareness of common trends, and shed light on the implications for multiple stakeholders, including regulators, the industry, and patients.

Using agreed-upon criteria for core document acceptance, the average core document acceptance rate across the US, European Union (EU), Canada, and Japan is 54% for synthetic and biologic products. When this overall acceptance rate (54%) is translated into the likelihood of core documents being accepted by all four countries, it results in a probability of 8.7%. This underscores the subjectivity involved in determining an acceptable control strategy. A fundamental issue for control strategy divergence is that the current version of ICH M4Q(R1) does not explicitly state where or how an overall, end-to-end control strategy is described in a regulatory submission [4].

There have been discussions about structured data and cloud-based submissions to streamline the regulatory review process. However, as data can be interpreted in different ways, it is important to balance data and narrative to understand the overall benefits and risks of the product to the patient. Thus, as part of this article, we explore each of these interconnected processes and present an innovative visual roadmap for the overall control strategy. This strategy uses structured data- and science-driven risk-based assessments to describe the product quality for the intended patient population within a cloud-based submission.

This concept of presenting structured data within the context of a narrative can serve as a valuable tool for facilitating collaborative reviews between sponsors and regulators. By integrating structured data with a coherent narrative, it can enhance the effectiveness of communication within the application process. This approach not only helps ensure clarity and understanding but also fosters a potential streamlined and productive exchange of information between the involved stakeholders. This contributes to a more efficient and informed decision of the application.

THE EVOLVING CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC) LANDSCAPE

New modalities and innovative manufacturing approaches are driving a wave of innovation as biopharmaceutical manufacturers must adopt novel approaches that incorporate advancements in technology and new ways of working. For example, advanced therapy medicinal products (ATMPs), which include cell and gene therapies, and tissue-engineered products offer potential to treat diseases and conditions that were previously considered incurable or that have limited treatment options.

Other examples are advanced technologies that include continuous manufacturing, 3D printing, use of digital twins, and digital tools to enhance patient compliance for treatments. In addition, the use of AI and machine learning (ML) is now prevalent. These technologies are helping reshape drug discovery, development, manufacturing and analytics. They help evaluate chemical and biological data sets to predict drug candidates, identify novel drug targets, optimize drug formulations ensuring the stability and bioavailability of the product, and enable real-time monitoring and predictive maintenance of the manufacturing process [5].

The combination of these advancements is transforming the way drugs are discovered, developed, manufactured, and delivered to patients. As advancement continues in the pharmaceutical industry, it is a struggle for global regulations to adapt to these new technologies in a timely manner, which can cause delays to the introduction and supply of critical medicines to patients. However, there are several ongoing initiatives that seek to address these challenges. For example, the revision of ICH M4Q (R1) was endorsed by the ICH management committee and the concept paper was published 15 November 2021 (ICH M4Q(R2)) [6].

The concept paper for ICH M4Q(R2) has several promising topics, which include improving registration and life cycle management, leveraging digital technologies, and accelerating access of medicines to patients. Also encouraging are global convergence of science- and risk-based approaches, enabling efficient use of digitals tools and benefit–risk considerations. One of the most significant topics is the proposed overall control strategy, which the concept paper states "should be the backbone of the revised M4Q structure" [6].

STRUCTURE PRODUCT QUALITY SUBMISSIONS

In a press release on 3 June 2020, the ICH Management Committee introduced a new topic called Structured Product Quality Submissions [7]. The use of structured CMC data for regulatory submissions will be a paradigm shift in how industry submits CMC information to regulators [8]. Several data standards will impact the CMC domain.

ISO IDMP

One example is International Organization for Standardization (ISO) Identification of Medicinal Products (IDMP), which is designed to establish a common framework for the identification, documentation, and exchange of information on the identification of drug products [9].

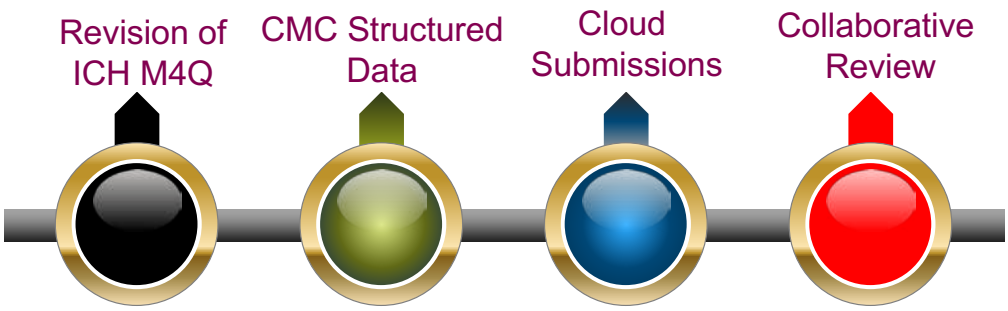
The goal is to improve the accuracy, consistency, and interoperability of data related to pharmaceutical products throughout their life cycle by structuring and standardizing product information [10]. Although IDMP is not exclusive to the quality aspects of a regulatory application, the standard includes a significant number of CMC-relevant attributes, including details about the active ingredient(s), strength, dosage form, route of administration, and packaging.

IDMP promotes global harmonization of product information standards, making it easier for pharmaceutical companies to submit consistent data to multiple regulatory agencies worldwide. Implementation of ISO IDMP standards is an ongoing process. Regulatory agencies worldwide are gradually adopting these standards and pharmaceutical companies are working to align their internal data management systems with IDMP requirements.

PQ/CMC

Another data standard being discussed is the US Food and Drug Administration (FDA) Pharmaceutical Quality - Chemistry, Manufacturing & Controls (PQ/CMC). It was introduced in the Federal Register in 2017 to present structured data elements and

Figure 1: Potential opportunities to accelerate access of medicines.



controlled terminology for Module 3 [11]. PQ/CMC uses the established healthcare data exchange standard from Health Level 7 (HL7), called Fast Health Interoperability Resources, which is widely in use in the greater healthcare ecosystem but is being newly adopted for pharmaceutical and regulatory applications [12].

The overall goal of the PQ/CMC project is to support application review by standardizing language and terminology to allow for preprocessing of data, population of review templates, and aggregation of data for inspections and general data retrieval [13].

PQ/CMC was designed and developed to be implemented in support of product assessment. Therefore, it provides detailed data element definitions, supporting controlled terminology, and the mandatory/optional aspect for each element to allow for consistent and standardized data in various sections of Module 3. The FDA attempted to map PQ/CMC data elements to the ISO IDMP standards, which showed similarities and differences between the two initiatives [14].

Need for Data Standards Alignment

Although there is some overlap in both concepts, the relationship between these emerging data standards and the work that will be pursued under the ICH Structured Product Quality Submissions guidelines is unclear at this time. The maximum benefits of these efforts can be achieved by ensuring alignment and agreement on one data standard, which can reduce divergence across the regions. Notably, the use of structured data enables CMC submissions to be amenable for cloud-based technologies.

CLOUD-BASED PLATFORMS

The introduction of cloud-based, data exchange platforms into the pharmaceutical landscape have emerged as a transformative tool. For example, the nonprofit industry association Accumulus Synergy is developing a cloud-based platform to enhance data information exchange for submission content and collaboration for regulatory submission pathways [15]. The adoption of cloud-based platforms within the pharmaceutical sector has many advantages, especially when it comes to fostering collaboration across diverse teams, organizations, and geographical boundaries. This accessibility transcends physical and geographical constraints, enabling real-time global collaboration in a protected shared environment (see Figure 1).

Currently, industry has collaborative initiatives such as Project Orbis [16], the Access Consortium [17], and the International Coalition of Medicines Regulatory Authorities (ICMRA) [18]. One of ICMRA's active working groups is Pharmaceutical Quality Knowledge Management (PQ KMS). This group has conducted postapproval collaborative pilots; engaged and coordinated with external organizations such as ICH, International Pharmaceutical Regulators Programme (IPRP), and Pharmaceutical Inspection Co-operation Scheme (PIC/S); and developed high-level reflection papers to promote collaboration [19]. These initiatives provide an excellent starting point for global harmonization efforts across the regulatory agencies and are currently accomplished without the use of cloud computing technology.

The use of a cloud-based platform enables further collaboration and facilitates a greater number of regulators to participate in these initiatives in a seamless manner. However, there are challenges to adopting cloud-based technologies, such as cybersecurity concerns and country-specific legislations. For example, the EU's data privacy and security law, General Data Protection Regulations (GDPR), is one of the toughest privacy and security laws in the world [20]. GDPR requires that any information collected from citizens of the EU must reside in servers located in EU jurisdictions or in countries with a similar scope and rigor with their privacy laws.

Automated Data Interpretation and Computer-Aided Data Analysis

As we approach this exciting stage for industry, there should be caution around the interpretation of data using automated tools. Data in its raw form can be interpreted in a myriad of ways, but to fully grasp its scope and utility, context is needed. For sponsors, context is needed to distinguish nuances in the data that are relevant to the underlying production approach and technology. Additionally, the degree to which evidence can be supplemented

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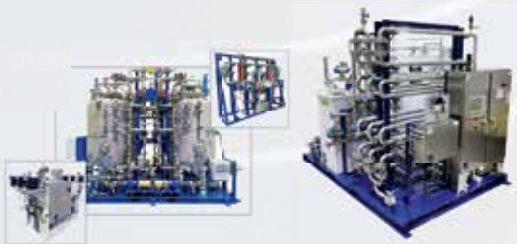

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Figure 2: Linking the overall control strategy to product quality.

by prior knowledge could drive significant differences in the data package between sponsors, which would be imperceptible to the reviewer with significant context in the application.

For health authorities, the incorporation of structured data into CMC submissions holds the potential to leverage data analytics and AI/ML to enhance the efficiency of regulatory reviews. A case in point is the FDA's adoption of the Knowledge-Aided Assessment and Structured Application (KASA). KASA establishes rules and algorithms for risk assessment, control, and communication related to product, manufacturing, and facilities [21]. KASA also facilitates computer-aided analysis of the applicant's submission to FDA's institutional knowledge instead of relying solely on the summarized narratives provided in submissions.

Balance of Data and Narrative

Although the comparison of dosage forms, manufacturing processes, and other relevant CMC attributes can provide valuable data-driven assessments, CMC attributes should be considered within the context of the intended patient population to ensure that a pharmaceutical product is safe and effective. For example, patient-centric factors such as disease state, treatment duration, age, and characteristics of the patient population are important to understand the overall risk of the administered drug product.

It is therefore critical to have a balance between data and narrative to understand the benefits and risks of the product to the patient. One strategy is to use the overall control strategy to bridge data and narrative to demonstrate the overall benefit–risk details of the medicine to the patient population.

OVERALL CONTROL STRATEGY

The understanding of the overall control strategy plays a pivotal role in the product's risk assessment and in safeguarding drug product quality (see Figure 2). It also ensures that the quality attributes and performance characteristics of the product are consistently maintained throughout its entire life cycle.

The concept and aspects of the control strategy are addressed in several ICH guidelines, including ICH Q8–Q14 and in the concept paper for ICH M4Q(R2) [22–28]. The ICH guidelines emphasize the importance of designing a robust control strategy as part of the pharmaceutical development process. This ensures that pharmaceutical companies have a comprehensive plan in place to consistently deliver safe and effective medicines to patients. At the same time, it allows them to consider scientific understanding, risk assessment, and regulatory compliance.

The control strategy is a pivotal component of pharmaceutical development, representing a structured approach to ensuring product quality, safety, and efficacy throughout its life cycle. It is fundamentally linked to the concept of quality by design (QbD), which promotes a proactive and science- and risk-based approach to development strategies for the CMC controls of the product.

The sponsor's institutional knowledge is combined with specific drug product information, including:

- The target product profile (TPP), which identifies the characteristics of the drug product necessary for the patient population and disease indication
- The patient quality target product profile, which outlines the quality characteristics of the drug product necessary to meet the TPP
- Critical quality attributes (CQAs)
- Critical process parameters (CPPs)

These specifications, as well as continual improvement, are key elements of the control strategy. Its primary objective is to ensure that the drug product consistently meets its intended quality attributes, thus delivering safe and effective medicines to patients worldwide.

Table 1: Risk communication for product quality.

Risk Assessment			Risk Control		Result of Quality Risk Management (QRM) Process/Risk Review
Hazard Identification	Risk Analysis	Risk Evaluation	Risk Reduction	Risk Acceptance	Risk Rating

Table 2: Risk rating and definition.

Risk Rating	Risk Definition
Low	Low impact on quality affecting safety and efficacy of medicinal product
Medium	Medium impact on quality affecting safety and efficacy of medicinal product, if no further controls are put in place
High	High impact on quality affecting safety and efficacy of medicinal product, if no further significant/novel controls are put in place

OVERALL CONTROL STRATEGY WITH THE USE OF STRUCTURED DATA

One innovative approach to understand product quality for the intended patient population is by creating a visual roadmap of the overall control strategy. The roadmap is created using structured data and risk-based assessments for cloud-based submissions. This entails organizing and presenting data in a structured and interconnected manner that provides reviewers with a holistic overview and in-depth understanding of the overall control strategy.

Tables 1 and 2 illustrate an example of how risk can be communicated to regulators by using quality risk management (QRM) principles from ICH Q9(R1) [23]. The evaluation of the risk to quality should be based on scientific knowledge and ultimately linked to the protection of the patient.

In the example shown in Table 1, the sponsor can communicate risks qualitatively by initiating a QRM process that describes the risk assessment, risk control, rating output, and review for the product. Table 1 provides an opportunity to discuss data and narratives that support a science-driven, risk-based approach that describes the risk in terms of how it can impact quality of the product. Table 2 provides an example of risk definitions that can be used for risk communication.

The goal for this approach is that risks are systematically and comprehensively evaluated by a weight of evidence approach to the sponsor's product-specific knowledge, overall control strategy, and benefit–risk assessment of the product with the intended patient population.

For example, risk should not be evaluated in isolation, but understood and assessed against the overall control strategy. This should be done with the understanding of how that risk impacts quality in terms of safety and efficacy for the intended patient population. This approach brings transparency and clarity to the dossier, enabling regulators to navigate through the application of the pharmaceutical products more efficiently and understand the risks in a patient-centric manner. It potentially can be a communication tool between regulatory bodies and the industry, fostering a collaborative environment for review and understanding of product quality.

Although the ICH guidelines stress the importance of developing a robust control strategy as part of the pharmaceutical development process, there is no current regulatory guidance that clearly states where or how a comprehensive end-to-end control strategy should be described in a regulatory submission. One innovative approach to understand product quality for the intended patient population is by creating a visual roadmap of the overall control strategy, using structured data, and providing a risk assessment for cloud-based submissions.

This concept has been initiated by the ISPE Risk-Based Quality Overall Summary (QOS) Working Group. The approach entails organizing and presenting data in a structured and interconnected manner that provides reviewers with a holistic overview and in-depth understanding of the overall control strategy.

Figure 3 presents an example of the visual roadmap concept for the overall control strategy of an antibody–drug conjugate (ADC). In a cloud-based environment, reviewers have the flexibility to choose specific sections of the control strategy for review. For instance, as depicted in Figure 3, the reviewer can opt to examine the cytotoxin control strategy by selecting the box. This will provide further details of the cytotoxin synthetic pathway and controls, as shown in Figure 4. If the reviewer wishes to delve deeper into the pure cytotoxin, they can access additional information, which is presented in Figure 5.

This interface empowers the reviewer to explore various options, gaining a comprehensive understanding of the cytotoxin's

quality. Reviewers can also download data for independent assessments while having a clear grasp of the innovator's provided control strategy. This interactive approach allows for a systematic exploration of the application. This facilitates an in-depth evaluation of the product's benefit–risk profile for the patient population. It's important to note that the ADC example illustrated in Figures 3–5 serves as a conceptual representation.

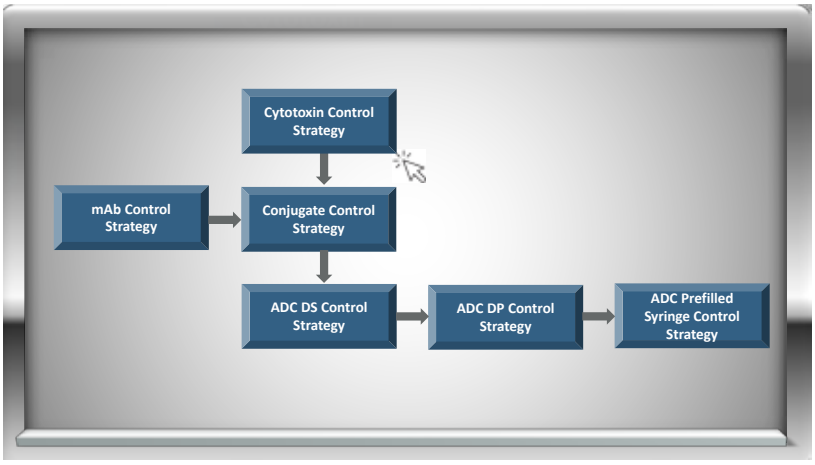
The ISPE Risk-Based QOS Working Group plans on illustrating this concept in a cloud environment by structuring a mock submission. This demonstration within a cloud environment shows one example of the potential use of structured data in cloud-based submissions.

CONCLUSION

The pharmaceutical industry plays an indispensable role in ensuring patients worldwide have access to essential medicines. However, it faces considerable challenges throughout the development, manufacturing, and supply of medicines. This is largely due to the intricate and divergent global regulatory landscape. The adoption of structured data standards and utilization of cloud-based platforms offer immense potential to overcome these challenges by facilitating faster and more efficient global collaborations between health authorities and the pharmaceutical industry. It is crucial to strike a balance between data-driven assessments and the narrative context to comprehensively evaluate the benefit–risk profile of the medicine for the patient population.

One innovative concept is the creation of a visual roadmap for the overall control strategy using structured data and science- and risk-based assessments that describe product quality for the intended patient population in cloud-based submissions. This approach allows reviewers to gain a holistic understanding of the control strategy. It also allows each piece of information linked to describe the medicine's quality in terms of benefit and risk for the specified patient population. Ultimately, these improvements may translate into better healthcare outcomes for patients across the globe, reaffirming the industry's crucial role in delivering quality medicines to patients.

Figure 3: Visual roadmap of the overall control strategy for ADC.



Note: Drug substance (DS), monoclonal antibodies (mAb), and drug product (DP).

Figure 4: Synthetic pathway of cytotoxin.

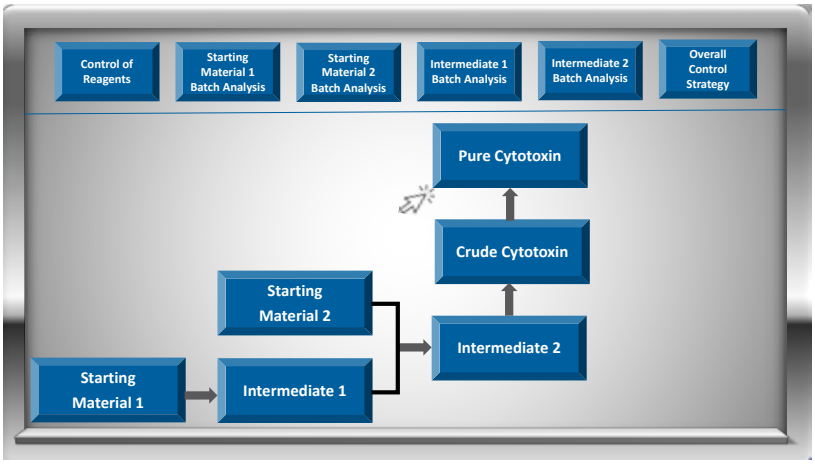
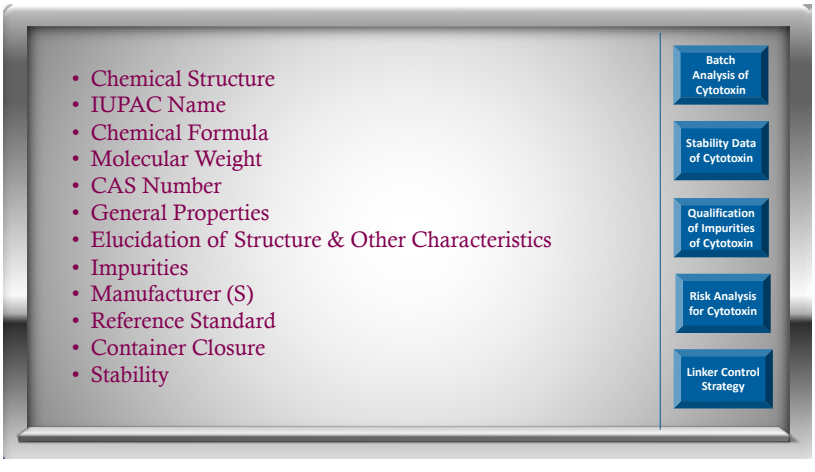


Figure 5: Information on pure cytotoxin.



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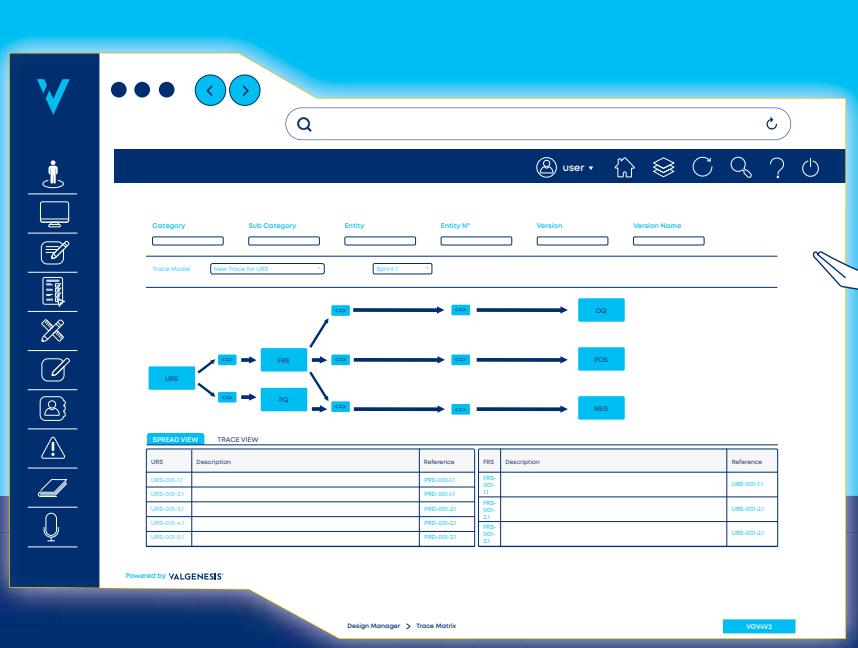

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INDUSTRY PERSPECTIVES ON PRACTICAL APPLICATION of Platform Analytical Procedures

By Timothy W. Graul, PhD, Nina S. Cauchon, PhD, Frank Bernardoni, Bryan C. Castle, PhD, Christof Finkler, PhD, Suminda Hapuarachchi, PhD, John Harrahy, PhD, Daniel Hemminghaus, Elisabeth Krug, PhD, Sachin Lohani, PhD, Amir Malek, He Meng, Hetalben Patel, PhD, Mary Beth Pelletier, PhD, MBA, Karen Rule, and Jason Starkey

Pharmaceutical and biotechnology companies employ platform analytical procedures in the development stages of their synthetic and biological drug products and are beginning to leverage them for commercial products. This shift is supported by the acceptance of platform procedures in the recently adopted ICH Q2(R2) and ICH Q14. Six case studies are shared in this article to highlight how platform procedures are developed, applied to products in development, and assessed for extent of validation needed to determine if appropriate for use.

The recent revision to ICH Q2(R2) Validation of Analytical Procedures [1] and new guideline ICH Q14 Analytical Procedure Development [2] have provided a pathway for pharmaceutical and biotechnology companies to develop and use platform analytical procedures for commercial products.

ICH Q2(R2) defines a platform analytical procedure as "an analytical procedure that is suitable to test quality attributes of different products without significant change to its operational conditions, system suitability, and reporting structure. This type of analytical procedure can be used to analyze molecules that are sufficiently alike with respect to the attributes that the platform analytical procedure is intended to measure" [1].

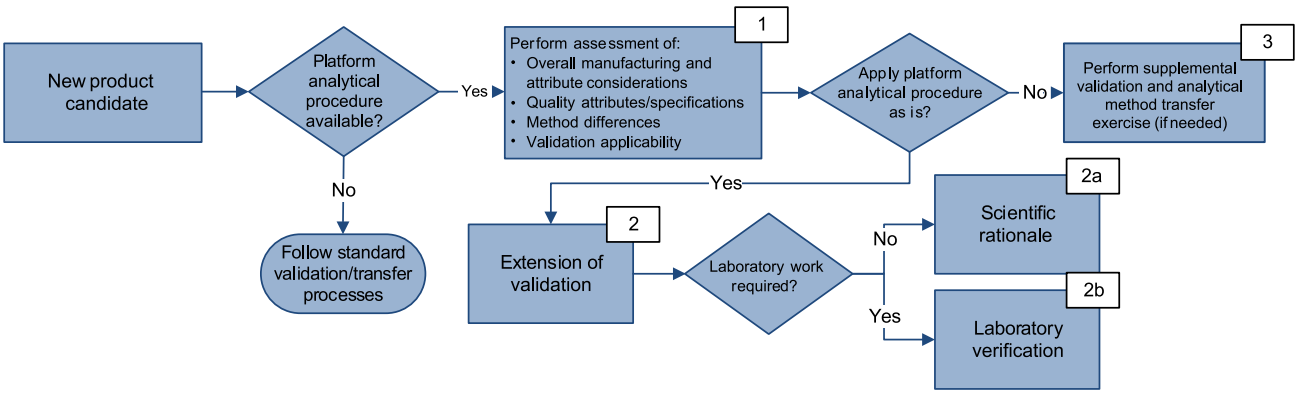
BACKGROUND

Platform analytical procedures have been commonly used across industry to streamline clinical development by making analytical development and validation activities more efficient. The inclusion of the platform analytical procedure concept in ICH Q2(R2) formalizes the idea in guidance for the first time. ICH Q2(R2) states, "when an established platform analytical procedure is used for a new purpose, validation testing can be abbreviated, if scientifically justified" [1].

ICH Q14 further describes the rationale for application of platform analytical procedures and reduction of subsequent development activities: "In certain cases, an analytical procedure can be applied to multiple products with little or no modification of measurement conditions. For a new application of such platform analytical procedures, the subsequent development can be abbreviated, and certain validation tests can be omitted based on a science- and risk-based justification" [2].

The Food and Drug Omnibus Reform Act (FDORA)—a US Food and Drug administration (FDA) "rider" that is part of the Consolidated Appropriations Act, 2023—required the US FDA to establish a program for the designation of platform technologies [3]. It states that the sponsor of a drug application should demonstrate that the platform technology has the potential to be incorporated in, or utilized by, more than one drug without an adverse effect on quality, manufacturing, or safety. Although FDORA applies to manufacturing technologies, some concepts may also relate to platform analytical procedures, which this article aims to explore.

Figure 1: Analytical platform procedure assessment.



To date, industry has used the platform analytical procedure approach primarily for biological products and nearly exclusively in clinical development [4–6]. However, recent research applied a platform approach to the analysis of residual solvents in small molecules [7] and has offered suggestions for submitting information on analytical platform technologies in regulatory filings [5]. Monoclonal antibodies (mAbs) are good candidates for platform analytical procedures. This is because most attributes can be analyzed by an established set of conditions where the mAbs are of similar size and structure.

In a recent guideline from the World Health Organization (WHO), platform technologies were defined for methods and processes as they apply to mAbs [8]. Similarly, messenger RNA (mRNA) vaccines are good candidates to adopt platform analytical procedure strategies, as they may have common structural elements with only the codon-optimized sequence encoding the target antigen being unique to each new mRNA construct/variant. Moreover, many platform analytical procedures with established conditions, system suitability, and reporting structure have been used to analyze mRNA attributes for a commercial product [9].

The article showcases examples from six different companies to demonstrate the efficiencies and opportunities afforded by platform analytical procedures across techniques and modalities, leveraging prior knowledge and historical data. Although a pathway has been recognized through the adoption of ICH Q2(R2) and Q14, challenges lie ahead in preparing and gaining approval for global submissions.

By sharing these examples, the aim is to provide awareness of and create dialogue around global acceptance of platform analytical procedures. The objective of this article is to describe how the implementation of platform analytical procedures benefits industry and regulators alike.

PFIZER: PLATFORM ANALYTICAL PROCEDURES FOR mRNA VACCINES

The following case study shows the use of platform analytical procedures to support mRNA vaccine technology. All analytical procedures supporting release and stability testing for an mRNA COVID-19 vaccine were fully validated in conformance with existing ICH guidelines. Platforms have been established through extensive method development, validation, transfer, and testing of mRNA vaccine products—and their effectiveness was demonstrated through an application to change an mRNA strain for the already approved product.

The approach outlined in this example can be used for any mRNA vaccine product or product change by following the appropriate assessment, described next.

The critical elements of a procedure and the rationale to support any reduced validation requirements are determined using a science- and risk-based approach. Figure 1 shows a decision tree used to apply the strategy with consistency and considers the following elements in box 1:

- Overall considerations of the manufacturing processes, matrices, and attributes
- Quality attributes and alignment of acceptance criteria (specification) to the analytical procedure's intended use
- Changes to analytical methodology, reference materials, and critical reagents
- Applicability and coverage of the validation, e.g., validated range and transfer activities

The assessment described in box 1 of Figure 1 concluded that there is no change for the changed mRNA product other than the sequence in the platform manufacturing process, the target concentration, and the specification. The analytical procedures

By sharing these examples, the aim is to provide awareness of and create dialogue around global acceptance of platform analytical procedures.

have already been established at the commercial testing sites. Next, one example of each outcome—scientific rationale (Figure 1, box 2a), laboratory verification (Figure 1, box 2b), and supplemental validation (Figure 1, box 3) and the rationale are given.

Extension of Validation: Scientific Rationale

For box 2a in Figure 1, RNA concentration by ultraviolet (UV) spectroscopy was selected as the example. The sequence change from mRNA-to-mRNA products does not alter the basic structural components—the purine and pyrimidine bases that absorb UV—of DNA or RNA. This allows for determination of RNA concentration by the Beer–Lambert law when measuring absorbance at 260 nanometers (nm).

The UV spectroscopy platform procedure was previously validated per ICH Q2 and transferred to the testing site. No changes to the platform analytical procedure are required to support testing of the new product. The procedure could be run without impacting system suitability criteria, operating conditions, and parameters.

Extension of Validation: Laboratory Verification

For box 2b in Figure 1, mRNA integrity (purity) using capillary gel electrophoresis (CGE) was selected as the example. Considering no significant change in size/valency, the sequence length of the new mRNA product/strain may affect migration time and the electrophoretic profile of fragments and intact species without impacting the ability of the method to accurately measure RNA integrity.

Verification was performed to confirm that the potentially impacted characteristics of the platform analytical procedure remain in a validated state. For this example, precision and specificity were challenged under a protocol with the same acceptance criteria. The CGE platform procedure was previously validated per ICH Q2 and transferred to the testing site.

No changes to the platform analytical procedures are required to support testing of the new product. The same assay control, sample preparations, and instrument conditions are used. The analytical procedure is applied without significant change to its operational conditions, system suitability, and reporting structure.

Supplemental Validation

For box 3 in Figure 1, identification of mRNA using digital droplet polymerase chain reaction (ddPCR) was selected as the example. The procedure requires mRNA product/strain-specific primers and probes (for specificity). Challenge validation characteristics (e.g., specificity) were considered under a protocol with acceptance criteria against both the formulation buffer and other mRNA constructs. The ddPCR platform procedure was previously validated per ICH Q2 and transferred to the intended testing site.

Platform Documentation for Regulatory Submissions

Although there are multiple ways to document this work within a company, the documentation within a regulatory submission should be considered early in the process. The full validation for each analytical procedure is a combination of the platform procedure validation, scientific rationale, and product-specific data.

For any extension of validation or supplemental validation leveraging historical knowledge and/or previous validations, a validation report or summary in the appropriate common technical document sections should be provided. This includes the scientific rationale justifying the strategy for each analytical procedure. In addition, product-specific results from laboratory verifications and supplemental validations should be shared within the submission.

The mRNA technology presents an application of the platform analytical procedure approach for an already approved product upon a variant change. The same principles can be applied to other products generated with a similar manufacturing process (for example, a new mRNA vaccine candidate). The subsequent case studies aim to expand the approach to other modalities.

GENENTECH: CAPILLARY ELECTROPHORESIS SODIUM DODECYL SULFATE (CE-SDS) METHODS

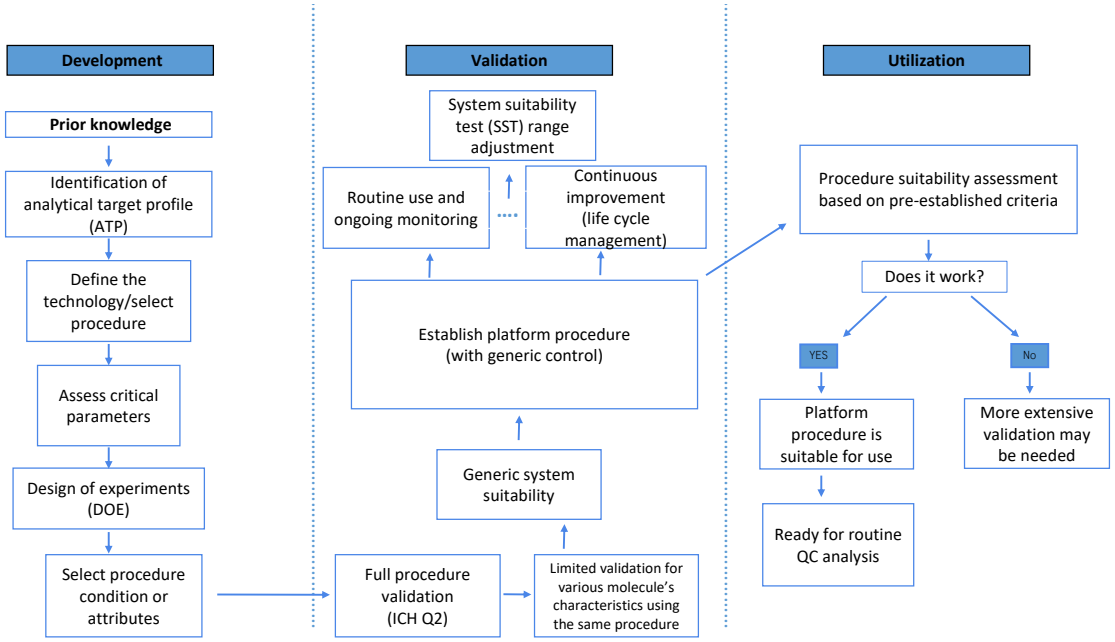
Workflow

The platform analytical procedure workflow consists of three phases: development, validation, and utilization (see Figure 2). Measurement requirements for a given quality attribute or a set of quality attributes can be defined in an analytical target profile (ATP). This predefined approach to analytical development can ensure that the analytical procedure is robust across its life cycle.

To achieve the optimal procedural conditions, a design of experiments (DOE) for screening of critical method parameters is executed. During the second phase, a validation strategy is devised per ICH Q2. To ensure suitability of the platform analytical procedure for new molecules, an assessment along with a generic control is completed.

The platform analytical procedure control is used for system suitability testing, which ensures the proper performance of the analytical procedure during assessment. The platform procedure is monitored to maintain performance and prevent potential drifting through the system suitability criterion. Using a common control for system suitability across multiple labs, instruments, and analysts enables collecting more relevant data and improves the precision

Figure 2: Workflow for platform analytical procedure.



assessment of the platform analytical procedure. Furthermore, the control enables evaluation of any changes introduced by suppliers, such as column resins or equipment configurations.

Application

CE-SDS analytical procedures are commonly used to evaluate the size heterogeneity, purity, and manufacturing consistency of biologics, under non-reduced and/or reduced conditions. The non-reduced CE-SDS method separates, detects, and quantitates distribution of product-related size variants (e.g., hinge fragments, main peak, or partially reduced cysteine-linked subunits). Reduced CE-SDS separates and quantitates light chain (LC), non-glycosylated heavy chain (HC), HC components, and other size variants such as non-specific polypeptide cleavages (e.g., LC and HC clips).

CE-SDS is a good candidate for a platform analytical procedure due to wide applicability and well-established robustness for usage in testing of mAbs. During the developmental phase, a combination of single- and multi-factorial studies are completed to identify critical method parameters, minimize the method variation, and increase applicability of usage as a platform across multiple mAb formats.

This approach was applied to the determination of critical dye-labeling conditions for a fluorescent-based platform CE-SDS method [10]. Critical parameters such as SDS-protein complexation, dye labeling, gel-lot variation, and auto-sampler stability are confirmed during validation.

The conditions for platform analytical procedures are established by leveraging prior learnings and knowledge from previous product-specific and platform-validation studies. During the utilization phase, the feasibility of the platform analytical procedure for new mAbs is evaluated through limited assessment studies, such as precision, specificity, stability indication, and comparison of UV and fluorescence electropherograms to ensure proper dye labeling.

Inclusion of a preestablished platform assay control during the assessment studies ensures proper performance of the analytical procedure. This approach creates a rigorous process to ensure that new molecules that meet the predefined criterion during the utilization phase can be tested by the platform CE-SDS method.

ELI LILLY AND COMPANY: CAPILLARY ELECTROPHORESIS TO INVESTIGATE FRAGMENTATION OF MABS

As previously mentioned, reduced and non-reduced CE-SDS are standard techniques employed in the purity assessment for large molecules. The following example offers another approach to establish a platform analytical procedure for CE-SDS analysis of size variants. The principle of the CE-SDS separation for both conditions—reducing (the addition of 2-mercaptoethanol [BME] to break disulfide linkages) and non-reducing—is based on the use of an electric field to separate proteins through a polymeric gel matrix based on their hydrodynamic radius.

SDS is a negatively charged ionic detergent used in sample preparation to promote denaturation and achieve uniform protein coating. This is to obtain a uniform mass-to-charge ratio. Under such conditions, molecular hydrodynamic volume is the determining factor, resulting in a size-based separation. "Ignoring" the diversity in the complementarity-determining regions that make mAbs

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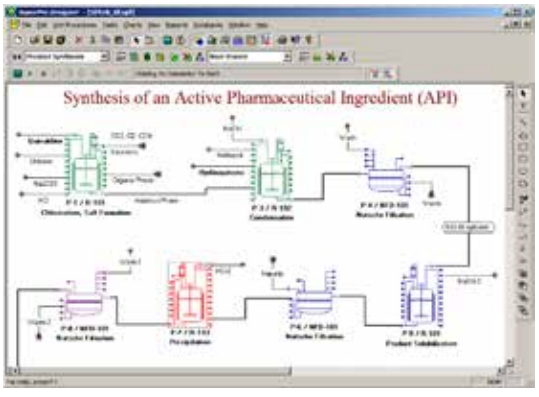

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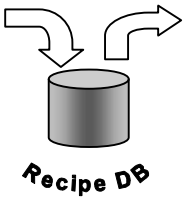

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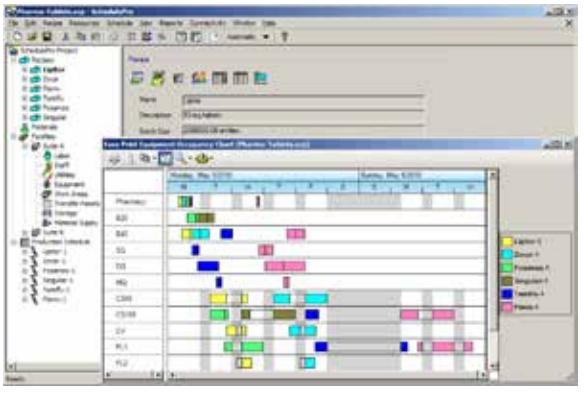

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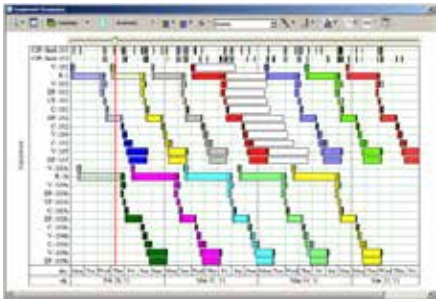
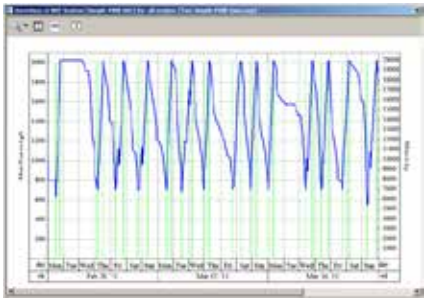


Easy production tracking, conflict resolution and rescheduling

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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The objective of this article is to describe how the implementation of platform analytical procedures benefits industry and regulators alike.

unique allows for common method conditions to be applied to mAbs of similar size and structure.

US Pharmacopoeia (USP) <1053> provides guidance and procedures used for characterization of biotechnology-derived articles by capillary electrophoresis [11]. That chapter is harmonized with the corresponding chapters in Japanese Pharmacopoeia (General Information 4) and European Pharmacopoeia <2.2.47> [12, 13].

Process

Four platform analytical procedures are established (reducing and non-reducing conditions with pressure or electrokinetic injection) based on prior knowledge and experience with allowable ranges around the main parameters. When a new molecule enters the portfolio, experiments (e.g., exploratory DOEs) are conducted. This is to confirm that the two main factors found to be molecule-dependent—heating time and temperature—fall within the established allowable ranges for the platform analytical procedures. The same is true for slight alterations of other method conditions that are covered by the underlying dataset used, e.g., minor adjustments in BME concentration.

Molecule-specific instructions for sample preparation that differ from the platform analytical procedures text are documented. The analysts are pointed to this documentation when executing the platform analytical procedure. If more significant modifications were needed to achieve the intended separation (e.g., changes to gel buffer detergent, reductant, wavelength, polarity, separation voltage, or instrument model), non-platform method conditions would have to be developed. These changes would result in a molecule-specific procedure.

Based on scientific evaluation (e.g., matrix components, analyte concentration, and selectivity need), a decision is made to use the pressure or electrokinetic injection platform analytical procedures. They are used throughout development for final drug substance/drug product, as well as in-process and characterization testing. The procedures are stability indicating, consistent with global regulatory guidance and industry expectations for mAbs.

During the clinical stages of development, method qualification for the platform analytical procedure is abbreviated. Linearity across the purity range, extrapolated linearity, accuracy, and matrix specificity are not executed. The only experiments performed are those to determine precision/intermediate precision, prepared sample stability, and stability indication using a stressed sample.

Molecule-specific procedure codes are then introduced at the time of marketing authorization. The validation exercise employs a mixed model of using historical data, generated across the platform, in addition to molecule-specific data. Robustness parameters are determined based on platform knowledge: the experiments conducted for each molecule.

AMGEN: LEVERAGING A PLATFORM-SIZE EXCLUSION CHROMATOGRAPHY (SEC) ANALYTICAL PROCEDURE FOR MAB ANALYSIS

Purity methods, such as SEC, are ideal candidates for platform execution. SEC can be consistently applied across different mAbs due to its versatility and ability to handle diverse protein samples. SEC methods developed for one mAb can often be transferred and applied to others without any changes to the method.

This makes SEC a convenient and time-saving approach when analyzing different mAbs within a project or across multiple projects. SEC is compatible with a wide range of sample matrices, including different formulations, buffers, and excipients. It can handle mAbs derived from various sources (e.g., mammalian and microbial) or subclasses (immunoglobulin G (IgG)1 and IgG2). This versatility allows for the use of SEC as a consistent platform method across a mAb portfolio.

By selecting an appropriate column, laboratories can achieve optimal resolution and separation for different mAbs to generate a platform procedure, ensuring accurate and reliable analysis. SEC is extensively used in quality control laboratories for mAb analysis. Its ability to provide quantitative information about mAb size distribution, aggregate content, and purity makes it a reliable method for routine analysis of different mAb samples for both release and stability purposes. By using SEC as a platform method, laboratories can streamline their analytical processes and maintain consistent performance.

Method Development

Typically, the development of analytical procedure commences after preclinical development for new active substances. Method development should align with the expectations of an analytical platform, which encompasses the ability to monitor relevant quality attributes, attribute sensitivity, and reporting intervals. The initiation of qualification and robustness experiments should occur after finalized method conditions and initial system suitability criteria are established.

The completion of initial robustness is a prerequisite before the method can be used for release and stability testing of clinical materials. As illustrated in Figure 3, if the method is applicable for platform use, the initial qualification and robustness lay the foundation for implementation. After the platform method is adopted in the laboratory, the method can be applied to a new

Figure 3: Platform procedure development and implementation workflow.

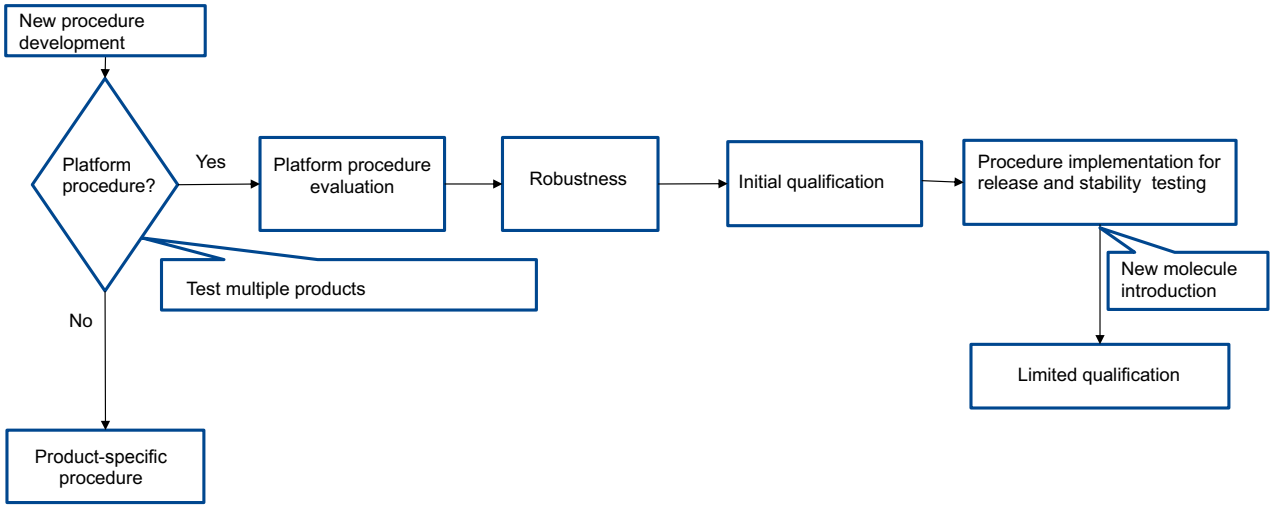
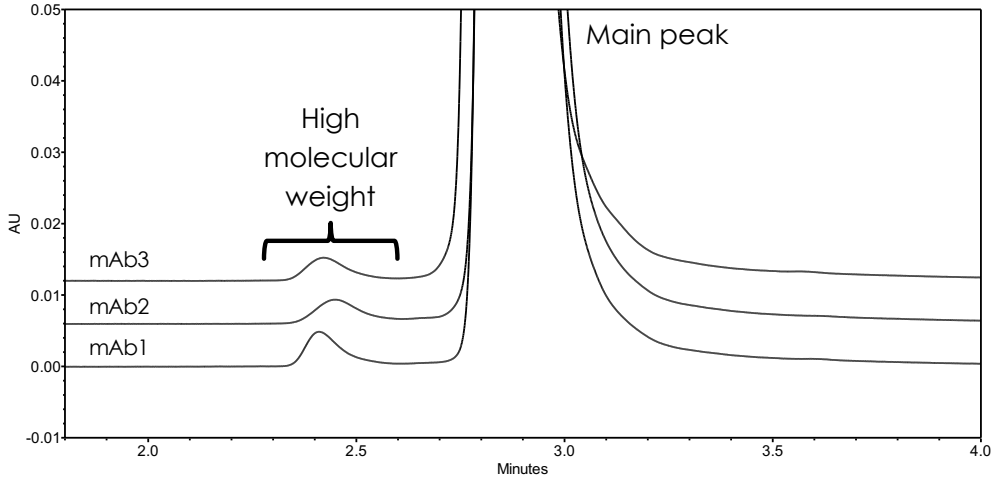


Figure 4: Profiles for three mAbs analyzed by a platform-size exclusion procedure; chromatograms are offset for clarity.



molecule with minimal method qualification and robustness to demonstrate that the method is fit for purpose.

Having a subset of method qualification parameters tested prior to new product introduction is generally adequate in development. If product-specific information, such as example chromatograms and integration events, is needed to facilitate attribute testing of the new molecule, it can be achieved by maintaining specific supplemental documents. For regulatory submissions, platform and any product-specific qualification data can be provided to justify use of the platform procedure.

In summary, SEC's compatibility, transferability, and suitability for diverse mAb samples make it an excellent candidate as a platform methodology. Its consistency and reliability contribute to efficient and robust analysis across different projects, as shown in Figure 4. It facilitates comparability studies and quality control and ensures the product quality of mAb-based therapies.

SANOFI: PEPTIDE MAPPING AS A GLOBAL PLATFORM ANALYTICAL PROCEDURE

Peptide mapping has been developed and implemented as a platform procedure for identity testing of mAb and mAb-like molecules to support lot release at Sanofi. Despite being a comparative and platform procedure, peptide mapping is not a "generic" method. A specific map, or a fingerprint, needs to be developed for each

protein under the same/similar operational conditions, system suitability, and reporting requirements. General guidance and procedures for this method are provided in *USP <1055>: Peptide Mapping* [14] and harmonized with corresponding chapters in the Japanese Pharmacopoeia <G3-3-142> and European Pharmacopoeia <2.2.55> [12, 13].

Platform Procedure

The platform procedure consists of disulfide reduction under denaturing conditions, cysteine alkylation, buffer exchange, enzymatic digestion, chromatographic separation of peptide fragments with UV detection, and data analysis. Identity is confirmed based on a comparison of the chromatographic profile and the relative peak area ratios of selected marker peptides of a test sample against a reference standard.

To ensure the platform procedure is robust and fit for its intended purpose, an enhanced approach—as delineated in ICH Q14—was used during development. Sample preparation (from reduction to digestion), separation and detection of peptide fragments, and data analysis are three major parts of the procedure. The potential variations that may occur in the first two parts are known to introduce artifacts or impact the method performance (e.g., chemical modifications, miscleavage, and poor resolution of peptides), and thus may lead to invalid results.

The risks associated with performance were assessed based on prior knowledge using a systematic approach (e.g., failure mode and effects analysis [FMEA] or Ishikawa diagram), and risk probability numbers were generated for the various method parameters. The method operable design region (MODR) was then defined based on the results from three representative mAbs (two IgG subtypes) using DOE and one-factor-at-a-time experiments. These MODRs are expected to be applicable to many other mAbs. Thus, the platform approach affords reduced method development for new mAbs. For molecules that behave differently and do not fit the platform, a product-specific method will be developed.

Specificity, as a key requirement for identity, was assessed based on the overall chromatographic profile and through a set of purposely selected marker peptides. The finalization of marker peptides was based on ultra performance liquid chromatography with ultraviolet detection and mass spectrometry (UPLC-UV-MS), e.g., quadrupole time-of-flight MS detector, data from the target molecule, and their chromatographic behaviors. The development of the peptide map generally requires the identification of most, if not all, peptide fragments by MS.

To prepare the platform procedure for release testing of new mAbs, an abbreviated qualification (e.g., only the specificity performance characteristic with a limited number of samples) is performed for early-stage programs. A validation is completed with additional parameters considered (e.g., intermediate precision, column lot-to-lot variations) to support late-stage programs. The robustness data from development may be included into the validation report as ICH Q14 states. The platform procedure has been implemented for multiple mAbs and mAb-like molecules across different UPLC instrument platforms and data analyses applications.

MERCK & CO: PLATFORM GAS CHROMATOGRAPHY PROCEDURE FOR RESIDUAL SOLVENT QUANTIFICATION IN SMALL-MOLECULE PHARMACEUTICALS

Organic solvents are commonly used in the production of small-molecule pharmaceuticals, primarily for drug substance and occasionally for formulated drug product. Ensuring that the levels of residual solvents are within acceptable limits, as defined by ICH Q3C (R8) [15], is crucial for both clinical and commercial release. Therefore, it is essential to analyze and control the organic solvents used in the manufacturing process.

Gas chromatography with flame ionization detection (GC-FID) is the preferred technique for quantifying residual solvent levels. This is due to its compatibility with solvents of different boiling points, availability of various stationary phases for different selectivity, separation capability of capillary columns, and the universality and sensitivity of FID.

Analyzing Residual Solvents

When analyzing residual solvents with GC-FID, two main factors to consider are sample preparation/introduction (direct injection or static headspace sampling) and chromatographic procedure. The chromatographic procedure typically employs single capillary columns and an oven temperature program for baseline resolution of the analytes.

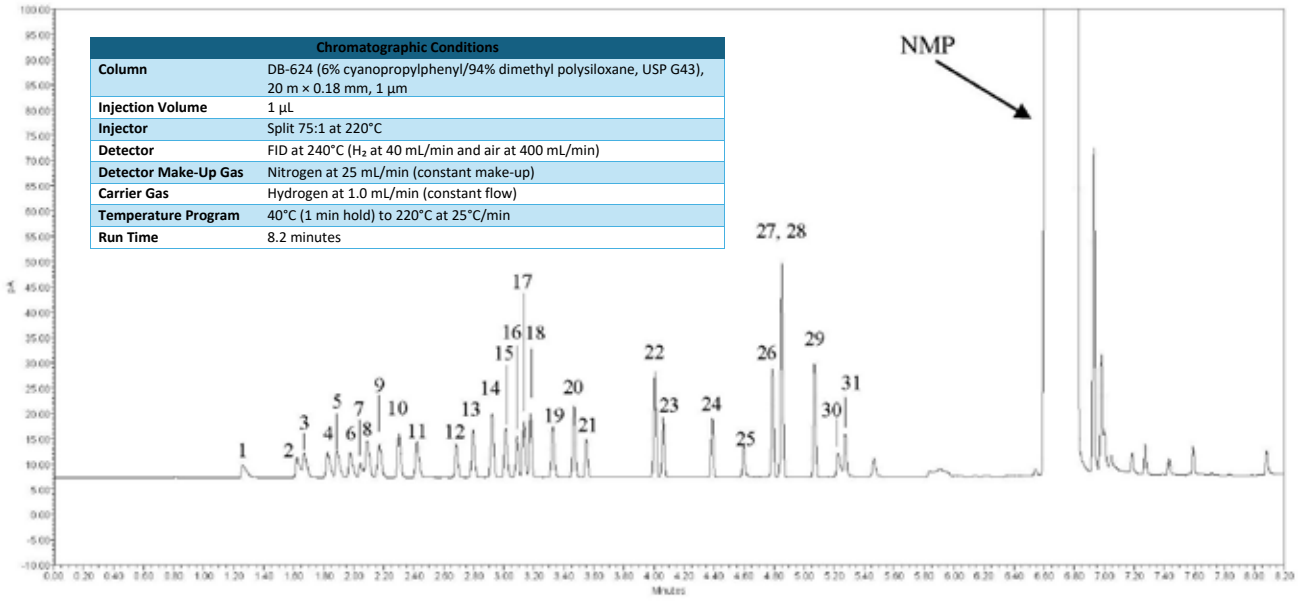
USP <467>: Residual Solvents [16], which is harmonized with European Pharmacopoeia Chapter 2.4.24, Identification and Control of Residual Solvents [13], describes three headspace GC-FID procedures that employ capillary columns and static headspace injection. These procedures use hydrogen, nitrogen, or helium as the carrier gas for the determination of solvents. They have a chromatographic runtime of approximately 60 minutes and use capillary columns with different phases and coating thickness as well as temperature programs.

During development, the drug substance process undergoes frequent changes and optimization to enhance cost, yield, and process robustness. This necessitates the rapid analysis of samples produced under diverse conditions. It involves conducting solvent tests for isolated intermediates at different stages of synthesis and for the final drug substance. Having a platform GC-FID procedure simplifies analysis for residual solvents under these varying conditions, minimizing method development, accelerating key results, and reducing validation activities.

Developing a Platform GC-FID Procedure

A platform GC-FID procedure based on direct injection has been developed and validated using five different diluents to achieve this goal [7]. The procedure uses hydrogen as the carrier gas and can resolve over 30 commonly used solvents within a short runtime (eight minutes), which also makes it amenable to high-throughput analysis.

Figure 5: A representative chromatogram for the analysis of residual solvents.



Chromatographic Conditions	
Column	DB-624 (6% cyanopropylphenyl/94% dimethyl polysiloxane, USP G43), 20 m × 0.18 mm, 1 µm
Injection Volume	1 µL
Injector	Split 75:1 at 220°C
Detector	FID at 240°C (H_2 at 40 mL/min and air at 400 mL/min)
Detector Make-Up Gas	Nitrogen at 25 mL/min (constant make-up)
Carrier Gas	Hydrogen at 1.0 mL/min (constant flow)
Temperature Program	40°C (1 min hold) to 220°C at 25°C/min
Run Time	8.2 minutes

FID: flame ionization detector, NMP: N-methyl-2-pyrrolidone

The procedure was established by conducting extensive development and validated using standards for sample independent attributes, such as linearity, sensitivity (limit of detection/limit of quantitation [LOD/LOQ]), and precision. Various clinical-stage compounds, approved drug substances, and commercially available materials were used as model compounds to assess matrix effects, and the method's accuracy was demonstrated through spike and recovery experiments for solvents likely to be present in the respective compound (see Figure 5 for a representative chromatogram and Table 1 for procedure details).

The platform GC-FID procedure is commonly used during development of small-molecule programs at Merck & Co. When considering a new program in early clinical development, the suitability of the platform procedure is evaluated based on its ability to separate the desired solvent(s) from process impurities and sample matrix interferences (specificity). Additionally, the stability of the sample solution is assessed to ensure an appropriate analysis window after preparation. If the peak resolution and solution stability results are acceptable, the method can be implemented without the need for further validation.

For commercial programs, supplemental validation of the platform procedure has been performed for application to drug substance. This includes accuracy assessment through spike/recovery, intermediate precision, and robustness evaluation using specific solvents of interest. Additional program-specific requirements are determined through a case-by-case assessment, and prior knowledge of the platform procedure is leveraged to support validation studies as needed.

Table 1: Platform GC-FID procedure details.

Analyte Number	Analyte	Analyte Number	Analyte	Analyte Number	Analyte
1	Methanol	11	n-Propanol	21	1,4-Dioxane
2	Ethanol	12	Ethyl Acetate	22	Toluene
3	Diethyl Ether	13	Tetrahydrofuran (THF)	23	i-Butyl Acetate
4	Acetone	14	Cyclohexane	24	n-Butyl Acetate
5	i-Propanol	15	i-Butanol	25	Dimethylformamide
6	Acetonitrile	16	Isopropyl acetate (IPAc)	26	Ethyl Benzene
7	Dichloromethane	17	2-Methyltetraydrofuran	27,28	p-Xylene/m-Xylene
8	t-Butanol	18	n-Heptane	29	o-Xylene
9	Methyl tertiary-butyl ether (MTBE)	19	n-Butanol	30	Dimethyl sulfoxide
10	n-Hexane	20	Methylcyclohexane	31	Dimethylacetamide

With accelerating clinical development, streamlining analytical activities without negatively impacting the assessment of product quality becomes essential.

In many cases, no further validation may be needed to apply this method to regulatory starting materials, intermediates, and in-process testing. Using a platform procedure for residual solvents has significantly accelerated process development and reduced validation requirements for introducing new small-molecule compounds to clinic as well as for commercialization.

DISCUSSION AND EXAMPLE COMPARISON

Six companies shared examples that highlight how platform procedures are developed, applied to products across modalities in development, and assessed for extent of validation needed to demonstrate fitness. The two CE-SDS examples illustrate that multiple approaches are suitable to establish platform analytical procedures for the assessment of the same quality attributes.

Although one example was applied to commercial registration of mRNA analytical procedures, the remaining examples describe use of platform procedures for the clinical development of mAbs and small molecules. However, consistent with ICH Q2(R2), the principles described in these examples can be applied to commercial products beyond the modalities discussed previously.

Each example leveraged a science- and risk-based approach and followed similar approaches to those outlined in the presented flow charts. Extensive prior knowledge is employed in the development of the platform analytical procedure. This consists of knowledge of the modality as well as requirements of the measurement, analytical technique, and procedure parameters. Measurement requirements for the quality attribute(s) can be described in an ATP, which guides technology selection. An evaluation can be performed if the platform analytical procedure meets the performance requirements of the ATP.

ICH Q14 states, "prior product knowledge plays an important role in identifying the appropriate analytical technique. Knowledge of best practices and current state-of-the-art technologies as well as current regulatory expectations contributes to the selection of the most suitable technology for a given purpose. Existing platform analytical procedures (e.g., protein content determination by UV spectroscopy for a protein drug) can be leveraged to evaluate the attributes of a specific product without conducting additional procedure development" [2]. A risk analysis is completed to evaluate if the platform can be applied to a product with or without any modifications, then the extent of validation experiments required can be determined.

Benefits of Platform Analytical Procedures

There are many benefits to the application of platform analytical procedures, particularly in the commercial environment. With accelerating clinical development, streamlining analytical activities without negatively impacting the assessment of product

quality becomes essential. Platform analytical procedures can enable rapid support of new products during development and subsequent commercialization. This also leads to an increased probability for enhanced robustness. They offer operational, compliance, and training advantages for analysts that do not need to learn unique procedure parameters for every test of every product.

Beyond a reduction in validation activities, transfer activities may be streamlined where testing is consolidated in the same commercial testing laboratory. Additionally, platform analytical procedures provide opportunities for automation that can increase throughput. These advantages may lead to greater reliability of the supply chain, providing value to companies, regulators, and patients. Using the same procedure parameters and validation results additionally leads to more rapid completion of registration documents and inspection readiness. This increases efficiency for health authorities during review and inspection where the procedure has previously been registered and implemented.

Once the product and procedure are registered, there are additional benefits throughout the product life cycle. Continuous monitoring of analytical procedures in the commercial environment is a resource-intensive, yet necessary, activity. Continually monitoring a platform across multiple products is more efficient and increases detectability of performance issues requiring mitigation. Management of this knowledge is critical due to the larger amount of data for one procedure and should lead to rapid and effective troubleshooting with any issues that may arise during routine use.

Although there are many benefits to the use of platform analytical procedures, there are challenges moving forward with this approach in commercial registrations. ICH Q2(R2) allows for validation testing to be abbreviated if scientifically justified. However, the extent of studies required to satisfy health authorities from non-ICH members may delay global acceptance of platform procedures and realization of their benefits. Applicants would also need to address documentation concerns, as the validation results would be provided in the dossier of another product. How that information is linked or copied for a new product would be of concern to the applicant.

The analytical procedure control strategy for the platform, including system suitability, and specific control and/or reference materials used to ensure acceptable performance should be considered. Also, the risk analysis for why a platform analytical procedure was applied to the new product and the extent of validation required would need to be communicated. Perhaps the most challenging aspect would be addressing the change management strategy.

The need to change parameters in a platform procedure for one product would require assessment for all other products that use the platform. These concerns may be reason for some applicants to reconsider or delay registering platform procedures. However, the six examples provide an excellent overview of the science- and risk-based approach that the authors believe are representative of the principles described in ICH Q2(R2) and Q14.

CONCLUSION

The recent adoption of ICH Q2(R2) and ICH Q14 supports the potential for registering platform analytical procedures. This publication describes six examples that outline varying yet scientifically sound approaches for developing, applying, and implementing platform procedures. Primarily, these examples have been successfully used in clinical development, but the principles can be applied to commercial registration.

Applying platform analytical procedures from one product to another has many benefits that facilitate efficient pathways to registration. Beyond registration, a more streamlined path for postapproval changes is important for the life cycle management of the product. With increasing pressures of cost, speed to market, and product quality, the use of analytical procedure platforms is one aspect of a science- and risk-based strategy for product commercialization that will ultimately benefit patients today.

Acknowledgments

The authors would like to acknowledge the ISPE Product Quality Lifecycle Implementation (PQLI)® Analytical Methods technical team for its contributions to the subject matter discussed in this paper, and David Michels, Anjana Patel, and Matt Sampson for their support with manuscript preparation and review of the publication.

For more information about ISPE's PQLI®, visit ispe.org/initiatives/pqli

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Conflicts of Interest

All authors are employees of their respective companies. All authors contributed to the writing of the report, approved the final version of the manuscript, and agreed to submit the manuscript for publication.

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Global Drug Shortage Prevention Convergence Opportunities

By Jessica Hale, PharmD

The regulatory landscape related to drug shortage prevention has changed in recent years due to large-scale, highly visible events (e.g., COVID-19 pandemic, geopolitical issues, hurricanes).

This has created rapidly evolving drug shortage requirements, generating nuanced differences in definitions, approaches, reporting expectations, and risk management planning across multiple markets. As a result, ISPE formed a Global Convergence Opportunities team within its Drug Shortages Initiative. This team conducted a study to assess trends in drug shortage–related requirements and identify opportunities to harmonize definitions and proactive approaches for drug shortage prevention across markets.

STUDY FINDINGS

A preliminary readout of the study findings was presented at the 2024 ISPE Europe Annual Conference, and the final readout will be presented at the 2024 ISPE Annual Meeting & Expo. Please see the online article at ispe.org/pharmaceutical-engineering/section/online-exclusives for a detailed discussion of the findings and correlated recommendations in the interest of bolstering supply chain resiliency. Proposals presented in the article are intended to serve as a starting point for further discussion on drug shortage prevention regulatory requirements that could be optimally harmonized, as well as approaches to provide a holistic framework worldwide, for industry and regulators.

GLOBAL CONVERGENCE

Given the importance of ensuring continuous supply of biopharmaceutical products for patients, the increasing pressures on global supply chains, and the rapidly evolving regulatory drug shortage landscape, we anticipate diversity in health authority expectations intended to ensure or bolster product availability could continue to grow. We believe considering convergence proposals specific to drug shortage prevention activities are important, as global convergence can allow faster reactions to disruptive events and correspondingly increase patients' accessibility to medicines.

Any effort to effectively address the complex and multifaceted issues contributing to drug shortages requires close technical collaboration and clear communication between the pharmaceutical industry and global health authorities. ISPE has had a long-standing commitment to facilitating communication and progress between the different sectors of the pharmaceutical industry and global health authorities related to drug shortages [1]. ISPE and its Drug Shortages Initiative Team of industry experts continue to be prepared to provide platforms for discussion with appropriate government or regulatory agencies in support of global harmonization activities [2].

Read the complete Global Convergence Opportunities Report at ispe.org/pharmaceutical-engineering/section/online-exclusives

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About the author

Jessica Hale, PharmD, is an Associate Director in Global Regulatory Affairs at Merck & Co. Inc. (Rahway, NJ), where she is responsible for leading regulatory activities related to US drug shortages and deletions and to emerging device and digital health development. She serves as a subject matter expert on FDA and other health authority regulations regarding these topics. Prior to her current role, she led drug shortage prevention and global product strategy as a Regulatory Affairs Associate Director at Organon. She joined Merck & Co. as a regulatory affairs intern in 2017, with prior pharmacy experience in both the hospital and community settings, in addition to conducting pharmaceutical formulation research. Jessica received her Doctor of Pharmacy from Western New England University College of Pharmacy and Health Sciences. She joined ISPE in 2021.

2024 ISPE Aseptic Regulatory Panel Q&A

By Jörg Zimmermann

On 13 March 2024, ISPE concluded the 2024 Aseptic Conference with a regulatory panel question and answer session. Attendees were invited to submit questions to representatives from the Austrian Agency for Health and Food Safety (AGES), US Food and Drug Administration (FDA), Regierungspraesidium Tübingen (RP Tübingen), World Health Organization (WHO), Therapeutic Goods Administration (TGA), and Swissmedic.

The panelists provided valuable insights and perspectives from their areas of work. Please note that views expressed by the panelists are not necessarily representative of the position of the AGES, FDA, RP Tübingen, WHO, TGA, or Swissmedic, and that questions and responses are lightly edited for clarity.

The panelists included:

- Christina Meissner, GMP Inspector, AGES
- Daniel Müller, GMP Inspector, RP Tübingen
- Rick Friedman, Deputy Director, Office of Manufacturing Quality, FDA/CDER (virtual)
- Vimal Sachdeva, GMP Inspector, WHO (virtual)
- Matt Davis, Senior GMP Inspector, Inspections Team Leader, TGA (virtual)
- Christian Schärer, PhD, Head Inspectorate, Division of Inspectorate and Licenses, Swissmedic (virtual)

This article offers highlights from the discussion. For the complete report, visit ispe.org/pharmaceutical-engineering/section/online-exclusives

Annex 1 has been in effect since August 2023 and section 8.123 will come into effect in August 2024. What are the high-level learnings from inspections using the current Annex 1 version?

Christian Schärer

Although Swissmedic had been part of the drafting group, Annex 1 is a big document and we had to go through the document and evaluate the differences to the previous version of Annex 1 and identify the impact on our inspections. This was also the trigger which led us to drafting the Swissmedic Q&A document.

Industry was proactively asking questions on what the impact on our inspections would be and what the impact would be on their facilities. Companies started very early to make gap assessments to the new Annex 1. We saw companies going into projects where they wanted to modify their own zoning concepts, for example. Everybody knew the document very well, so there were no big surprises in the content. Industry had enough time to prepare themselves. In our experience, the industry really took the changes in Annex 1 seriously.

Rick Friedman

The evolution to new technologies always has challenges as they might have different failure modes and we learn new things. The great thing about Annex 1 is that it is solidifying where European, US, and Pharmaceutical Inspection Co-operation Scheme (PIC/S) authorities have been going for a long time. In the year 2024, there should be extensive barrier systems like restricted-access barrier systems (RABSs) and isolators used as the baseline in any facility—unless there's an extremely strong rationale [to grant an exception for a conventional type of cleanroom].

With that comes questions like, how often do you sterilize the RABS gloves and do integrity testing on them? The same of course also applies to the integrity testing of isolator gloves, but that seems to be a little better understood. What do you do if you have a leaking isolator glove? Do you need to replace them more frequently? Do you have the right thickness of those gloves, or the right material, and still have dexterity for the operators? Are you making the right choices in terms of your vendor?

Another thing in legacy facilities is insufficient space for operators to perform work and poorly designed human–machine interaction.

Vimal Sachdeva

This has been a very similar case for WHO. We have been doing a lot of inspections, mainly in the low- and middle-income countries, and we are seeing some deficiencies. The companies have not used the time when Annex 1 (WHO TRS 1044, Annex 2) was in draft to do their gap assessments. If they had, they would be much more ready by now. During the inspections, we have seen companies that are still struggling. One of the examples is a manufacturer that has difficulties because of the limited space in the production area. They would have to do a lot of work to comply with the current Annex 1 (WHO TRS 1044, Annex 2).

Matt Davis

Australia is in a unique position, as we haven't adopted the new Annex 1 under our legislation yet. However, I want to give you two examples from our experience so far. The first example would be very proactive organizations that we've inspected domestically and overseas that are looking at supplying to Australia. Some new facilities have really looked forward to the new annex and have adopted some amazing new technologies to help them achieve a good level of compliance but also futureproof them against the future adoption of Annex 1.

The second example is from an initial inspection of a manufacturer of radiopharmaceutical products. There were several issues, and it was kind of bittersweet because the issues that we identified are better explained in the new Annex 1; but because that manufacturer was looking to the previous version of Annex 1, they missed some of the salient points that are an existing requirement but maybe not spelt out as clearly. I get the feeling that the new Annex 1 is really going to facilitate a better understanding of what it takes to make quality sterile medicines.

Christina Meissner

The old version of Annex 1 told you what was acceptable. The new Annex 1 will tell you what the expectation is and how to move forward. I think that's a good vision for industry and for innovation.

Where do companies struggle most in the implementation of Annex 1?

Daniel Müller

Companies are usually struggling most with all cost-intensive requirements and time-consuming tasks, like upgrading of whole lines, introduction of PUPSIT [pre-use, post sterilization integrity testing of filters] into established equipment by rebuilding equipment. Even introduction of PUPSIT into a single-use filling assembly (SUS line) that has been developed over the last five years (the design was set before the new version of Annex 1), which now must be upgraded. It requires a complete redesign of the single-use assembly and a repetition of process validation. Both are time-consuming and costly.

Jörg Zimmermann

With high investments required, we might see some lines going out of operation. We might see some products disappearing from the market because there's no justification for the upgrades. That's always the challenge and the trade-off that could come from new requirements.

Vimal Sachdeva

The companies that WHO is inspecting are in the low- and middle-income countries. In addition to the cost and time, there is another thing that they may not have, and that is the expertise to understand and interpret the new Annex 1 (WHO TRS 1044, Annex 2) before they implement it. There is also a silver lining. While inspecting some of the sites in Indonesia, we have seen that the manufacturers have decided to go ahead with this revised guideline and they have started a big engineering project to comply, implementing PUPSIT and the removal of all conventional cleanroom setup, replacing it with open RABS and barriers. For a lot of companies, it is not easy because the products have very little profit margin. They are contemplating whether this investment is viable or not.

Matt Davis

My answer to that question is based on discussions with industry associations and manufacturers in this space. It's the change in mindset where we're asking manufacturers to really understand their processes and better define how they're controlling their processes. It boils down to interpretation of the requirements in the sense of we're asking people to take another look at something they may have just taken for granted. PUPSIT is a good example: Previously, people would give us a risk assessment that just said, "It's a business risk, we are not doing anything about it." Now, Annex 1 says, "It's not just a business risk. You need to understand the process."

PUPSIT is a default requirement. You really need to understand the nature of your process and the risk to the sterilizing filter to then look at whether it should be performed or not. That's additional knowledge around your processes and people need to take a deeper dive into that.

Have you seen major engineering projects that have been started because of Annex 1?

Vimal Sachdeva

We have seen engineering projects that have been initiated by some of the manufacturers as a consequence of Annex 1 (WHO TRS 1044, Annex 2). For example, two sterile product manufacturers have decided to go ahead and make significant changes to their vial filling lines by removing all flexible curtains, replacing them with barrier systems, and implementing PUPSIT—all based on their contamination control strategy. We have also seen a company that has decided to expand their manufacturing area, as space was minimal around the filling line.

Christian Schärer

We see companies looking at the requirement for zoning concepts on the airlocks and upgrading some zones. Some companies are challenging their facility to understand what the right zone concept in their facility is. Based on that, engineering projects have been initiated, which will take some time to implement. This includes shutdown of the facility for a certain time. We understand that those changes cannot be done immediately and that's why we also accept a longer implementation period. Annex 1 also brings in clarification on some terminology: e.g., what is an open isolator, what is a closed isolator, what is a RABS, which again can be open or closed. Industry is starting to use this new terminology now.

Industry has seen requests for smoke studies on isolators during setup. Smoke studies with open doors is something that the industry is really struggling with.

Rick Friedman

Annex 1 mandates that both direct and indirect contact parts must be sterile. That means that there is installation of parts in isolators that have gone through validated sterilization cycles. This includes sterilization of stopper hoppers or rails to convey the stopper or other equipment that will be installed in the isolator prior to the decontaminating cycle. That means that you do have to use asepsis so as not to contaminate the sterilized processing equipment.

I think what's most important is that personnel who set up isolators are fully gowned in sterile gowns. They should not be shedding particles into the isolator. They should handle setup with care and basically follow the aseptic setup they would use on a conventional process line to prevent introduction of contamination into the isolator's surfaces or the presterilized parts of contact equipment. Maybe my colleagues who perform inspections want to provide further insight into whether smoke studies are an expectation. I'm not sure that is something that always would need to be done. I think most important is asepsis.

Matt Davis

It all comes back to the function of the isolator and how it's being used. In Annex 1, section 4.19 is the most relevant clause whereby if it's an open isolator, you must demonstrate that the critical parts of the machinery are subject to first air only and that a directional airflow is kept. If it is a closed isolator, then there's discretion about airflow. It may not be unidirectional, but you still need to understand how the isolator operates, and what the airflow is within the isolator.

The people who are interacting with these pieces of machinery when they're setting them up, if it's an aseptic setup, need to understand the airflows and need to understand the function of the system so that they can use asepsis; they can handle things and transfer things in an appropriate manner without breaking first air principles or without operating in a manner that is close to the bottom of the isolator where you might see bounce-back or some other kind of contamination of the isolator.

So how do you do that? How do you demonstrate the airflows? You could do it through computational modeling, I'm sure. But smoke studies would be another way of achieving it. I don't know if we would necessarily mandate smoke studies as the only way of achieving this. But I think if you're trying to demonstrate that a) the isolator functions in the way it's meant to do as per the design and b) when you interact in operation, you are maintaining the cleanliness of the isolator, you are going to have to come up with some methodology to demonstrate to yourselves primarily, but also to an inspector, that it's working correctly.

I would ask: How do you know it functions properly, and how do you know your in-operation activities don't affect the isolator in a negative way? It would be up to the manufacturer to demonstrate how you ascertain that and smoke studies may be a very reasonable way to do that.

Based on lyophilizer loading, section 8.123, will manual lyophilizer loading be acceptable after August 2024 and under which circumstances?

Rick Friedman

FDA has often cited 483 deviations relating to ill-advised transfers into lyophilizers. We have also cited lyophilizer sterilization frequencies that are insufficient. Generally, the sterilization frequency should be every cycle. For charging and discharging, at least the charging of units into the lyophilizer must be done under unidirectional air conditions and asepsis must be observed throughout all loading. If it's not done correctly, there's a lot of risk in manual loading.

There are a lot of aerodynamic issues with the full door openings of many of the old open lyophilizers, where air bounces off the floor and people are standing in front of the big open door. And, as the engineers in the audience know, that creates a lot of issues of space and management of air and the ability of air to ingress into the lyophilizer and contaminate units on shelves.

Pizza oven doors on lyophilizers are common these days, but also other automated loading approaches are common. You could do a risk assessment based upon Annex 1 principles, which align with FDA standards, and perhaps justify less frequent sterilization frequency for a lyophilizer than each cycle under certain conditions. Specifically, it would need to be automated loading and better be well-justified, and nonetheless use a cautious approach so that sterilizations still occur every couple or few cycles.

Daniel Müller

In my area of Germany, the last manual loading/unloading was discontinued almost eight years ago. What is the major contamination source in a cleanroom? It's ourselves; it's people. We need to keep personnel away from the open product if we want to get better in aseptic processing, for example, by using barrier systems. Is it forbidden to have manual loading at this stage? It's not clearly forbidden, but the industry needs to move to automation.

In many isolated and non-isolated aseptic fill lines, there are several components that break first air: tubing, needles, stopper mechanisms, and so on. What is the guidance for what is allowed to break first?

Matt Davis

Ideally nothing should break first air, but if something does, that equipment should be sterile. That way you largely mitigate the risk associated with it, assuming that it doesn't affect the airflow downstream of it to a point where it's going to negatively affect product. If the item itself that is breaking first air is sterile, then you're mitigating a lot of the risk. With some of the designs of

new isolators and automated filling machines, the designs are now moving toward no breakage of first air at all, which is great.

But there are existing systems, as the question mentioned, where you do have other components above open product. Now tubing should have been sterilized with the filling needles themselves, but there may be other parts of the filling equipment, like the blocks in which the needle sits. You're going to have to do some assessment as a manufacturer as to whether these items need to be sterilized or not and decide as to whether the sterility of those items that break first air is directly affecting the sterility of your product. If the answer is yes, then your risk assessment should drive you to maybe undertake further sterilization of the components. And if you have equipment that you cannot sterilize, you're really going to have to look at risk management tools and improvements to the system to make sure that contamination control is achieved.

Rick Friedman

I want to note that the first air is defined in Annex 1, so I refer the audience to the Annex 1 definition.

Why is WHO Annex 2 worded differently than Annex 1, replacing the words "working position" with "working level" on the airspeed requirements of 0.45 meters per second?

Vimal Sachdeva

WHO has its own mechanism of writing guidelines and must consider several factors. We have 194 member states that we are responsible for. Whenever any of the guidelines are drafted, finalized, and adopted, we do form a consensus. But that's the only thing I can say here.

Jörg Zimmermann

This gives me the opportunity to remind everybody to refer to the article "Air Speed Qualification: At Working Position or Working Level?" in the September/October 2023 issue of *Pharmaceutical Engineering®*, where we published the data on what the difference is and what kind of effect it has.

CONCLUSION

Annex 1 implementation is well underway, with some deficiencies still noted by the regulators during inspections. The answers provided by the panelists will help companies move toward better, more accurate compliance, resulting in safe processes for sterile products.

Acknowledgments

ISPE thanks the panelists for their open discussion of the audience questions. We look forward to the next regulatory panel at the 2025 ISPE Aseptic Conference in Washington D.C., 17–18 March 2025. For more information, please visit ispe.org/conferences

About the author

Jörg Zimmermann is Vice President of External Affairs for Vetter Pharma Fertigung GmbH & Co. KG, Ravensburg, Germany. He manages relationships with regulatory agencies, professional organizations, and other pharmaceutical industry partners. Previously, he was responsible for Vetter Development Service, which includes manufacturing science and process development, technology and process transfers, project and service analytics, and drug delivery systems. He was Production Manager before becoming Director of Production of Vetter's production site at Lake Constance. Within Vetter, Jörg has held various positions in process implementation, new product introduction, and lyophilization process development. He has volunteered as conference chair, track leader, and speaker at conferences by ISPE, PDA, and Concept Heidelberg. In 2016, Jörg was elected to the ISPE International Board of Directors and previously served as Chair. Jörg studied pharmacy in Freiburg, Germany, and Cardiff, Wales, and is a registered pharmacist. He joined ISPE in 2006.

Meet the ISPE STAFF

Wendy McGhee
Hometown:
Fort Worth, Texas

In each issue of *Pharmaceutical Engineering®*, we introduce a member of the ISPE staff who provides ISPE members with key information and services. Meet Wendy McGhee, Health Authority Outreach Manager in the Regulatory Operations group.

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

Overall, my role is heavy in professional writing, project management, and relationship building. It requires strong communication, organizational, and interpersonal skills to convey ideas, manage tasks, and cultivate productive relationships. I manage various ISPE initiatives, including ISPE's regulatory commenting, which is a member benefit.

The Publications team and I work closely together to ensure draft ISPE guides are reviewed for regulatory compliance. I collaborate with the Training team to develop training for regulatory agencies. Finally, I am responsible for coordinating requests for regulatory speakers to speak at ISPE conferences and events held by Chapters, Affiliates, webinars, and Communities of Practice.

What do you love about your job?

What I love the most is my job working at conferences. I love the energy, the teamwork, wearing many hats, the members, the regulators—everything about it.

I thrive on the challenges that come with my job. I enjoy the opportunity to collaborate with my colleagues and contribute to our collective goals. I am a lifelong learner, and I am grateful for the opportunity to continually develop my skills and knowledge.

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

My goal is to read as much as possible on weeknights to stay current with quality and regulatory activities. In addition, it is helpful to me when I am engaging with members and regulators. It is not uncommon for me to be on the go every weekend with friends or family members. I enjoy attending local events in the Dallas-Fort Worth area, such as festivals and shows, and my husband and I also have a camper so we can take our dogs on excursions. Additionally, I am active in my local community.

VOLUNTEER PROFILE

REGULATORY STEERING COMMITTEE CHAIR

SARAH POPE MIKSINSKI, PHD

After completing her doctoral degree at Oklahoma State University, Sarah Pope Miksinski received a fellowship at the National Institutes of Health. While working there, she realized that research was not the best career path for her.

"It was kind of an identity crisis because I had gone to school for all these years for a PhD, which by definition is a research degree and then to realize I didn't really like research and could not work by myself in a lab all day. I decided I needed to think in terms of a career where I would be talking to people and challenging myself."

"I sent out more than 80 resumes and one of my interviews was with the FDA. During the interview, I asked them what kind of work I would be doing. I was told it would be a lot of writing and analysis and that sounded like something I would be more interested in, and I was hired to work there as a primary reviewer."

"Now, when I mentor someone, I tell them, 'If you want to know what a job is like, find someone who has it and talk to them.' There are lots of options out there for scientists and engineers, but as an undergraduate and graduate student you don't always know what they are."

After working at the FDA as a primary, secondary, and tertiary reviewer, Sarah was promoted to head of two offices in the FDA's Office of Pharmaceutical Quality—serving as the Director of the Office of New Drug Products and the interim director of the Office of Surveillance. "There's not as much difference between the FDA and industry as people might think. Both are trying to ensure the supply of medication to patients."

Now at Gilead, Sarah is the Executive Director/Head of Chemistry, Manufacturing and Controls (CMC) Policy, Advisory, and Intelligence, and the interim Head of Synthetic Molecules, CMC Regulatory Affairs. "I work with people from all across the industry, regulators, nonprofit organizations, lobbying firms, international companies. I've always liked working with people and solving challenging problems. The pharmaceutical industry is complicated, and regulatory and pharmaceutical manufacturing are not straightforward fields. I like being able to use my technical and personal skills to solve some of the very complicated challenges in the field."

Even outside of work, Sarah uses her knowledge to help solve issues in the pharmaceutical industry. In 2021, she was appointed as the PhRMA Topic Lead for International Council for Harmonisation (ICH) M4Q(R2) and also serves as the Rapporteur of the ICH Quality Discussion Group (QDG).

"It's an international effort with a great group of people discussing a really difficult topic. It has been more than 20 years since the guideline was updated and a lot has changed in that time. The update requires a lot of international collaboration, creativity, commitment, and understanding. You have to take into consideration all the different viewpoints from industry and regulators and negotiate to discover and create common ground."

Additionally, Sarah is very active with ISPE. She serves as Chair of the Regulatory Steering Committee and is a Director on the ISPE International Board of Directors. "I am incredibly grateful for the opportunity ISPE has given me to work with other leaders across industry. I come away from every ISPE project I work on thinking that it is such a privilege to work with the other volunteers, to have these opportunities to lead and gain experience, and to use my own experience to help a collaborative organization that is very directly connected to patients."

— Marcy Sanford, ISPE Publications Coordinator

VOLUNTEER
PROFILE

PHARMACEUTICAL COMPOUNDING COMMUNITY OF PRACTICE CHAIR

ANIL MATHAI

Anil Mathai first heard about ISPE 30 years ago. "I attended Drexel University, where you are required to complete three cooperative education jobs. One of mine was for Rhône-Poulenc Rorer, Inc. in Collegeville, Pennsylvania. While I was there, I learned about validation and decided that I wanted to be in pharmaceuticals as a chemical engineer."

"After I graduated and got my first job, someone suggested I join ISPE to stay up to date on the latest industry standards and I have been a member since then. ISPE and all the Communities of Practice (CoPs) have been helpful to me throughout my career. If you have a question, there is a CoP with experts who are willing to help you."

Anil recently became Chair of the new Pharmaceutical Compounding CoP. "We want to bring issues of concern to the community and start providing consistent guidance. Every state has its own variance and regulations combined with the FDA's. We want people to join us for discussions on the current state of the industry. Even if you're not in pharmaceutical compounding but are in pharmaceuticals or you have some kind of related experience, we'd like you to join the group, as it will help us have robust discussions."

Anil has more than 27 years of experience in the field and has worked with KMI/Parexel, Centocor (a subsidiary of Johnson & Johnson), Schering-Plough, and Merck. He has validation experience with medical devices and pharmaceuticals in the US and Europe, as well as other countries. As Vice President of Quality & Regulatory Compliance at STAQ Pharma, he specializes in developing quality systems, adhering to regulatory expectations and ensuring safe, timely product delivery.

An FDA-registered 503B Outsourcing Facility, STAQ Pharma provides cGMP prepared and ready-to-administer medications to healthcare providers and patients across the US. STAQ has a particular focus on addressing drug shortages and providing critical medications that are short and in need.

At STAQ Pharma, Anil oversees quality assurance and regulatory affairs at the company's Denver, Colorado, and Columbus, Ohio, sites. "Every day we send out syringes, pumps, and IV bags of ready-to-administer medications across the country to hospitals. We focus on 'right first time' to make sure that we are able to get the product through our processes and to providers and their patients. At our Columbus facility, we're planning to take on more contract manufacturing opportunities as they present themselves."

"We would like to help clinical trials, small start-up companies, research efforts, and others that need clinical trial help in making their medications under cGMP. We want to provide support in that area so that if their information, product, and design are correct, it'll give them leverage to move forward toward larger-scale manufacturing and producing medicines to help patients."

Anil says one of the most interesting aspects of his current position is predicting what the company will look like in the future and developing strategies to get it there, including leading the company and his team through process improvements.

"We're trying to move away from more and more paper, because as we grow, the paper process for batch records becomes more of a speed bump. We've installed an electronic quality management system that will help us move away from paper and allow us to close out issues quicker. We are always looking at our processes and asking ourselves, 'What does it look like today and where do we want to go?' Our team is always trying to get ahead of any issues and resolve them before they become a problem. That's one of the ways that we add value to our customers."

— Marcy Sanford, ISPE Publications Coordinator

ISPE Global Pharmaceutical Innovation Survey Findings: A Review

By Christopher Potter, PhD

In 2023, ISPE launched an expansive and significant initiative, Enabling Global Pharmaceutical Innovation: Delivering for Patients, to address the barriers to technological innovation in the pharmaceutical industry. The first activity of the initiative was to conduct a three-part survey of ISPE members to understand the circumstances and confirm the sources that create barriers to innovation.

The rationale for this initiative is given in an iSpeak blog, "ISPE Launches Enabling Global Pharma Innovation: Delivering for Patients" [1], which was published as part of the initiative's launch. In late 2022, ISPE assembled a team of industry leaders with expertise in advancing innovative technology and products and with experience in addressing regulatory divergence.

This ISPE team developed a comprehensive survey to understand the specific origins, extent, and magnitude of challenges and barriers that limit and reduce both the development and implementation of innovative technologies. A full report of the survey was published in April 2024 on the ISPE website [2].

BACKGROUND

Regulatory authorities globally have embraced technological innovation to improve product quality assurance, accelerate product development, reinforce supply chain reliability, and increase patient access to medicines. Several regulatory authorities—including the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA)—have actively promoted the adoption of innovative and advanced pharmaceutical manufacturing technology. They have done this by introducing regulatory options that enable industry to develop and implement advanced manufacturing technologies.

Although it is incumbent upon industry to modernize manufacturing processes to improve productivity and increase confidence in product quality assurance by introducing novel technology and modalities, economic and regulatory barriers discourage the development and implementation of new, innovative technology globally. Perhaps most significantly, the conspicuous lack of global regulatory harmonization reduces incentives for industry to invest in innovations, which indirectly limits access to safe, effective, and quality drug products to patients globally.

THE INITIATIVE

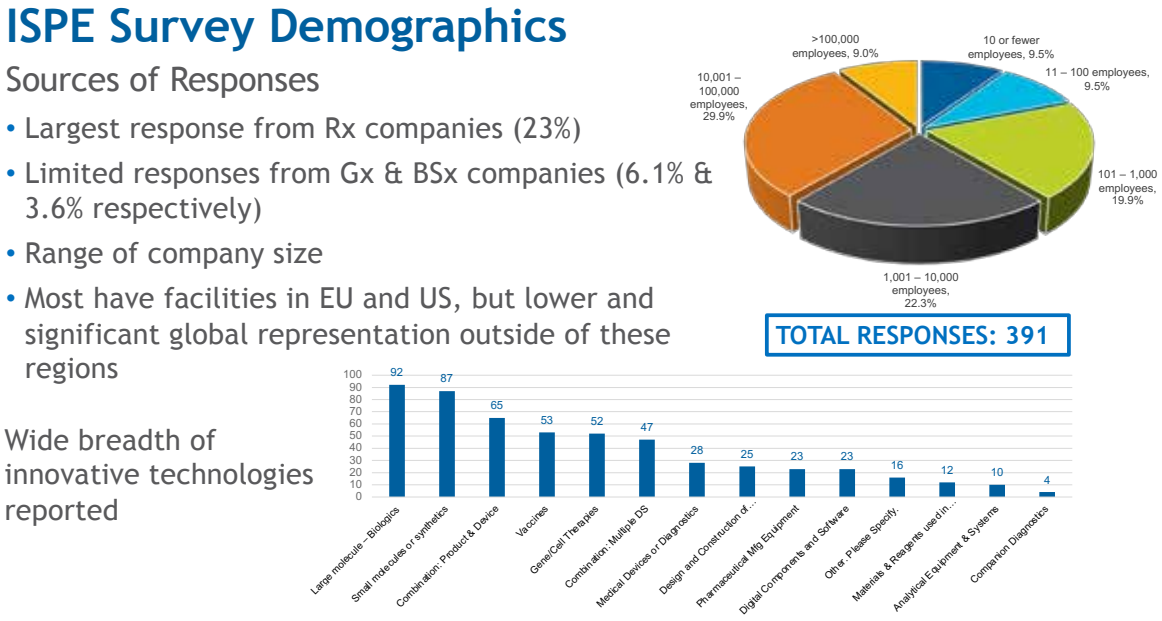
This initiative is consistent with ISPE's mission and vision [3] and is aligned with the advancement of ISPE's Pharma 4.0™ program [4]. It aims to catalyze consistent, harmonized interpretation and implementation of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines to improve global patient access to innovative medicines and technology [5].

The phrase "enabling pharmaceutical innovation" encompasses technical innovations in pharmaceutical manufacturing and analytical technology, the introduction of new medical modalities, modes of delivery and administration of medicines, and digital transformation (Pharma 4.0™). The phrase "delivering for patients" addresses improved assurance of product quality, supply consistency and reliability, improved product convenience and use, expedited patient access globally, and, where applicable, improved productivity and reduced manufacturing costs.

Seven pivotal objectives describe the scope of the initiative:

1. Contemporize manufacturing technologies, i.e., advanced modeling and simulation, digitalized technologies
2. Reinforce globally harmonized interpretation and implementation of ICH guidelines necessary to advance innovative technology and industry approaches such as Pharma 4.0™, establishing criteria for a globally accepted drug product control strategy
3. Identify sources of regulatory challenges that are barriers or create limitations in applicability across multiple therapeutic modalities
4. Increase the level of clarity and consistency in harmonized approaches and identify and promote incentives for implementation of innovative technology

Figure 1: ISPE pharmaceutical innovation survey demographic.



5. Leverage relevant regulatory harmonization initiatives and convergent regulatory approaches that are in progress regionally, and accelerate the adoption and implementation of ICH guidelines and other harmonization proposals, i.e., mutual reliance/recognition as promoted by the International Coalition of Medicines Regulatory Authorities (ICMRA), World Health Organization (WHO), and Pharmaceutical Inspection Co-operation Scheme (PIC/S)
6. Identify incentives for regulatory authorities to collaborate
7. Assess learnings from the COVID-19 pandemic, where global regulatory and supply distribution experience can serve as a roadmap, i.e., mutual reliance, parallel development, regulator engagement

SURVEY DESIGN

The survey consisted of three parts, with the option to respond to all or any of the parts. Part 1 was a list of questions requiring simple multiple-choice answers focused on demographics and summary-level innovation experience. Part 2 requested brief but specific examples of innovation development experience. Part 3 requested more detailed information and, where appropriate, anecdotal examples and case studies describing innovation challenges. The survey launched in April 2023 and closed on 12 December 2023.

SUMMARY OF SURVEY FINDINGS

Responses to the survey were relatively high (391 respondents) and reflected a representative sector of the pharmaceutical industry. This included a diverse mix of large to small pharmaceutical manufacturers, contract manufacturing and development organizations, component and equipment suppliers, and facilities and software service providers located in multiple countries and reflecting multiple product modalities (see Figure 1).

Although the majority of responses came from innovator (brand name) companies (23%), a small proportion of responses came from companies responsible for manufacturing generic products (6.1%) and biosimilar products (3.6%).

Embracing Innovative Technologies

Companies manufacturing generic products were asked, "If you are a supplier or manufacturer of generic products, do your partners/clients embrace innovative technology? Why or why not?" Generally, respondents (22) indicated that companies manufacturing generic products do not embrace new technology mainly due to economic factors and the risk of disrupting supply chains. Several companies and partners to companies manufacturing generic products indicated, however, that some companies do embrace new technology when the business case supporting cost reduction is strong.

Respondents also identified a variety of product types for which they were responsible. These included large and small molecules, combination products and vaccines, medical devices, and companion diagnostics, as well as vendors of manufacturing and analytical equipment, components, and facilities; digital software; process materials; and reagents (see Figure 1).

From this broad cohort of companies, 545 wide-ranging innovations were reported. Biologics manufacturing (11.7%),

Figure 2: Manufacturing and control operations for technical innovations.

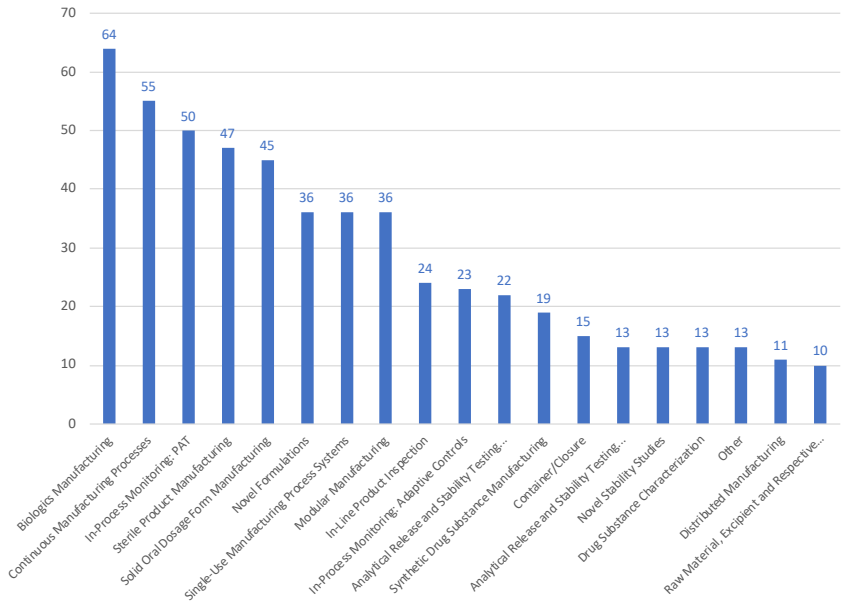
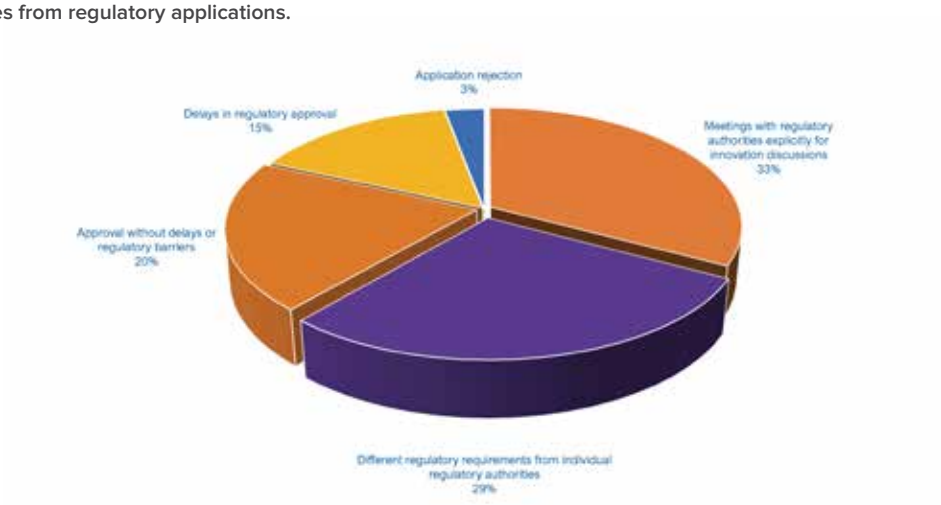


Figure 3: Outcomes from regulatory applications.



continuous manufacturing processes (10.1%), and in-process monitoring process analytical technology (9.1%) were the top innovations reported (see Figure 2).

Of these innovations, not all were submitted in regulatory applications for approval. However, a wide range of innovative technologies, most notably with respect to biologics manufacturing (13.5%) and novel product formulations (11.0%), were submitted in regulatory applications predominantly in the US (21.8%) and the European Union (EU) (18.3%), with fewer application submissions in the other geographic regions globally.

Respondents reported a range of experiences with submission of applications for innovative technologies. A number of responses indicated their applications for innovative technologies were approved (20.4%). However, different regulatory expectations from individual regulatory authorities (28.5%) and delays in application assessments/inspections (15.3%) also were reported. A relatively low number of rejections (2.9%, or 4 of 152 reported) indicate that regulatory authorities have generally accepted applications containing innovative technologies (see Figure 3).

Investment Considerations

When determining cost and benefit for capital investment, in general, respondents indicated that economic factors were the primary drivers. The potential for long-term revenues and the anticipated efficiency or productivity (ranked as the top factor by 33.6% and 14.3% of respondents, respectively) determine

whether a company proceeds with developing and implementing an innovative technology.

Table 1 outlines the top five critical factors cited in determining the cost of and benefit for investment, which also included improving assurance of quality, global regulatory acceptability, and manufacturing flexibility (ranked first by 10.1%, 15.1%, and 18.5% of respondents, respectively). Table 1 shows the top five factors, the percent of respondents that ranked each factor first, and the percent of respondents who selected that factor as a top-five critical factor.

Respondents reported a range of business factors that led to the discontinuation of innovation projects, such as economic considerations, "fear of change," levels of competence—including that of contract development manufacturing organizations (CDMOs)—and concern that short-term risks would incur delays in regulatory approvals. Certain improvements in manufacturing or analytics may be addressed directly by technical teams during development; however, decisions to invest in significant technological innovations are made at senior levels within organizations.

Regulatory Acceptability

Regulatory challenges were reported as a significant factor influencing decisions to develop innovative technology. For a large proportion (48%) of respondents, these regulatory challenges were deemed most significant or significantly greater than other factors (see Figure 4). The top five concerns with regulatory acceptability are summarized in the first column in the following table (see Table 2).

The top three concerns with regulatory acceptability were:

1. Challenges during application review: regulator adherence to conventional expectations that do not apply
2. Lack of globally harmonized regulations
3. Challenges during application review: regulator understanding of innovative technology

Responses to the questions in parts 2 and 3 confirm and amplify these concerns and provide additional specificity. For example, these concerns were confirmed in responses to the question, "Has your company/organization received divergent recommendations from different regulatory authorities regarding approval and implementation of innovative technologies and has this created a significant obstacle to implementing innovative technologies?"

A significant number of respondents (14 of 38 relevant responses) reported not receiving different recommendations from different regulatory authorities. However, a larger proportion of respondents (18 of 38) reported receiving different regulatory expectations from different regulatory authorities and provided many examples. Divergent regulatory expectations were reported in both assessment and inspection criteria. Examples were not limited to specific issues or technologies but reflected differences in regulatory expectations for innovative formulations and devices, processes, and analytical methods.

Of particular interest was the response that COVID-related medicines did not face regulatory differences . However, for

Table 1: Critical factors in determining cost/benefit for investment.

Factor	Ranked First (%)	Percent That Ranked Factor in Top Five
Long-term revenues	33.6	89.1
Manufacturing flexibility	18.5	95.0
Global regulatory authority acceptability	15.1	61.3
Efficiency/productivity/minimizing SKUs	14.3	90.7
Quality assurance	10.1	95.9

Figure 4: Regulatory challenges as a factor influencing development of innovative technology.

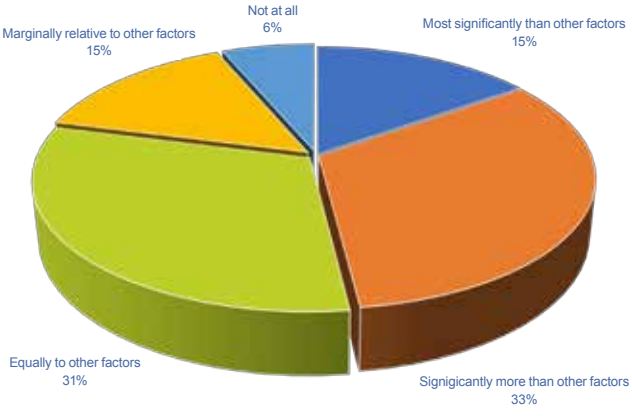


Table 2: Top five concerns with regulatory acceptability.

Concern	Ranked First (%)	Percent That Ranked Factor in Top Five
Challenges during application review: regulator adherence to conventional expectations that do not apply	29.6	90.0
Lack of globally harmonized regulations and guidance	19.7	67.7
Challenges during application review: regulator understanding of innovative technology	14.5	93.8
Challenges during inspections	8.6	41.4
Lack of implementation of globally harmonized guidelines, i.e., ICH	7.9	57.1

other projects, such as new development approaches (quality by design) and less common manufacturing processes, differences in regulatory divergence that challenged implementation were observed. Understandably, healthcare leaders and regulatory authorities desperate for certain therapies to address significant threats to local health are prepared to be more flexible than they might be for conventional therapeutic products. The responses to this question imply that where technological innovations can improve therapeutic platforms a similar level of regulatory flexibility may be warranted.

Similar findings were found in responses to the question, "Have cGMP inspections from multiple regulatory authorities resulted in increased quality/regulatory requirements, i.e., implementation of excessive or duplicative controls due to a lack of global regulatory harmonization?" A significant number of respondents (14 of 40 relevant responses) reported not receiving different recommendations from different regulatory authorities.

However, a larger proportion (20 of 40) of respondents reported receiving different regulatory expectations from different regulatory authorities and provided many examples. Although no direct correlation between divergent regulatory expectations and impact on specific innovative technology applications can be established, divergence implicitly leads to increased costs and potentially to delays in approvals.

Respondents indicated an overwhelming advantage in engaging with a regulatory authority innovation pathway—such as the FDA's Emerging Technology Program (ETP) [6] or Center for Biologics Evaluation and Research (CBER)'s Advanced Technologies Team (CATT) program [7], and the EMA's Quality Innovation Group (QIG) [8]. However, a significant proportion of respondents also reported a relatively low level of engagement with these two groups: 22% for the FDA Emerging Technology Team (ETT) and 14.5% for the QIG.

Generally, respondents reported that meetings with a single regulatory authority were positive and appeared to reduce concerns. Engaging with the FDA's ETT was reported as being very positive, and the EMA's QIG was also mentioned as being helpful. However, specific respondent feedback indicated experiences where there were differences in outcomes from different regulatory authorities and disconnects between regulators reviewing the merits of innovative technologies with regulatory personnel involved in inspections.

Meeting with multiple regulatory authorities was reported in 13 of 41 relevant responses as not a problem. A larger proportion (21 of 41), however, did report meeting with multiple regulatory authorities as a challenge. This indicates that the possibility of different regulatory expectations or outcomes was a deterrent to the introduction of new technology. In addition, several respondents highlighted the burden associated with preparing for and conducting separate and multiple meetings. Relevant comments could be summarized as "there is lack of harmonization and meeting multiple agencies is burdensome."

In summary, divergent global regulatory expectations, based on previous experience, are a primary concern and create a concomitant challenge for a majority of respondents:

- Agreements at meetings with senior-level regulators do not always lead to the same interpretation and acceptance by reviewers and inspectors that perform the assessments and inspect facilities.
- Engagements with multiple individual regulatory authorities frequently lead to different regulatory expectations for innovative technologies, i.e., separate specification acceptance criteria, different operational process parameters, and level of registered details.
- Engagements with multiple regulators is a logistical and resource-intensive burden and generally extends over a long time.

In addition, it was also mentioned that there is no regulatory pathway yet available in any market to facilitate the review and approval of chemistry manufacturing controls (CMC) platform technologies. These include, for example, analytical methods that are developed as applicable to multiple products.

Summary of Regulatory Challenges

According to respondents, these differences in regulatory authority expectations ultimately result in:

- Increases in regulatory commitments and resource costs
- Extended timescales due to delays to accommodate alternative or additional product development and characterization studies, which adversely impact estimated return on investment (ROI) benefits
- Increased compliance complexity and inventory management due to multiple control strategies for a single process or the most conservative control strategy governing a manufacturing process

When the level of uncertainty associated with divergent regulatory expectations is relatively high, the potential value of an innovation relative to its ROI becomes difficult to estimate and justify. According to many respondents, innovative approaches are subsequently postponed until the regulatory environment is more favorable or are simply terminated.

Indeed, the factors associated with perceived and real regulatory barriers by which decisions to proceed with an innovative technology are made, have led to a "it's all too difficult, let's not change" or "we don't want to be the first to prosecute an innovative approach" mindset within the industry.

SUMMARY OF REGULATORY INITIATIVES

Multiple initiatives focused on eliminating or reducing barriers to innovation are currently being addressed by several organizations. The following is a nonexclusive list of global initiatives; more explanation is given in the full survey report [2].

United States

The US FDA established the Framework for Regulatory Advanced Manufacturing Evaluation (FRAME) [9] and the ETP [6] under

the Center for Drug Evaluation and Research (CDER) and the CATT program [7] under the CBER. It also established Project Orbis, a framework for concurrent submission and review of oncology products [10]. The Duke Margolis Institute for Health Policy established the Advanced Manufacturing and Innovation Program [11].

European Union and the UK

The EU EMA created the Innovation Task Force and QIG [8]. The UK MHRA Innovation Office "provides free and confidential expert regulatory information, advice and guidance to organisations of all backgrounds and sizes based nationally or internationally" [12].

Asia Pacific

Japan's Pharmaceuticals and Medical Devices Agency established the Innovative Manufacturing Technology working group (IMT-WG) [13]. Singapore Health Services Authority's Innovation Office provides a "pilot to provide a conducive regulatory environment that will also support the development of the biomedical sector" [14].

International

A number of guidelines and initiatives inform more globally: ICH guidelines [5]; the International Coalition of Medicines Regulatory Authorities' Pharmaceutical Quality Knowledge Management System (PQKMS) pilot programs [15]; the WHO's Collaborative Registration Procedure (CRA) using Stringent Regulatory Authorities' (SRA) medicines evaluation [16]; PIC/S's harmonized Good Manufacturing Practice (GMP) standards [17]; and the Access Consortium [18].

WHAT DID THE SURVEY CONFIRM?

The survey confirmed that, in addition to developing innovative technology, the pharmaceutical industry is committed to continual improvement to ensure a reliable and sustainable supply chain, and to increase quality assurance and patient access to medicines globally. However, it is also clear from the survey feedback and responses that the current global regulatory environment poses a significant challenge to implementing continual improvement and innovative technologies.

Although several respondents indicated that regulatory pathways, like the ETP and CATT programs and the QIG, offer effective approaches that enable development and implementation of innovative technologies, globally divergent regulatory expectations remain a conspicuous concern and challenge. In fact, collective industry feedback clearly indicates that collaboration with regulatory authorities globally—either to revise existing regulatory options or introduce alternative global regulatory pathways—will facilitate the introduction, development, and implementation of innovative technology.

Survey Suggestions

The following suggestions summarize the survey recommendations.

- Establish an efficient system that connects regulatory authorities and fosters opportunities for companies and vendors to propose and establish innovations for global consideration, acceptance, and implementation.
- Align application review/assessment processes that cultivate a convergent approach to evaluate the merits of innovative technologies and produce a combined list of queries from global regulatory authorities.
- Adopt a single or limited GMP inspection schedule for assessing the implementation of innovative technologies per manufacturing facility (when required) in accordance with global inspection standards, i.e., PIC/s, and a focus on the requisite Pharmaceutical Quality Standards that support the innovative qualities of the product control strategy that is acceptable globally.
- Initiate global regulatory authority approvals that rely on mutual reliance/recognition. Several respondents emphasized that this conceptual approach, where appropriately established to reduce the chronic regulatory lag for global approval of post-approval changes associated with continual improvement, could serve as a key enabler to innovative technologies.
- Establish a predictable global regulatory authority review/assessment/inspection and approval schedule that ensures global supply chain reliability and patient access.
- Introduce a globally harmonized regulatory process to support review, inspection, and approval of platform technologies (e.g., analytical procedures) which may apply to multiple products.

A concerted globally aligned/integrated regulatory approach would undoubtedly increase the confidence within the industry to overcome regulatory risks and effectively enable the development of innovative technology. In addition, it would improve the industry's commitment to continual improvement, cultivating the curation of a life cycle mindset. The unequivocal success with the introduction of the FDA's ETP and CATT programs and the anticipated success of the EMA's newer QIG program should serve as the basis for these recommended global regulatory approaches. It is worth noting the industry experience during the COVID-19 pandemic. The expedient regulatory assessment and distribution of vaccines could not have occurred without regulatory authority collaboration and mutual reliance.

NEXT STEPS FOR THE ENABLING GLOBAL PHARMACEUTICAL INNOVATION INITIATIVE

Data and information from the survey—supported by in-depth discussion with several respondents who have direct experience developing, adopting, and implementing innovative technologies—will serve as the basis for case studies. This also provides opportunities for potential solutions, which could serve as substrate for engagement with regulatory assessors and inspectors globally.

ISPE's Enabling Global Pharmaceutical Innovation Initiative Team will present proposals to multiple regulatory agencies at appropriate forums dedicated to advancing globally accepted regulatory approaches. These efforts are intended to promote

practical incentives for both industry and regulatory authorities to address specific challenges to innovation and continual improvement initiatives.

The ISPE team will work with industry and equipment suppliers to understand the steps to introduce innovative technologies and develop a "points to consider document" of how to present these internally and externally to regulatory authorities.

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FDA'S 2011 PROCESS VALIDATION GUIDANCE: 10 YEARS ON

By the ISPE Process Validation Team

In 2011, the US Food and Drug Administration (FDA) introduced the revised "Guidance for Industry: Process Validation: General Principles and Practices" [1]. The document incorporated principles from existing ICH guidance in place since 2005 (ICH Q8 and Q9) and 2008 (ICH Q10) [2–4]. ISPE formed their Product Quality Lifecycle Implementation (PQLI)® initiative to provide guidance [5] on the practical implementation of the concepts described in these ICH guidelines.

When the process validation (PV) guidance was published, the pharmaceutical industry was adopting quality by design (QbD) approaches to pharmaceutical development. This brought awareness of critical quality attributes and allowed critical process parameters to find their way into industry discussion and regulatory submissions. However, the FDA PV guidance created significant change to PV approaches with the introduction of the now-familiar three-stage life cycle approach and other science- and risk-based terminology and requirements. It was also known that the European Union (EU) regulatory authorities were planning to publish similar guidance for the EU.

THE ISPE PROCESS VALIDATION TEAM

Thus, the ISPE PQLI Team recognized the need for specific support around PV and a working group which became ISPE's Process Validation Team. This team has remained active since then, publishing a number of discussion papers [6]. In 2019, they also published a comprehensive Good Practice Guide, titled *ISPE Good Practice Guide: Practical Implementation of the Lifecycle Approach to Process Validation* [7].

In addition to publication of discussion papers and the Good Practice Guide, the group has facilitated industry and regulatory dialogue and discussion through many forums, including:

- Presenting best practices from ISPE member companies
- Hosting work groups and discussions on challenging subtopics
- Publishing articles in ISPE's *Pharmaceutical Engineering*® magazine and other industry journals
- Delivering relevant conference and workshop sessions

The team regularly facilitates full sessions at the ISPE Annual Meeting & Expo on PV-related topics and has organized five well-attended stand-alone PV workshops in 2012, 2013, 2015, 2016, 2017, and 2019. Additionally, the team developed the content for ISPE's popular three-day process validation training course and has provided the core group of instructors who present and maintain this offering.

LIFE CYCLE PV IMPLEMENTATION

Now that over a decade has passed since the publication of the 2011 US FDA Process Validation guidance, the team posed the question: What does the implementation of life cycle PV look like? This article is a collection of individual and collective responses from team members who are practitioners and industry participants in this field, representing a cross-section of pharmaceutical organizations, locations, and roles from all parts of the world.

Implementation and maturity of the life cycle approach to PV varies widely across the pharmaceutical sectors (including biotechnology) and markets around the world. For some early adopters, the principles and practices are now part of business as usual. However, even in these organizations, there can still be challenges to implementation or understanding. Some organizations recognize the business benefits of the life cycle approach, whereas others have implemented programs with a minimalist compliance perspective. The following summarizes our team's key observations regarding the evolution and current state of this approach.

THE KEY TO LIFE CYCLE PV: PLANNING WELL

It may first appear that the three stages of life cycle PV are wrapping Stages 1 and 3 around an existing proven validation program. To some extent that is true. However, it's not that simple, and the consequences of that simplification vary. The most benefit is realized when organizations break the traditional walls between development, technology transfer, validation, and operations and approach validation cross-functionally across the product life cycle.

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Stage 1

For new product introductions, the concept of a new "Stage 1" output demands increased effort and reliance on good science- and risk-based approaches to product development and technology transfer. While the 2011 FDA PV guidance was being finalized, the incorporation of ICH concepts, such as control strategy, was becoming an expectation for the registration of new products. To some extent this has been an evolution of development and regulatory practices moving in tandem so that regulatory submissions contain information compatible with Stage 1 concepts.

Although the concept of a "design space" submission was found to be challenging and did not always afford the anticipated regulatory flexibility, the efficient development and understanding of multivariate relationships of attributes and parameters using a design of experiments (DOE) approach has become more commonplace.

The situation becomes considerably more clouded in the case of existing products where development information is not necessarily aligned with ICH principles. In this case, organizations may need to evaluate development knowledge and/or retrospectively develop a control strategy using risk-based principles. Members of the PV team continue to see challenges with this approach where lack of science, process understanding, or data complicates implementation. Executing effective and complete Stage 1 programs can be a challenge for late-product acquisitions and breakthrough therapies.

Stage 2

The concept and related activities of intra- and inter-batch variability (within and between batches) introduced in the FDA guidance was initially challenging for most manufacturers. Although the sampling and analysis necessary to provide adequate evidence of control of both variability components has become well-established for some manufacturers, it remains unclear for other organizations.

The introduction of the life cycle approach to PV eliminated the automatic magic number of three batches for PV Stage 2. It even opened the door for potentially fewer than three PV batches for highly automated processes, or process changes with very limited risk. However, most manufacturing organizations deliver products globally and many markets still expect a three-batch PV. Organizations that execute a risk analysis prior to PV, to determine the number of batches, will often perform additional PV Stage 1 development work, in lieu of doing more than three PV batches.

The level of input variability already studied or level of experience in the commercial manufacturing setting are not always key factors in the evaluation. Due to supply availability or lack of planning, it is not always possible to include worst case variability as part of PV. Although between-batch variability evaluation is required per the life cycle approach to PV, most organizations delay statistical analysis of this component until Stage 3 (continued process verification [CPV]).

Stage 3

Creating a CPV/ongoing process verification (OPV) program (like those required for Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-Operation Scheme [PIC/S] and the EU) can seem reasonably straightforward. The concepts and tools are readily understood. However, the program can become problematic without careful planning and well-designed procedures. It is not as simple as trending all results of heightened and routine testing. Such an approach could result in an unmanageable and wasteful increase in data and effort for its management. Thus, most adopters have come to recognize that you cannot effectively implement Stage 3 without Stage 1.

Stage 1 understanding gives an organization the foundation required to manage resources and focus efforts where it matters most, and the framework to manage responses to the variation we see in processes when monitoring these more frequently. Understanding interactions between material characteristics, process parameters, and extended control strategy variables—such as different operators, equipment trains, and shifts—is vital to establishing a meaningful testing and monitoring plan.

With no real Stage 1 inputs, the resources required to adopt and manage Stage 3 can quickly become overwhelming. This impacts the validation or technical operations departments and the quality department, which manages the additional process information and its significance (or insignificance) to product quality. They must assure batches are not released until all heightened testing results are confirmed within limits.

Our first observation: If an organization has a life cycle PV program in place (and hopefully most do), it is understood that this is a journey that requires considerable effort and will evolve as you gain experience. For those just starting the journey, a comprehensive plan is required. This will take considerable time to implement and there are many potential pitfalls, beyond what may appear to be resource needs.

EXPECTATIONS FOR LIFE CYCLE PV COMPLIANCE VARY GLOBALLY

Life cycle PV is founded on the principles of process understanding and control, which has obvious business and patient benefit. However, there is also a compliance component, which in our experience, varies substantially across the global pharmaceutical sector.

Based on recent (and not so recent) 483 observations in the US and other markets, it is clear that the FDA has adopted principles and concepts of life cycle PV. However, it would appear from our experience that other regulatory authorities may be slower to observe deficiencies to validation programs in this area. It is our impression that there is a gap in the level of implementation of these principles based on geography and market. This gap is unlikely to persist, and ISPE has recently seen significant international demand for content related to original concepts developed by the PV team when it was presented in webinar format.

There appears to be a delay with adoption of these principles in audits in some markets and jurisdictions. We expect part of this delay is to permit some inspectorates to develop the process and statistical skill sets necessary to inspect in this area. Nonetheless, industry should not be waiting for inspection observations to change to implement life cycle PV.

We feel this lag is not due to hesitancy; it is recognition of the challenge inherent in application of science- and risk-based principles to a pharmaceutical process. Essentially, it takes some time to develop the skill set. For instance, proper use of statistical methods requires knowledge of both the process and the appropriate statistical tool. However, few process experts are statisticians and even fewer statisticians are process experts. Building the necessary capability within an organization to effectively leverage statistical methods requires an investment of time and resources.

Our second observation: The best adopters have planned to make sensible tools and decisions available widely. They have structured a learning environment where knowledge and understanding of the process grows within the business. These organizations generally build capability at the processing level and leverage subject matter experts as needed for specific issues and situations.

ADOPTION OF CPV/OPV IS BECOMING EMBEDDED AND WELL UNDERSTOOD

Once the initial challenges of managing resources and processes for implementation of a CPV/OPV program are overcome, the process is generally easy to understand for staff and management. There are clear business benefits to having increased visibility over process performance. However, some refinement and learnings are required.

Early in the program, organizations must reconcile the balance between the cost of data collection (sample size and effort) and process understanding. Early estimates of process variation can paint a conservative picture of process control. Gathering insufficient information to truly understand underlying sources of variability in processing can make control look less effective. True process control understanding requires a good data set, which takes time to collect and process. Once initial data collection efforts commence, focus is required to ensure that efforts are prioritized into areas that improve product quality and reduce risk.

CPV/OPV programs must maintain the flexibility to allow process owners the ability to manage and react to learning while operating within the pharmaceutical quality system (PQS) and GMP rules. Frequent data collection and evaluation (both formal and informal) are key to an effective program. Operations that are out of trend are not necessarily out of specification, and terms such as "not under control" can have different meanings across the business and to management. Successful CPV/OPV implementation requires a common understanding of the intent and language of process control across multiple functions.

Our third observation: The CPV/OPV program is the stage where adoption of life cycle PV is most advanced in many organizations. Once the initial framework is established, the program provides business, operational, and patient benefits that are clear to those involved and serves a mutual purpose to improve process understanding and management. CPV/OPV is not simply an extension of the annual product quality review (APQR) program; it is more nuanced than this.

LIFE CYCLE PV FORMS THE BASIS FOR PRODUCT ROBUSTNESS PROGRAMS

Although there are compliance requirements for implementing CPV, organizations can realize significant benefits. But these can only be achieved if an organization truly understands how to use CPV to leverage process knowledge and understanding.

The deliverables of CPV should be seen as:

- Confirming the ongoing robustness of the manufacturing process
- Creating a proactive approach that provides early identification of a performance change and potential intervention, thereby avoiding process quality issues (e.g., out-of-trend [OOT] and out-of-specification [OOS] results)
- Using routine CPV trending and process understanding to support process changes
- Supporting the identification of improvement projects

The CPV plan should define what parameters/attributes should be trended; the frequency of trending; and whether additional samples are required to support assessment of process robustness/capability. These details will depend on the robustness of the manufacturing process, the process capability of the parameters/attributes, the level of process knowledge that exists (e.g., development batches, data from other manufacturing sites), and the level of input variability already experienced by the process, and relationship to allowable limits.

Some organizations may judge these activities as requiring too many resources and choose to implement the plan to only meet the compliance requirements. It is only by fully implementing CPV that the wider benefits can be realized. Many organizations have recognized the benefits of enhanced process understanding and are using the data and information to build additional robustness into manufacturing and business processes. Information from life

The CPV/OPV program is the stage where adoption of life cycle PV is most advanced in many organizations.

cycle PV can be used to enhance "platform knowledge," enabling faster and smoother tech transfers and more rapid new product introductions.

Understanding external sources of variability in processes—such as factors within supplier networks—can enable significant improvements to products and processes. It can also reduce the risk and effort required for onboarding new suppliers and developing efficiencies in materials management, in turn helping assure the reliability of supply.

Understanding the capability and variability of a process can prioritize efforts elsewhere in the manufacturing organization to maximize benefit and minimize risk; for example, reduction of measurement error, optimal quality control testing, in-process monitoring, and automation.

As process understanding grows, the effort required to maintain and improve a process decreases. For well-understood processes, smaller and more focused efforts often bring measurable or significant improvements, and the process becomes self-perpetuating as the risk associated with improving diminishes.

Our fourth observation: Organizations with relatively mature CPV/OPV programs soon recognize benefits and begin leveraging PV efforts to improve manufacturing robustness.

DEVELOPING OF SCIENCE- AND RISK-BASED UNDERSTANDING IS NOT EASY

Although realizing gains through measurement and improvement is somewhat intuitive to manufacturing organizations, the development of science- and risk-based understanding and application to develop more robust processes or improve them is less tangible and more difficult to implement.

Most manufacturing organizations hold inherent process knowledge and when presented with new data or information can reconcile that in the context of that knowledge. However, more fundamental or new process understanding can be more difficult to master when organizations do not expect or understand this.

For example, multivariate interactions can occur in quite simple unit operations and may be difficult to measure or explain, even to experienced operators. When a process is tolerant to these interactions, this may not be material to process control. However, if these interactions are significant to the process and resulting product, they need to be understood.

Understanding and communicating or transferring process knowledge still presents challenges in some organizations, even those with a high level of competency in other areas of PV. It can be a struggle to capture, maintain, and communicate this knowledge effectively, which can impede realizing all the benefits of a life cycle PV program or recognizing sources of variability in processing. We have observed—from ISPE training and workshops, as well as experience in our own companies—that the utility of risk management and control strategy for knowledge management is underutilized.

The risk assessment tools traditionally used in the pharmaceutical industry may not be optimal to communicate science- and risk-based knowledge. Successful development and validation programs are more effective at managing this knowledge and can effectively transfer process understanding to operations in a format that is readily understood and can be maintained and improved. Effective quality risk management links knowledge and understanding from all phases of the product life cycle. When this does not occur, suboptimal risk assessments or failure to recognize and control risks can result.

Facilitating the linkage between development and manufacturing as well as feedback from the process in operation requires careful planning and can be difficult to achieve. Common errors include:

- Poorly founded or developed hazard analysis that does not reflect the true situation
- Difficulty in recovering platform-relevant data when it has been collated in product-specific databases
- Subjective scoring or ranking, which distorts residual risk levels or the relative importance of risks
- Difficulty in capturing actual capability in risk estimates, due to lack of visibility and feedback

Our fifth observation: Organizations with highly effective PV programs have structured tools for capture and communication of science- and risk-based information. These tools are interactive, allowing for learning and improvements.

NOT YET SEEING FULL BENEFITS THROUGH REGULATORY ACTIVITY AND CHANGES

Industry and regulatory authorities have long desired a state where regulatory flexibility could occur with product submissions based on understanding of science and risk. The adoption of ICH Q12 internationally has created a framework where this is possible. A few organizations are using this approach for new product registrations, and there is general interest in the potential benefits from these approaches within industry. Although the number of new products registered in this manner is increasing, the proportion of approvals worldwide remains relatively small.

The use of science- and risk-based approaches for development and validation facilitates product and process understanding, which would support plans for regulatory flexibility but does not directly enable it. This knowledge certainly assists in managing operations and potentially reduces issues, including those that are reportable or of concern. There is some potential leverage from an effective PV program for compliance programs such as annual product quality review (APQR), but while these programs overlap in terms of their focus on process variability, both PV and APQR are required to be operated within the organization's PQS.

It can be difficult to realize the benefits of effective product and process understanding when the rationale for reduction of compliance efforts is not clearly justified—an issue related to challenges in communication and maintenance of knowledge.

Some regulatory authorities and inspectors appear, like industry, to be still building the technical competence to confidently operate a science- and risk-based environment. They may distrust the motivation of a manufacturer using these techniques unless they fully comprehend the data. While organizations are looking to register products in a number of markets, the divergence of understanding and the rate of adoption for this life cycle approach presents an unintended impediment to the realization of full benefits, such as regulatory flexibility. Some organizations are championing this by presenting packages that reflect high levels of process control and understanding.

Recent trends to accelerate medicine approvals for products such as vaccines or new-generation medicines appears to have encouraged both manufacturers and regulatory agencies to focus more on the use of science- and risk-based approaches and understanding to facilitate availability of medicines.

Our sixth observation: Organizations with well-established product and process understanding are often those that seek and gain some degree of regulatory flexibility.

CONCLUSION

Technology for pharmaceutical development, manufacturing, and data management is advancing and the products are becoming more specialized. At the same time, industry and regulators are being exposed to techniques and applications that demand better utilization of science- and risk-based techniques. These products and technologies challenge the paradigm of historical risk, knowledge-management practices, and our application of PV. They also create an environment that encourages our industry to explore new techniques.

The pace of learning is increasing, but there is a significant gap between understanding and application of science- and risk-based techniques for older products and in some markets. This gap might be accentuated as pharmaceutical organizations look to divest or rationalize. As an industry, we need to focus on building robustness into manufacturing pharmaceutical products at both ends of the spectrum to ensure better outcomes for our operations and patients worldwide.

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POTENCY MEASUREMENTS
for Cellular and Gene Therapy Products

By Maria Amaya, PhD, Andrew Chang, PhD, Keith Wonnacott, PhD, Derek T. Scholes, PhD, John MacNair, PhD, Lawrence C. Starke, PhD, and Lesbeth C. Rodriguez, MS

Cell and gene therapy (C&GT) products address various diseases at the cellular or genetic level, offer innovative treatment approaches, and represent a significant advancement in the field of medicine. However, developers of C&GT products face unique challenges due to their complexity, such as establishing assays that show a clear link between potency, mechanism of action (MoA), and clinical performance. Sponsors face a significant risk of a clinical hold if an adequate "potency assay" has not been established by the pivotal phase of clinical trials.

BACKGROUND ON GUIDANCE

The US Food and Drug Administration (FDA) has defined potency in the Code of Federal Regulations (CFR) Title 21 as "the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result" [1].

Similarly, ICH Q6B "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products" describes potency as "the measure of the biological activity using a suitably quantitative biological assay (also called potency assay or bioassay), based on the attribute of the product which is linked to the relevant biological properties" [2].

Furthermore, the FDA 2011 guidance on potency tests for C&GT products states that "potency measurements are a necessary part of product characterization testing, comparability studies, and stability protocols, which are used to establish that a consistently manufactured product is administered during all phases of clinical investigation" [3].

The 2011 guidance [3] emphasizes the importance of accurate measurement methods to ensure product quality and outlines specific considerations and methodologies for assessing potency. However, it acknowledges challenges to assay development for these products, such as the inherent variability of starting materials, limited lot size, material for testing, and stability; lack of appropriate reference standards; multiple active ingredients; the potential for interference or synergy between active ingredients; common MoA(s); and in vivo fate of the product. Consequently, it suggests that a single assay may not be sufficient to measure the product attributes, and multiple assays in combination may be required.

In December 2023, the FDA published "Draft Guidance for Industry: Potency Assurance for Cellular and Gene Therapy Products" [4], which provides recommendations for a science- and risk-based strategy to ensure the potency of human C&GT products. The potency assurance strategy proposed in this guidance document includes manufacturing process design, control, material management, in-process testing, and release potency assays to minimize risks and ensure the intended therapeutic effect for each product lot.

The draft guidance [4] advocates for the application of quality risk management principles throughout the product life cycle, which is similar to the recommendations outlined in ICH Q9(R1) [5]. These principles are adapted to C&GT products by using formal risk assessment tools to identify and mitigate factors affecting potency.

The 2023 guidance also addresses assay development [4]. However, it reduces rather than elaborates on principles related to assay selection and development. Though it provides a holistic overview and addresses assay development, it lacks depth when it comes to elucidating principles related to the selection and development of potency assays when compared to the 2011 guidance. Once the 2023 draft guidance becomes final, it will replace the 2011 guidance.

In Europe, the European Commission's 2017 guidelines on GMP for advanced therapy medicinal products (ATMPs) [6] address scenarios where traditional release testing may not be feasible due to various constraints. For investigational ATMPs, alternatives such as testing key intermediates or in-process controls, real-time testing for short shelf-life products, and increased reliance on process validation are suggested.

Moreover, as routine testing may be limited, the importance of process validation becomes heightened, though any adjustments to release testing strategies require approval from competent authorities. The European Medicines Agency guidelines, similar to the FDA guidance, offer concrete instances of adaptation strategies. Nevertheless, much like the 2023 FDA guidance, it falls short in delving into the foundational principles governing the selection and refinement of potency assays.

CURRENT CHALLENGES TO C&GT PRODUCT POTENCY TESTING

The challenges that manufacturers face in developing potency assays are described in the FDA's 2011 guidance and continue to be relevant. Acknowledging that the challenges will require creativity and flexibility, the guidance states that "FDA regulations allow for considerable flexibility in determining the appropriate measurements of potency for each product" [3].

To illustrate that flexibility, the guidance pointed out three ways in which potency could be measured: a biological assay, an analytical assay that is a surrogate for a biological assay, and a matrix of "complementary assays that measure different product attributes…that are correlated to a relevant biological activity" [3].

Despite the publication of the 2011 guidance, potency testing remained a significant challenge for the C&GT field. Sponsors have found that application of regulatory flexibility has been minimal and that regulators have linked the three different approaches to potency (bioassay, single surrogate, or matrixed surrogate) more frequently by an "and" statement rather than the "or" statement implied in the guidance.

This has created an expectation of adhering to all three methods simultaneously rather than choosing one based on context. When surrogate measures and matrix approaches have been tried, the pathway to establishing meaningful correlations between analytical assays and biological activities has proven difficult.

Additionally, the 2023 guidance emphasizes that "because C&GT products usually have multiple potency-related critical quality attributes (CQAs) that cannot be controlled adequately without release testing, your potency assurance strategy should typically include multiple release assays" [4]. Examples of the challenges identified for the development of C&GT products are described in Table 1.

The release of the 2023 Draft Guidance for Industry marks a continued evolution in the FDA's approach to potency for C&GT products. With the introduction of a potency assurance strategy, instead of viewing potency solely as a test, it is now recognized as a matrix and as a strategic imperative. However, due to the newness of the potency assurance strategy, and the uncertainty around FDA implementation, this article will not cover testing aspects of the potency assurance strategy.

Moreover, our accumulated knowledge on potency testing suggests that the 2023 guidance does not significantly change our understanding in this regard. The 2023 guidance eliminates the use of surrogate potency measures or potency matrices, emphasizing instead that potency testing usually involves a combination of multiple methods and expects sponsors to establish correlations between potency measures and proposed MoA.

Table 1: Challenges identified for the development of C&GT products.

Complex, multicomponent MoA	• Lack of one assay to cover all aspects of potency • Multiple MoA—matrix approach may result in redundant testing • Animal models may not be relevant or sufficiently robust [7] • The functional biological activity of a product may not be induced until engraftment and final maturation has taken place post administration • Certain elements of the MoA might serve solely for characterization purposes • As cell therapies progress, adaptability becomes crucial due to the evolving nature of understanding their MoA
Inherent variability of cell-based assays	• Complex sample matrix • Lack of reference materials and/or assay controls
Product-specific vs. patient-specific attributes may be difficult to predict and control	• Only product-specific attributes can be tested • Patient-specific attributes of the MoA cannot be measured a priori batch • Composition is not available until it is manufactured
Assays evolving as clinical development progresses	• Increased understanding of CQAs, product, and process

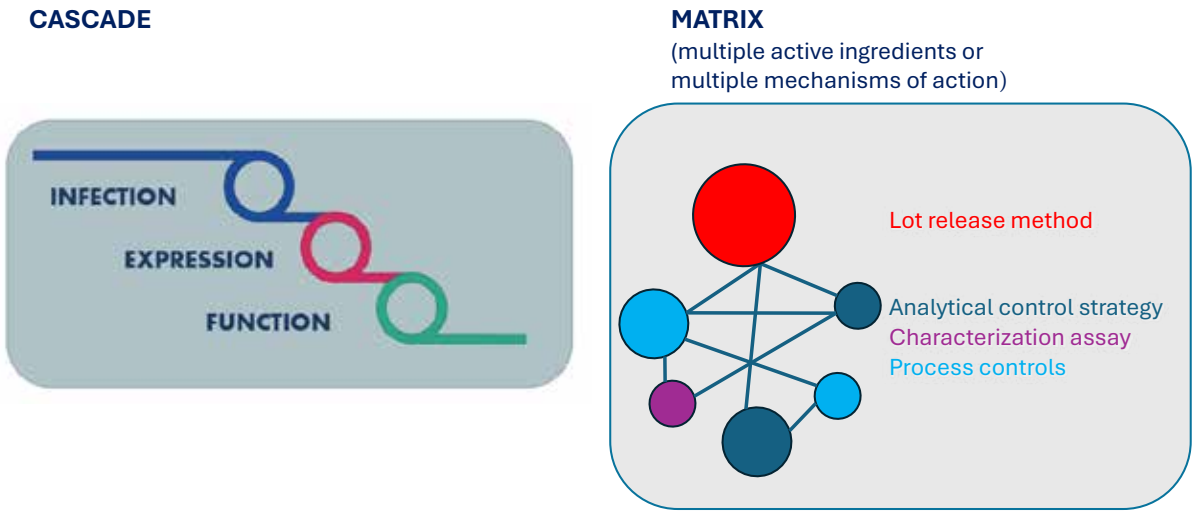
In this article, we introduce proposals to overcome some of the challenges identified. We expect that these proposals will help sponsors and regulatory agencies advance the discussion on the topic of potency for C&GT products.

POINTS TO CONSIDER

The ideal potency assay is relevant, reliable, and can quantify the functional biological activity related to the MoA. For a gene therapy, the ideal potency assay should be able to determine whether a particular environmental factor, storage condition/duration, presence of impurity(ies), post-translational modification of the product, or other such factors influence the biological activity associated with the MoA. This may, in turn, have an impact on clinical performance. In addition, for gene replacement therapy, the ideal potency assay should normally encompass an evaluation of efficiency of gene transfer (infectivity/transduction/delivery) and the levels of expression of the therapeutic sequence to its direct activity.

Potency assays should detect meaningful changes related to biological activity, have a defined product-specific acceptance criterion, have meaningful system suitability controls, and be stability-indicating. The ability to develop the ideal potency assay for C&GT products is variable and depends on the type of challenges

Figure 1: Primary strategies for potency assessment.



the developers face, which include but are not limited to complex and usually not fully known MoA, lack of assay sensitivity, and variability of cell-based assays (see Figure 1).

Potency Attributes

Potency is considered a CQA and the development of the relevant assays are the center of many challenges and discussions amongst developers of C&GT products and regulators. Measurement of potency plays an essential role not only for ensuring consistent bioactivity in each therapeutic dose administered to patients but also in quality control and batch release, product characterization, comparability, and stability.

An ideal potency assay's results should be quantitative, be stability-indicating, confirm lot-to-lot consistency, meet predefined acceptance and/or rejection criteria, and measure a biological activity that correlates with clinical function in the best-case scenario.

Fit-For-Purpose Solutions

As described in the 2011 FDA guidance "Potency Tests for Cellular and Gene Therapy Products" [3], the complexity and diversity of C&GT products can present significant challenges for the development of potency assays. Challenges such as variability of starting and raw materials, multiple active ingredients, complex mechanisms of action, variable CQAs, and complex manufacturing processes, make the development of fit-for purpose solutions a necessity.

As stated in the paper "Addressing Potency-Assay Related Development Delays for Cell and Gene Therapies" [8], "gene and cell therapies often undergo a series of processing events that ultimately result in the functional therapeutic entity. Further downstream events may be required to achieve the final therapeutic outcome, which itself may be another cascade. These biological steps are often referred to as a 'biological cascade.'"

As an alternative, the matrix approach to potency assessment recognizes that a single potency assay may not capture the full spectrum of therapeutic activity, and advocates for the integration of multiple assays tailored to the diverse MoA exhibited by these products. In essence, absent a singular potency assay, a matrix of assays is employed, each designed to reflect specific facets of the product's therapeutic potential. Figure 1 illustrates two primary strategies for potency assessment: the cascade approach and the matrix approach.

Potency is almost never univariate. In the cascade approach, as seen in Figure 1, potency assessment progresses through a series of assays, each addressing specific aspects of the product's MoA or biological activity. The matrix approach involves the simultaneous use of multiple assays, each capturing different dimensions of potency. These assays may encompass various methodologies, such as cell-based assays, biochemical assays, and molecular assays. Integration of data from these diverse assays provides a comprehensive understanding of the product's potency profile.

Biological Assays

Biological assays inherently exhibit variability, and in the context of cell therapies like chimeric antigen receptor (CAR) T cell therapy, this variability is compounded by differences in starting materials. These challenges underscore the difficulty in selecting the most suitable activity for validation and specification setting, especially concerning its proximity to drug delivery. Despite this, regulatory agencies often prioritize evaluating downstream protein activity

alongside gene activity. Consequently, developing assays that capture various levels of the activity cascade becomes imperative for product characterization and may even be mandated.

Multiple Distinct or Orthogonal Assays

Based on the MoA, the question of whether one assay is sufficient or if multiple assays will be needed is not always easily determined. When multiple components come together to make up a product, multiple potency measures may be needed. Examples might include when a lentiviral vector and a T cell are brought together to make a CAR T cell or when the various components (guide ribonucleic acid [RNA] and nuclease) of gene editing are brought together in a delivery vector. Multiple assays may also be needed if multiple MoAs are intended by the product either due to the presence of multiple transgenes or the presence of multifunctional cells.

The FDA strongly recommends [3] developing multiple assays in parallel during early clinical investigations. This may include the development of orthogonal methods that measure the same attribute of potency. Having multiple assays improves the likelihood that an acceptable assay can be found and agreed upon with the FDA and increases product characterization and understanding.

The 2023 guidance recognizes that redundant assays can be eliminated when multiple options are available [4]. It also states that one assay may be sufficient if it is a later step in the chain of biological activities that is completely dependent on the earlier steps. However, many sponsors have not experienced the stated flexibility that the draft guidance offers.

Surrogate Assays

Although the concept of surrogacy assays remains beneficial, the agency omitted the use of this term in the 2023 guidance [4]. The adequacy of a surrogate measure is often determined by the strength of the correlation to the proposed biological function. However, in some cases where the MoA is highly complex, conventional measurement methods may yield insensitive or highly variable results. In such scenarios, surrogate assays such as those quantifying clinically relevant biomarkers, may offer a more meaningful source of quantitative data.

A surrogate assay, instead of capturing the entire mechanism of "functional activity" in a single method, provides an alternative measure. Presumably, one that is physiologically and molecularly linked to functional activity and ideally whose outcome may be predictive of preclinical or clinical activity. This may include characterization of one molecular aspect of functional activity particularly when the functional activity of a transgene product is complex and involves multiple molecular events. The use of surrogate assays can strengthen the confidence of potency assessments for C&GT products, especially when there are limitations to establish a functional potency assay and/or the MoA is not clear.

Points to consider for establishing a surrogate potency assay follow. The extent of the linkage between a surrogate assay related to potency (e.g., T cell activation) and clinical performance should be established through bridging studies during product development. The surrogate assay may not be a bioassay: Surrogate assays may be less variable as compared to a bioassay, which provides an advantage for establishing product consistency and dosing recommendation.

Multiple assays may be needed, and, in some cases, a matrix approach could be considered. Different purposes may require different assays. For example: Bioassays are more meaningful and practical for product characterization, comparability, and stability studies. However, performing a cell-based functional biological assay for release of drug product (DP) is not practical due to limited time from formulation of the cell clusters to administration to the patients. Surrogate measurements (e.g., surface markers) for cellular products may be more appropriate and practical for DP lot release.

Example surrogate measures include biochemical, immunochemical, physical (e.g., phenotype, viable cell numbers), and assays that correlate with biological activity (e.g., messenger ribonucleic acid (mRNA) or protein expression, the activity measure of a single functional domain or protein binding).

Bridging Studies

Bridging studies are performed to build a relationship between a surrogate assay and the performance of the product. The purpose of bridging studies is to explore the relationship between product quality attributes (in this case, surrogate potency assays) and the clinical profile (efficacy). Some aspects of bridging could be done at the preclinical level rather than clinical and it could be used to demonstrate that certain iterations of the product (i.e., forced degradation, presence of certain post-translational modifications, impurities, etc.) do not have the intended functional impact.

Points to consider for the development of bridging studies include the following.

Quantitative linkage

If possible, sponsors should establish a quantitative linkage between the surrogate assay and the biological activity as measured using in vivo studies, in vitro studies, or other characterization of the products biological activity performed as part of the product development.

The FDA's 2011 potency guidance states that "the correlative relationship between the surrogate measurement and biological activity may be established using various approaches, including comparison to preclinical/proof of concept data, in vivo data (animal or clinical), or in vitro cellular or biochemical data" [3]. Previously established scientific knowledge or a platform approach could also provide good rationale for bridging a chosen surrogate measurement to the biological activity.

Processes and models

The outcome of the bridging studies and relevance of the correlation made will guide the decision-making process for choosing the right surrogate assay for potency. Bridging studies used to demonstrate that the product doesn't have the intended functional activity

Embracing this shift toward platform-based methodologies holds the potential to drive advancements across the entire C&GT field, ultimately enhancing product development and regulatory processes.

would be very challenging for indications that do not have reliable preclinical animal models. In some cases, extremely novel assays may require use of an assay bridging protocol/plan to ensure effective bridging to more conventional assays.

Changes over time and development

It should be recognized that potency assays may change over time and with stages of clinical development. With new scientific information, the test may be optimized, or new tests may be added. When a surrogate method(s) is introduced at a later phase of product development, a bridging study or head-to-head comparison is expected to ensure the adequacy of the replacement of the original test.

More versatile platform approaches

Furthermore, as collaboration between the FDA and developers progresses, there is a growing consensus on the need to transition from highly specialized, product-specific potency assessments to more versatile platform approaches. Analogous to the evolution seen in the monoclonal antibody field, where binding assays replaced highly specific biological assays, such platform approaches offer greater predictability and higher-quality data outputs. Embracing this shift toward platform-based methodologies holds the potential to drive advancements across the entire C&GT field, ultimately enhancing product development and regulatory processes.

CONCLUSION

Although there is a need for regulatory flexibility, quality standards should not be compromised for C&GT products and new approaches may be needed to ensure sufficiently high standards. Even though C&GT products pose many new challenges, they also bring new concepts and opportunities. In the case of the development of C&GT potency assays, there is no one-size-fits-all approach. Instead, fit-for-purpose approaches focused on developing activity-based methods or on the use of matrixed surrogate measures can provide a regulatory framework for potency assays that is flexible around some core requirements.

Specifically, we advocate for the following objectives. We encourage continued improvement of product and process understanding, as well as a subsequent evolution to the control strategy enabled through regulatory flexibility, e.g., persistent regulatory recognition that potency assays may change over time and with stage of clinical development given the limited materials available, often with high variability. We advocate for using surrogate measures, especially when the MoA is not clear. We recommend better understanding instances when regulatory flexibility can be applied. For example: a) where testing each component separately is necessary, particularly when the product comprises multiple components that function collectively as a final product; and b) assessing the final product without mandating multiple separate assays, enhancing efficiency without compromising the integrity of the assessment process.

Channels for enhanced communication and increased dialogue with health authorities regarding potency assay approaches will support the development of a roadmap for success. Finally, we encourage efforts for global harmonization on potency considerations for C&GT products and regulatory convergence in chemistry, manufacturing, and controls (CMC) development, including approaches for potency assays. Reliance and work-sharing approaches will facilitate timely access to safe, effective, and quality-assured medical products on a global scale.

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FINDING THE ASSURANCE in Computer Software Assurance

By Charlie Wakeham, Lorrie Vuolo-Schuessler, and Siôn Wyn

Computer software assurance (CSA) has been discussed widely in industry over the past five years. While the principles are well understood and welcomed, until now some of the practical detail on how exactly to implement CSA into an organization has been missing.

This article reaffirms CSA's background and alignment with published GAMP® guidance. It discusses the results of the workshop "Computer Software Assurance: Next Steps for Better Compliance" conducted at the 2022 ISPE Annual Meeting in Orlando, Florida. Finally, it delivers a practical analysis of the organizational changes and mindset needed to successfully implement CSA, critical thinking, and improved risk management.

CSA WORKSHOPS

In a GAMP® South Asia webinar in March 2024, only 14% of the 71 respondents claimed a strong understanding of CSA, with 31% having no prior knowledge (see Figure 1). The remaining 55% were unclear around the differences between CSA and computerized systems validation (CSV).

ISPE developed a two-part series on CSA in conjunction with the Society of Quality Assurance (SQA). The first workshop, in September 2022 and titled "SQA-CVIC and ISPE joint Workshop on CSA," was attended by 60 industry members. The second, in October 2022, took the output from the first workshop as the starting point for further investigation and brainstorming.

The second workshop was hosted by the following presenters (affiliations current at the time of the events):

- Charlie Wakeham, ISPE GAMP
- Lorrie Vuolo-Schuessler, ISPE GAMP and SQA
- Petch Ashida-Druar, ISPE GAMP and SQA
- Joseph Franchetti, SQA
- Ken Shitamoto, ISPE GAMP and FDA Industry CSA team
- Khaled Moussally, ISPE GAMP and FDA Industry CSA team
- Mike Rutherford, ISPE Chair and ISPE GAMP

Over 80 industry professionals invested their time and expertise in Orlando to explore overcoming the perceived barriers of CSA adoption. Those solutions are presented in this article, along with our grateful thanks to the attendees of both workshops for their participation.

BACKGROUND ON CSA

The US FDA Center for Devices and Radiological Health (CDRH) Case for Quality program [1] and the associated guidance document, "Computer Software Assurance for Production and Quality System Software, Draft Guidance for Industry and Food and Drug Administration Staff" [2], promote a risk-based, product quality–focused, and patient-centric approach to computerized systems. This approach encourages critical thinking based on product and process knowledge and quality risk management over prescriptive documentation-driven approaches.

The draft guidance has been prepared by the CDRH and the Center for Biologics Evaluation and Research (CBER) in consultation with the Center for Drug Evaluation and Research (CDER), Office of Combination Products, and Office of Regulatory Affairs. It states that when finalized, the guidance will supplement the FDA's "General Principles of Software Validation Guidance for Industry and FDA Staff" guidance document [3].

The FDA's 21 CFR Part 11 [4] document, which is applicable to all FDA program areas, describes the FDA approach to CSV. It specifically refers to the general principles of software validation guidance and to GAMP guidance. It is natural and logical for FDA

Figure 1: **Results from GAMP South Asia survey question "What knowledge do you have of CSA?"**

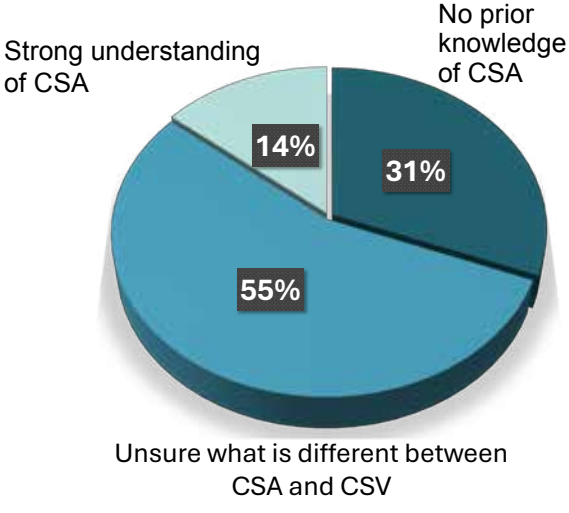
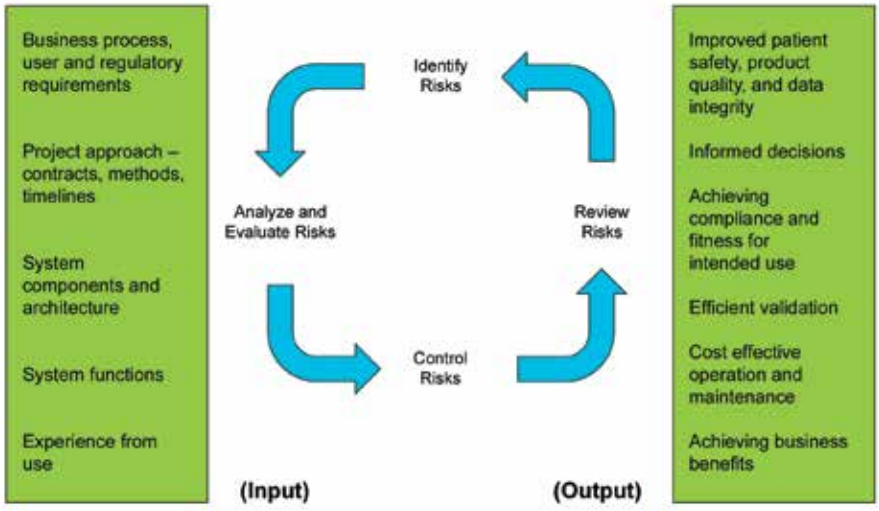


Figure 2: Overview and benefits of risk management [5].



centers to cross-refer to already existing guidance created by other centers rather than create their own. The guidance should not be seen as applicable only within CDRH or CBER program areas.

The ISPE GAMP Community of Practice and its global leadership strongly supports FDA's risk- and quality-based approach to the assurance of computerized systems, and believes that current ISPE GAMP guidance, and specifically *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)* [5], is already fully aligned and consistent with such an approach.

We believe that the extremely valuable benefits and objectives of the CSA draft guidance can be fully achieved by applying *GAMP® 5 (Second Edition)*. This approach encourages critical thinking based on product and process knowledge, applies effective quality risk management over prescriptive documentation-driven approaches, and favors a focus on true quality over compliance. We judge that the draft guidance has already been very helpful in countering fears of perceived regulatory inflexibility that have traditionally contributed to outdated compliance practices.

We applaud the FDA's decision to apply modified terminology based on "assurance" to underline the fact that industry would greatly benefit from a change from old-fashioned, outmoded, paper-heavy compliance-focused approaches. A simple name change can be effective, as it draws attention to the fact that change is possible and desirable.

The use of the term "assurance" rather than "validation" is also logical as it is wider in scope and covers all the essential life cycle, operational, and governance activities involved. Current GAMP terminology is sufficiently flexible to support this thinking. The European Union, the FDA, and other regulations use the term "validation," but are not prescriptive on how this should be achieved. We believe that any detailed differences in approach or terminology are vastly outnumbered by the similarities in key concepts and shared objectives and benefits.

ALIGNMENT WITH GAMP

Here we highlight some key principles and objectives of the draft guidance and show how they are supported by and aligned with the GAMP approach.

The draft guidance reminds us that testing alone is not sufficient to establish confidence that the software is fit for its intended use. It recommends a "software quality assurance" focus on preventing the introduction of defects into the life cycle. It also encourages the application of risk-based approaches for establishing confidence that software is fit for its intended use. This is completely aligned with the *GAMP® 5 (Second Edition)* life cycle and verification approach.

The draft guidance supports flexibility and agility by encouraging regulated companies to select and apply the most effective testing approaches for various circumstances, together with continuous performance monitoring and data monitoring in operation, as well as leveraging various activities performed by other entities such as suppliers and service providers. This is fully aligned with the GAMP verification and testing approach and the *GAMP® 5 (Second Edition)* key concept of leveraging supplier involvement [5].

The draft guidance recommends focusing on features, functions, or operations that support areas of high-process risk, rather than those that do not pose a high-process risk. Failure to perform as intended not related to high-process risks would not result in a quality problem that foreseeably compromises safety, even though those other systems and functions are still regulated. This is supported by and consistent with *GAMP® 5 (Second Edition)*, Section 5.2 Science-Based Quality Risk Management, and reflected in Figure 2 [5].

The draft guidance reminds us that when deciding on the appropriate assurance activities, regulated companies should consider additional controls or mechanisms in place throughout the quality system that may decrease the impact of compromised

Figure 3: Session topics within the workshop.

safety and/or quality if failure of the software feature, function, or operation were to occur. Examples of controls and mechanisms include:

- Technical and procedural controls for the production process and the integrity of the data generated within that process
- Processes for assessing, selecting, managing, and monitoring suppliers and service providers, including assessment of software supplier quality and life cycle activities
- Data and information periodically or continuously collected for the purposes of monitoring or detecting defects, issues, and anomalies in systems after implementation
- Life cycle management tools (e.g., for defect logging and management, testing, performance monitoring, release, deployment, and maintenance)
- Testing performed in iterative cycles and continuously throughout the system life cycle

These are described and recommended in multiple GAMP guidance documents, including *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)* [5], *ISPE GAMP® Good Practice Guide: Enabling Innovation – Critical Thinking, Agile, IT Service Management* [6], *ISPE GAMP® RDI Good Practice Guide: Data Integrity by Design* [7], and *ISPE GAMP® Guide: Records and Data Integrity* [8].

The draft guidance recommends the maintenance of sufficient objective evidence to demonstrate fitness for intended use and outlines what is generally required. The expectations listed are easily achieved by following an appropriate *GAMP® 5 (Second Edition)* life cycle [5]. For example:

- The intended use of the software feature, function, or operation: Defined in Requirements and other Specifications
- The determination of risk of the software feature, function, or operation: Captured in a justified and documented risk assessment
- Records of the assurance activities conducted, including description of the testing conducted, issues found and disposition, and conclusions: Captured in test specifications, reports, and life cycle tools

Finally, the draft guidance pragmatically and helpfully reminds us that documentation of assurance activities need not include more evidence than necessary to show that the system performs as intended for the risk identified. It should also be sufficient to serve as a baseline for maintenance and improvements or as a reference point if issues occur.

WORKSHOP OUTPUT

The workshop at the ISPE Annual Meeting in October 2022 comprised four sessions. Each session contained three questions focused on related aspects of the session topics, which are shown in Figure 3. Multiple breakout teams addressed each question, and their responses are presented here with additional input from GAMP global leadership.

Session 1: Critical Thinking, Quality, and CSA

Question 1: How can critical thinking become fundamental and utilized routinely throughout an organization?

For an organization to understand the value that critical thinking can bring to their operations, it's key to first develop a quality culture in which quality, information technology (IT), validation leads, and the business process owner(s) fully understand and embrace their roles and responsibilities to collaborate effectively. The quality culture should enable management to lead by example and drive a culture that questions the standard approach, breaks down organizational silos, and allows flexibility in approaches. Critical thinking should be prioritized through training initiatives and recruitment.

To institutionalize the incorporation of CSA and critical thinking, the entire organization must be trained in the value and purpose

of including critical thinking and risk management principles in all activities. Critical thinking and risk-based approaches then become operationalized as integral parts of the company's culture.

System-level risk assessments and functional risk assessments should be included in each project and include quality, IT, validation leads, and the business process owner(s), along with appropriate subject matter experts (SMEs) as needed. The risk factors associated with the particular product and process may be specific to that combination. These should be reflected in the assessment when considering the impact to both the patient and the business if the risk occurs.

Incorporating critical thinking into a process is intended to strengthen the controls and robustness of the process, not to offer shortcuts. It should not be misused to that end.

Question 2: How do we get company leadership, and especially the quality function, onboard and supportive of CSA concepts?

GAMP® 5 (Second Edition) defines the CSA concepts in clear terms positioned within the life cycle and should be the roadmap for any organization wishing to adopt these practices [5].

The benefits of CSA may be best achieved with the use of software tools supporting the life cycle (e.g., requirements management and automated testing tools). It may be challenging for an organization to move away from paper and "paper-based thinking" and adopt electronic workflows. An understanding of the potential efficiency gains with software tools and leveraging artifacts in the place of traditional documents can support this move.

However, it is important that an organization understands that investing in tools does create an increased upfront cost. Though, once implemented and adopted, the CSA approach should deliver a highly defensible system with reduced long-term cost.

CSA is an evolution of software validation, and the role of quality must evolve accordingly to bring their knowledge and expertise into this more flexible and adaptable approach. The quality function will transform from the gatekeepers (i.e., as essential approvers on formal documents) into stewards of life cycle activities. These stewards ensure the life cycle activities are consistent with the validation strategy and provide strong assurance of fitness for intended use.

Increased patient focus and critical thinking can optimize the assessment of requirements and increase effectiveness and coordination internally and between regulated companies and vendors.

Question 3: How does a culture of quality vs. a culture of compliance support the organization?

A culture of quality is one in which the focus is on producing the right evidence for critical areas. This is done with the goal of producing a system that is fit for use in the business process that it supports, inherently delivering both quality and compliance. It is supported by collaboration, critical thinking, and a risk-based approach focusing on ensuring patient safety, product quality, and data integrity. Conversely, a compliance culture focuses on meeting perceived regulatory expectations based on completing a fixed set of universally applied predefined activities for each system, without any assurance of consistently achieving quality. A quality culture can only be established within an organization when driven by a committed management team. It is important in such an organization that everyone recognizes quality as part of their job, that there is tailored training of all personnel, and that management focuses on rewarding behaviors that support the set goals. The use of multidisciplinary teams and membership diversity in governance boards will facilitate and encourage collaborative working and clear accountability. This is essential to the quality culture.

Session 2: Vendor Management Practices and Audit Approaches for CSA

Question 4: After a vendor audit, how do you use the information gained and leverage that knowledge in planning your validation and ongoing control activities?

Many organizations are now partnering with vendors and wanting to leverage vendor documentation. So, vendor assessments, clear service level agreements (SLAs), and quality agreements are critical to the success of the engagement. Only with knowledge of the vendor's quality practices is it possible for the regulated company to leverage activities performed by the vendor, and thus avoid repeating activities.

The CSA approach focuses resources on performing risk-based activities to complement and/or supplement previous activities where needed. The type and frequency of vendor assessment activities, including what follow-up and ongoing surveillance are needed, should be based on the product/services' intended use and associated risk. The information gained during the vendor assessment allows the regulated company to decide what level of confidence they have in the vendor's quality management system, life cycle, and records.

After an audit or vendor qualification, the regulated company may decide that the vendor does not have a sufficient quality system or knowledge of the industry and that they will not use the vendor. Alternatively, the regulated company may decide to proceed with using that vendor but establishing additional mitigating controls based on a thorough understanding of the business process and a documented risk assessment. A follow-up assessment can be used to determine if the vendor actions post-audit have been sufficient to mitigate risks identified during the audit.

If the vendor has a well-established quality system, the regulated company can assess their controls and test rigor and coverage (e.g., via the traceability matrix) against the intended use of the system. This will help determine what activities are needed to supplement the vendor life cycle. It is important to identify, assess, and mitigate risks associated with differences between the tested vendor configuration and the intended use; the validation plan should be used to justify and describe the use of any vendor information or activities. An action plan is needed to mitigate any remaining risks.

A vendor audit should only be performed when the information gathered during the audit will result in changes to the activities performed by the regulated company.

Question 5: How do you audit vendor testing in the system planning stage when you haven't done the risk assessment yet and do not understand the system?

It is important that a risk-based vendor assessment is performed by SMEs from an appropriate team (e.g., quality, IT, validation leads, and the business process owner(s)) as needed. The team should be selected based on the types of risks associated with the system/process and should meet prior to the first audit session. During this meeting, they should agree on the key focus areas relating to the intended use of the products/services.

The audit objective should be to evaluate the quality and maturity of the vendor processes, including their testing processes, to identify how the regulated company's project activities will be impacted in response to the assessment findings. This should be done while recognizing that the detail of the vendor's testing may need to be revisited later in the project by the validation team.

Question 6: How can a vendor do things differently with CSA, and where can critical thinking and risk management take a vendor in terms of more efficient and effective testing?

It is important that a vendor focuses on software development life cycle elements and applies critical thinking from a product perspective. The vendor procedures should ensure that the rationale for decisions impacting their product life cycle (e.g., evolving requirements or revising test coverage) is captured and maintained ongoing and can be clearly understood by personnel from diverse backgrounds (e.g., IT, quality, or business).

Many vendors follow Agile methodologies, including the use of automated tools supporting the life cycle. Careful selection of the language used to connect the information and artifacts in the tools to GxP validation terminology can help avoid duplicating information into a document set.

Session 3: Leveraging Vendor Activities and CSA in the Operational Phase

Question 7: Having used critical thinking, risk management, and CSA approaches during the project stage, how does this impact the ongoing maintenance of the validated state through the operational phase?

The use of these approaches during the project stage will ensure a deep understanding of the system and its use in support of the business process when entering the operational phase. This understanding should make it easy to continue risk-based CSA throughout the life of the system.

Lessons learned during the project phase can be used to tailor the operational procedures and ongoing management of the system. The SLA and/or quality agreement with the support provider can be strengthened to specifically address any areas of concern and/or potential risks identified during the system implementation.

Consideration of changes in the operational phase should involve quality, IT, validation leads, and the business process owner(s), just as in the project stage. When it is a change to a software application, rather than a change to infrastructure or process, the vendor release notes should be scrutinized to understand the changes.

All changes should be evaluated based on the impact the change will have on the intended use of the system. The risk assessment needs to be revisited to identify those changes impacting functionalities determined to be associated with high-risk processes (including impacts to any other systems that integrate with this system). Critical thinking should be used to develop test plans accordingly, and ideally automated test tools should be in place to provide regression testing on high-risk processes after each upgrade or set of changes.

It is important to note that automated regression testing is a valuable and consistent tool for ensuring previously correct functionality has not been impacted by the change; however, it is also important to recognize that automated test cases by their nature are scripted. Therefore, they will only test the same paths on each execution.

Low-risk changes can be operationalized through procedural controls and implemented with minimal disruption to business.

Question 8: If a vendor uses a combination of scripted and unscripted testing as part of their life cycle, how much can you leverage this testing and in what situations, if any, would you need to repeat any of this testing?

All vendor testing is suitable for leveraging if the vendor has a robust quality management system that defines the risk-based approach to testing, including scripted and unscripted testing, and if the unscripted testing was applied appropriately. However, vendor testing using undocumented, unscripted testing or using only unscripted testing as a blanket replacement for scripted testing in the interests of speed and convenience would not be suitable for leveraging by the regulated company.

If the vendor quality management system is not robust, then it may be necessary to repeat certain testing to confirm functionality relating to high-risk processes. The regulated company should apply additional testing where the software is configured or customized and perform scenario-based testing using their internal processes and data to ensure the system operates as intended in their environment.

Question 9: With continuous integration/continuous deployment (CI/CD) approaches, especially for software-as-a-service (SaaS) offerings, frequent incremental changes to our infrastructure and applications are becoming the norm. How much can the change management and validation burden be lightened on the regulated user?

If the vendor is managing changes on behalf of the regulated company, a closer relationship and oversight are required. This is because the vendor is now able to impact the compliance of the system in use directly. More rigorous assessment and engagement

with the vendor's internal processes are needed. This is to ensure the validation and controls are adequately maintained and managed for both the application and infrastructure through any changes.

With appropriate SLAs or quality agreements in place with the right supplier, CI/CD can significantly reduce the regulated company's burden for change management and validation when combined with the right mindset, appropriate process, and automated tools. The operationalization of low-risk (standard/routine) changes discussed in question 7 becomes essential in this scenario. Vendors will work on different release cadences and notification periods, so the regulated company must understand and manage the risks and impact these have when working with multiple vendors and solutions.

Session 4: Measuring CSA Benefits and Moving Forward with CSA

Question 10: What metrics can quantify and optimize the benefits of CSA in achieving and maintaining computerized systems as fit for intended use?

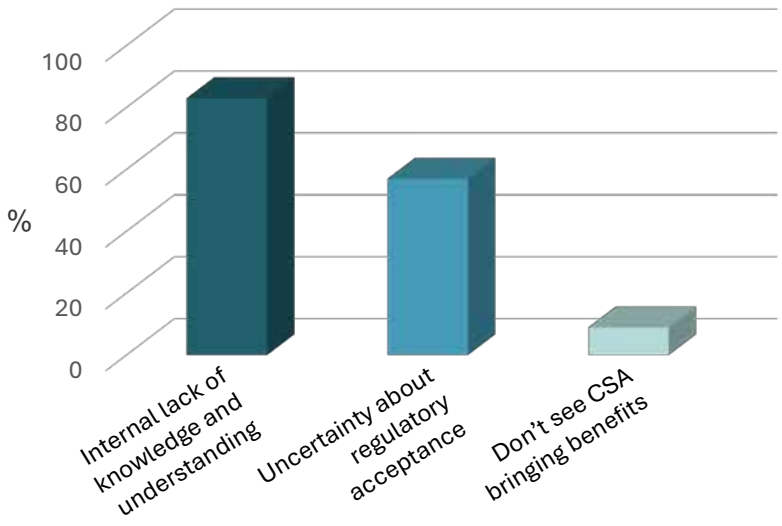
First, baseline metrics on the current validation process are needed. This is to provide a benchmark against which any differences arising from CSA changes could be measured. These need to be captured based on projects completed prior to CSA changes.

Second, both lagging and leading metrics should be used to capture process improvements and the effectiveness of a CSA approach. Examples of lagging metrics could include measuring the time to release a new system, level of validation resource used, duration of hypercare periods after a new implementation or major upgrade, number of deviations/incidents after go-live for functionalities associated to a high-risk process, and time to implement low-risk fixes/enhancements, with a reduction allowing an effective continual improvement program. These example metrics would all ideally decrease with an effective implementation of CSA approaches, risk management, and critical thinking.

Leading metrics could be based on items on a "punch list" of errors or issues to be added to the backlog and addressed in a future sprint. These could be predictive indicators of both the number of defects potentially within the software (high number of items on the punch list early in the testing suggests poor quality software) and of the amount of defect-resolution work still to be completed to close out the punch list items.

After a project, analyzing lessons learned and understanding the effectiveness as measured by the metrics could help optimize CSA approaches for future projects and releases. This is done by thinking critically about what updates need to occur to processes,

Figure 4: Results from GAMP South Asia survey "What barriers or challenges do you see to adopting CSA?"



systems, or records. Post optimization, the metrics should then show a corresponding further improvement.

Invest in software life cycle tools and training and use SMEs to ensure real understanding of risk management and critical thinking. This will help drive long-term success and efficiency gains. Companies need to understand the initial implementation cost of CSA (investment in software tools, upskilling, etc.) vs. the projected efficiency gains in the future.

Once the approach is fully implemented and matured, CSA benefits include process improvements that will reduce the incidence of issues in the operational phase. These will go hand-in-hand with improvements in the quality culture and the end product quality.

Question 11: What are the barriers to progressing with CSA and how can they be overcome?
Question 12: What can we do to confidently defend CSA approaches to other (non-FDA) regulators?

Note: Questions 11 and 12 are addressed together here, as the answers overlapped and complemented each other in a synergistic solution.

The concepts of the draft guidance are broadly applicable across all FDA-regulated areas, as discussed in the background earlier in this article. This applicability has led to the detailed inclusion of CSA approaches in ISPE's *GAMP® 5 (Second Edition)* [5], which applies to systems used in regulated activities under GMP, good laboratory practices, good clinical practices, good distribution practices, and good pharmacovigilance practices. *GAMP® 5 (Second Edition)* should also allay any fears that CSA is only acceptable to the US FDA and not to other regulators: GAMP guidance has provided a de facto standard for many years and has been accepted and referenced by regulatory agencies around the world.

CSA, as stated repeatedly by GAMP, is just a reinforcement of the risk-based approach. CSA builds on generally accepted principles of validation and fundamentally does not introduce a new way of working. This is because it aligns with the existing risk-based approach promoted since 2008 and recommended in the GxP regulations.

A more significant barrier to CSA adoption may come from the varied interpretation of CSA across industry (including regulated companies, vendors, and consultants) and regulators. In the April 2024 GAMP South Asia webinar, 83% of respondents cited the lack of knowledge and understanding of CSA within their own organizations as a barrier. This is compared to 57% being concerned about regulatory acceptance, as shown in Figure 4.

Again, GAMP guidance offers a common and pragmatic approach to implementing CSA and critical thinking; it can be used as the common interpretation. Investing in ISPE's training in GAMP methodologies and practices, as well as external training in critical thinking, will ensure a practical understanding of how to "do" critical thinking and how to capture and action the output of that critical thinking, i.e., the rationale for decisions and a risk-based approach. The increased understanding from such training will make explaining and justifying the validation approach during an inspection much easier to rationalize to regulators and other auditors.

There is unlikely to be a neat deadline by which all projects using the existing validation approach will be completed. Therefore, there will be ongoing projects using that approach running concurrently with newer projects using CSA approaches. Record the justification for the change in approach and demonstrate there is no decrease in control when transitioning from existing validation practices to new practices including, for example, the use of unscripted

Figure 5: Effective approaches for the implementation of CSA.

testing. An inspection may include review of projects with existing practices or new practices. Both of these—when executed according to good practice and documented processes—should be acceptable to the auditor.

CONCLUSION

CSA is an evolution of software validation using a risk- and quality-based approach to assure that computerized systems and applications are fit for purpose. The outputs from the workshop series demonstrate that the tools and techniques are already available to support industry adoption, and this article provides practical advice on managed and effective approaches for the implementation of CSA at the leadership and operational levels, as shown in Figure 5.

As with earlier approaches, CSA should be applied to the full life cycle of a system. This life cycle includes development to implementation and operation and eventually system decommissioning and destruction. A computerized system life cycle is best holistically managed by a multidisciplinary team. This team includes SMEs from quality, IT, validation leads, and the business process owner(s).

CSA is neither an alternative for, nor a shortcut to, validation. It will require initial financial investment in life cycle tools and training, and early projects may consume more resources as personnel learn and adapt to the improved way of working. The long-term benefits of CSA done well—potentially shorter implementation times and less defects in the operational phase—will justify this initial investment. The focus of the CSA approach is on quality over compliance, giving an operational system that is fit for intended use within its business process instead of hiding behind excessive documentation.

Fundamental to an organization using CSA approaches is for them to create a quality culture and embrace critical thinking and risk management approaches in all their activities. Get critical thinking and risk management adopted and embedded into the organization, and CSA will naturally follow. An open mindset and willingness to embrace change, including implementing life cycle tools, are vital to success.

Some less mature organizations may experience resistance in implementing CSA due to the corresponding change in roles and responsibilities. The role of quality in the project will need to evolve from a gatekeeper mindset of reviewing and approving documents to a steward mindset, ensuring the activities proceed in accordance with the company's internal policies and provide guidance where needed in a flexible and versatile way to ensure regulatory requirements are satisfied.

CSA as a reinforcement of risk management complemented by a wider choice of test approaches and the use of life cycle tools can be implemented by, and bring benefits to, vendors, providers, and regulated companies. For a regulated company to be able to leverage vendor activities and build a long-term partnership, it is important they establish a robust risk-based vendor assessment process that drives and reinforces mitigation of any vendor risks identified during assessments.

Ultimately, the intention of CSA is neither resource saving nor efficiency gains but rather a substantial improvement in patient safety. Since *GAMP® 4* was published in 2001 [9], GAMP has promoted a risk-based approach to computerized systems quality. *GAMP® 5 (Second Edition)* provides updated, detailed, and pragmatic guidance on a computerized system life cycle approach using CSA and critical thinking as a reinforcement to the risk-based approach [5]. This article discussed, in detail, the challenges and practicalities around adopting the improved approach and how it can be achieved. Industry now has everything it needs to make the transition and find the assurance in CSA.

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GUIDING PRINCIPLES for Combination Product Reliability

By Alan Stevens, Sherwin Shang, PhD, and Kent Abrahamson

Drug delivery devices have become an essential component for many modern medical therapies, and it's vital that they function as intended. However, the reality of marketed products shows that this is not always achieved because drug-device combination products are becoming increasingly complex, with an increasing number of potential failure modes. Significant challenges for engineers include understanding how to develop the reliability specifications, which tools to use, and when to use these tools.

The challenge of the correct tools to use is compounded by the increasing complexity of devices, like reusable, software controlled, electromechanical infusion pumps, and single-use devices, such as mechanical autoinjectors. As regulators and the international standards community increase their focus on patient risks associated with critical therapies, manufacturers must adapt to deliver reliable products through early implementation of reliability engineering techniques.

RELIABILITY ENGINEERING

Effective reliability engineering reduces the risk of product failures and other associated negative outcomes, such as harm to patients, recalls, enhanced regulatory oversight, cost, and damage to brand reputation. There are many examples of medical device recalls that may have been prevented through application of a formal reliability program. A review of recalls for infusion pumps identifies many reliability-related issues, including switch malfunctions, unresponsive user interface, and pump housing cracks allowing fluid ingress [1]. Reliability engineering is a set of tools to help manage these risks and this article discusses processes to plan and implement the use of these tools.

However, it is important to distinguish between reliability as an objective and reliability engineering as discipline. Reliability is an attribute of a product, which applies to both multi-use and single-use devices. Reliability engineering is a system of applying engineering principles to the life cycle of a product to achieve the desired reliability objectives.

It is essential that both reliability as an objective and reliability engineering as discipline are both core considerations throughout a combination product's life cycle. The level of effort should be commensurate with the complexity and risk of the product. Reliability growth has typically been used in a system level to monitor the product improvement and maturity—from design and development to commercialization and continuous improvement management.

The reliability outcome and deliverables can be quantified in terms of patient complaint rates and product failure rates. Reliability values can also provide estimated predictions of patient complaints before product launch based on the clinical data of patient uses of combination products for therapy and outline product failure risks after launch based on failure mode and effects analysis (FMEA), engineering confirmation testing, and the verifications and validation data from design and development.

Background

A core principle of developing a reliable product is that reliability engineering needs to occur at a system level where a fundamental understanding of the design must be established based on first principles. Every decision—from the number of parts to which software version updates, technologies, or testing strategies are used—needs to incorporate reliability engineers into the decision-making process.

Reliability starts with user needs. It then gets translated into product requirements and incorporated into risk management. It is a critical component of design development activities and a cornerstone of testing. Further, it influences manufacturing processes, directs on-market activities, and is critical for patient benefit.

Reliability engagement for combination products begins at product design and development, continues through the commercialization of product launch, and involves continuous improvement of patients' feedback and field observations. Reliability is more than testing or a demonstration. It is an application of scientific principles to a set of decisions that impacts patients, product performance, and business success.

Definition

Reliability of a manufactured product is defined as the probability that it will perform satisfactorily for a specific period, as

Figure 1: Key reliability considerations.

Design Inputs	Design Outputs	Design Verification	Design Validation	Design Transfer	On Market
Context of Use	Reliability Budget	Reliability Protocols	Real-Life Handling Studies and/or Clinical Studies	Design Margin Analysis	Updated Reliability Model
Reliability Requirements	Reliability Assessments	Reliability Testing		Updated Reliability Model	HASS (if applicable)
Reliability Plan	Reliability Model				

intended, without failure under specific conditions. It is typically specified as a R(t) = x%, where t = time and x% = the probability of performing without failure throughout expected manufacturing, environmental, storage, and use condition variability [2].

RECOMMENDED RELIABILITY APPROACH

We recommend that reliability be implemented within the existing design control process, as the chance of successfully integrating will be improved because the organization has already aligned around that mode of design and development. Key reliability considerations are shown in Figure 1.

Design Inputs

Reliability starts at the early stage of development as user needs, stakeholder needs, product requirements, and planning documents are established. For the reliability assessment, the design input process can be separated into three parts: a) define context of use, b) describe reliability requirements, and c) document the plan.

Define context of use

Development of the requirements and plan occurs with the context of use and should consider a broad range of issues, including the intended use of the combination product, patients, users, and risk to health if the device fails to function. Risk analysis should consider the intended use and the availability of other medical interventions when the device fails to function.

Based on these factors, the level of reliability needed will vary. For example, because alternative medical interventions may not be provided to the patient quickly enough to prevent harm when the delivery device fails, the reliability for an emergency use product will need to be high.

An example of an emergency use product is an autoinjector that contains epinephrine, a medication that can save a patient's life by mitigating the risk and decreasing a body's allergic reaction (relaxing the muscles in the airways to make breathing easier). If the injector device fails, the patient may not be able to access medical care before severe harm or death occurs [3].

Depending on the drug product and therapeutic requirements, other therapies may have reliability requirements less strict than this. For example, although insulin is a lifesaving medication, the diabetic patient is more likely to be able to obtain other medical care to mitigate harm should their device fail to deliver the insulin.

Figure 2: Example of a use profile table.

Line #	Condition Experienced by Device	Cycles/RangesEstimated Over Expected Service Life
1	Shipment and distribution to user, environmental conditions	
2	Temperature cycles with user	
3	Button activitions	
4	[Use profile truncated]	

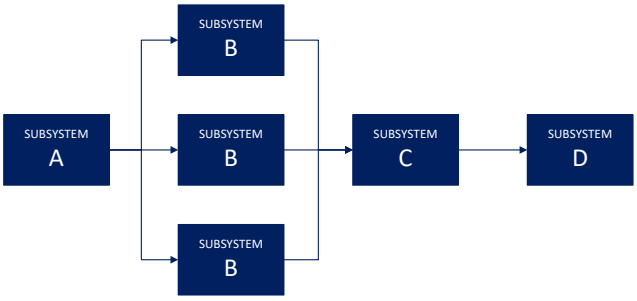
Other factors to consider for reliability requirements include the needs of healthcare providers, payors, regulators, and the manufacturer. Details of the use profile can be compiled into a use profile table (an example is shown in Figure 2).

Describe reliability requirements

It is important to correctly and completely write the reliability requirements [4]. The requirements should include the reliability target, definition of failure, shelf life (the duration of time up until the product is used or the expiry date is reached, whichever comes first), use life (the duration of time the device is used for drug delivery), and environments of use. Overall, it is critically important to avoid ambiguity and to write the specification in a verifiable manner.

Complex drug delivery systems should consider partitioning reliability requirements across subsystems (i.e., mechanical, electrical, and software) because the product requirements are partitioned into subsystem requirements. A component of reliability expectations is related to the use profile requirements.

Figure 3: An example RBD.



The use profile will define environmental impacts (patient uses and shelf life of storage), activation cycles, shipping conditions, and anticipated worst case conditions (i.e., drop, shock, etc.).

These conditions will provide an outline for reliability evaluations throughout development. The reliability requirements and reliability planning (established at the early stage of development) become the foundation for all subsequent work and should be discussed during the design input review.

Document the plan

Reliability should be included in planning documents. It can be a part of the design and development plan, or there can be a separate reliability plan for complex drug delivery systems. The reliability plan should outline activities from the feasibility phase through development and up to the commercialization phase.

It is expected that the plan will be updated to accommodate the increased understanding of the design and performance. Each device employing different architectures, technologies, and maturity of design solutions has a substantial impact on the time required to achieve suitable on-market reliability.

Design Outputs

Once the design inputs have been specified, design output activities can be initiated: a) establish a reliability budget, b) implement reliability assessment tools, and c) develop a reliability model.

Establish a reliability budget

The reliability requirement is used to evaluate product concepts and design decisions. The reliability budget is also established during this development process. The reliability budget is an apportionment of the overall reliability requirement across the various subsystems and interfaces.

For example, if a device that consists of four subsystems has a reliability target of 95% and the reliability target for each subsystem is equally divided across the subsystems, then the target reliability for those subsystems is $(.95)^{1/4}$, or 98.7%. For simplicity, this apportionment example is divided equally into each subsystem. However, the budget for each subsystem can be adjusted as needed to achieve the overall system-level reliability target.

Keep in mind that decisions about how to apportion reliability to subsystems should always consider the impact on safety and effectiveness (e.g., a safety-critical subsystem may have its own independent reliability requirements irrespective of what apportionment may permit). For example, a post-injection needle safety protection feature may require 99% reliability per a risk-based or a regulatory requirement.

Therefore, although it may be mathematically possible to allocate less reliability to this function, other external requirements may impact reliability apportionment decision-making. The overall reliability of the device is determined by the product of all subsystem and interface reliability components (see equation 1). Importantly, to achieve the reliability requirement for the device, the composite reliability of the subsystems and interfaces must be met.

Equation (1)

$$Reliability_{device} = (reliability_{subsystem,1} \times reliability_{subsystem,2} \times reliability_{subsystem,N}) \times (reliability_{interface,1} \times reliability_{interface,2} \times reliability_{interface,N})$$

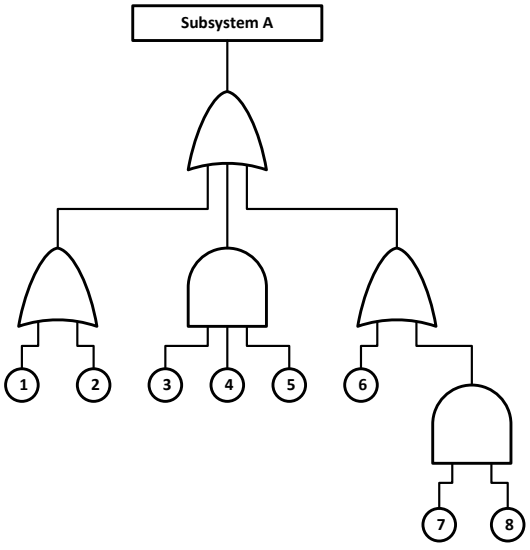
Using functional diagrams to depict major subsystems and interfaces is often useful to gain alignment on the subsystems and interfaces that warrant attention [5]. A reliability block diagram (RBD) is a diagrammatic method for showing how component reliability contributes to the success or failure of a redundant. RBD is also known as a dependence diagram. RBDs are a way of representing a system, including its subsystems and components, as a series of blocks. This is done in such a way that equipment failure rates, operating philosophies, and maintenance strategies can be quantitatively assessed in terms of the impact they are expected to have on a system [6].

An RBD is drawn as a series of blocks connected in parallel or a series configuration. Parallel blocks indicate redundant subsystems or components that contribute to a lower failure rate (see Figure 3). Each block represents a component of the system with a failure rate. RBDs will indicate the type of redundancy in the parallel path [1]. For example, a group of parallel blocks could require two out of three components to succeed for the system to succeed. By contrast, any failure along a series path causes the entire series path to fail.

An RBD may be drawn using switches in place of blocks, where a closed switch represents a working component and an open switch represents a failed component. If a path may be found through the network of switches from beginning to end, the system still works. An RBD may be converted to a success tree or a fault tree depending on how the RBD is defined. A success tree may then be converted to a fault tree or vice versa.

As the product is developed, the budget can be reallocated between subsystems as needed. However, as part of the product risk management process, efforts should be made to resolve any design weaknesses that may be contributing to difficulty meeting the pre-established budget.

Figure 4: An example of an FTA.



Implement reliability assessment tools

Once the initial reliability budget has been established, engineering analysis and testing can be used to create reliability estimates. These can then be compared to the initial reliability targets. These reliability estimates are expected to mature as the designs and analyses are refined and the amount of test data increases. During this time of engineering analysis and testing, it is important to establish an understanding of the variables that impact reliability and the robustness of the design. A first principle approach is strongly suggested to understand fundamental behaviors of the design and to establish an understanding of design margin.

An assessment can be accomplished using Monte Carlo analysis and/or direct test methods. Reliability at the component level can be initiated using available support tools [7, 8]. A first principle approach can be used to analyze components, subsystems, and systems for reliability assessment. It allows a total system approach for analyzing individual systems and components. The design team can leverage the initial reliability estimates from the prior knowledge of each similar component, even before the design team has any physical samples for lab testing and reliability assessment.

A first principle approach also offers a prescreen tool for component-level analysis and selection. Reliability testing should be done at the subsystem level during the design and development phases and ultimately at the system level for finished product analysis and assessment. Reliability growth is a useful indicator to show the reliability improvements at each version of design and development for any device-drug delivery systems. Accelerated test methods are often used to detect failures early in development as compared to real-time product assessment from a shelf-life-based analysis.

Other valuable tools should be used to probe the reliability of the design, and often these are used as part of the product risk management process. FMEA is a structured way to identify and address potential problems or failures and their resulting effects on the system or process before an adverse event occurs. In comparison, root cause analysis is a structured way to address problems after they occur.

Reliability tools to be considered for application during development include fault tree analysis (FTA), design FMEA (DFMEA), process FMEA (PFMEA), and use-related risk analysis (URRA). These tools can be used to understand failure modes and the causes of system-level failures, which can help prioritize design analysis and testing.

Fault tree analysis (FTA)

FTA is a type of failure analysis in which an undesired state of a system is examined. This analysis method is mainly used in reliability engineering to understand how systems can fail, to identify the best ways for minimized risk, and to determine a particular system-level (functional) failure. The FTA shows causes that can lead to the failure of a system using logic gates.

An FTA is especially helpful because it assesses the causes of failure using a top-down approach considering direct causes (shown with "OR" gates) and combined causes (shown with "AND" gates). An example of an FTA is shown in Figure 4. Estimating the individual probabilities of each failure mode should improve the accuracy of the budgeted reliability.

FTA has been widely used in pharmaceutical, aerospace, nuclear power, chemical and petrochemical, and other high-hazard industries. FTA is also used in software engineering for debugging purposes and is closely related to the cause-elimination technique used for the combination products of electromechanical drug-device systems.

DFMEAs and PFMEAs

DFMEAs are a bottom-up approach to evaluate device failures. The DFMEA provides an in-depth view of component and interface failures and an opportunity to incorporate mitigations early in development. This in-depth view of component performance may identify key drivers of reliability and provide justification for greater understanding and control. Similarly, PFMEAs are a bottom-up approach to evaluate process failures and provide an in-depth view of process performance that may influence reliability and provide justification for greater understanding and control.

URRAs

URRAs are another bottom-up approach to evaluate product-use-induced failures and provide an in-depth view into how the combination products are being used by patients. The URRA shows the impacts of therapeutical risk analysis on a device-drug delivery system that may influence reliability and provide justification for greater understanding and control of combination products at design-use perspectives by the targeted patients.

Process capability studies

Manufacturing processes should be assessed using process capability studies. The allowable specification ranges should be established by the preceding engineering analysis and testing. Those variables most impactful to reliability and essential performance should be flagged and considered as a part of the control strategy. The combination of design and manufacturing characterization will help define the expected robustness of the product and its ability to meet reliability requirements.

HALT and HASS

Highly accelerated life testing (HALT) and highly accelerated stress-screen (HASS) are means to understand and improve the ruggedness of the design and to create custom production screening prior to release for verification builds. HALT involves subjecting the device to fluctuating temperature and vibration loads to determine failure modes. Resolving HALT failures and extending HALT times and/or loads is an indicator of reliability growth. HASS is testing that can be incorporated in the manufacturing process to identify manufacturing defects that could lead to reliability failures.

Budget and risk management

The reliability budget should be assessed periodically during development to reflect the current level of confidence in meeting the reliability requirement. The confidence of meeting the reliability requirement is expected to increase throughout development.

There is a direct link between reliability and risk management. The reliability information is input to the device system risk assessment. Failure effects become a part of the sequence of events and the probability of failures becomes a part of the probability of harm. Specific actions to reduce the probability of failures become a part of risk mitigation.

Develop a reliability model

The culmination of these efforts is a reliability model that is used to demonstrate that the reliability requirements are met. These modeling approaches are of particular importance for single-use devices that cannot be directly tested prior to release. Although there are different modeling tools that can be used (e.g., RBDs), we recommend FTA due to its level of detail and flexibility to adapt the design, manufacturing, and control processes where necessary to achieve the reliability specifications.

Although we are not intending to delve into how FTA is conducted, we recommend the following recommendations when developing a fault tree for a drug delivery device:

- Tie the top-level fault to the definition of failure for the product.
- Tie second-level faults to drug delivery functions that are considered important for safety and effectiveness.
- Use the FMEA and other reliability assessment tools to assure that the FTA is comprehensive.
- Assure that redundancy in the FTA is handled appropriately during analysis of the FTA.

The reliability model is not intended to be a static activity and should be updated with current information as manufacturing is scaled up and continuously improved. In this way, reliability maturity can be assessed and documented.

DESIGN VERIFICATION

Reliability testing preparation begins with preconditioning of the test items, which should include environmental, storage, and use condition extremes and be done at the component and assembly level. The parameters should be consistent with the reliability specifications. Attention and careful justification must be given to the types of age acceleration, especially when using temperature and the Arrhenius equation. The age acceleration study would shorten the testing cycle; however, the materials attributes, particularly the glass transition temperature (Tg) of a specific polymeric base material, need to be considered for its accelerating study designs.

Once the polymer material has its Tg around the accelerating aging study temperature, it would introduce a ductile-brittle transition and change its material characterization and properties. The Arrhenius equation, accordingly, may not be suitable for the prediction of real-life reliability from the accelerating study results. In contrast, if a polymer material has its Tg far away from the accelerating aging study temperature, the assessment of acceleration is achieving the desired period [9].

The building of verification units provides an additional opportunity to assess the process capability (Cp) and process capability index (Cpk) values of those variables that impact reliability.

Reliability tests should assess all essential performance of the design. For multi-use drug delivery systems, the reliability at end of useful life needs to be demonstrated. In addition, multi-use test samples should be run to failure, as this will establish end of life to estimate the design margin. The reliability of a durable electromechanical pump can be targeted, for example, for reliability at a 95%, 90%, and 85% reliability level at 95% confidence at one, two, and three years of reliability performance, respectively.

In addition to demonstrating that the design meets the reliability requirements, the verification results can be used to estimate the reliability performance margin and estimate field performance.

DESIGN VALIDATION

The validation of reliability comprises several approaches and is aimed at assuring that the established reliability specifications are meeting user needs. This is conducted through analysis of available information that includes literature, risk analyses, standards, regulatory requirements, and prospective studies (e.g., human factors, real-life handling studies, and clinical studies).

Human factors summative studies provide an opportunity to evaluate how the patient responds to the physical device, instructions for use, product labeling, product displays, and alarms. Real-life handling studies are meant to simulate actual use conditions to assess performance. Clinical studies can also be used to further validate the design. Although these studies generally do

not include reliability endpoints, the information obtained should be used as part of the assessment (e.g., complaints, device failures, and use error). For example, if users interact with the device in an unexpected manner leading to a deficit of functional performance, the reliability analysis may need to be revised to account for or address the experience.

DESIGN TRANSFER

Design specifications, design margin analysis, manufacturing instructions, control strategy, risk management files, manufacturing capability assessments, and estimated field performance are the basis of transferring reliability to from research and development to operations. Operations activities related to reliability include monitoring manufacturing variability, HASS results (if applied), and product on-market field performance (to compare against expected reliability performance and to determine life cycle management activities to meet and exceed reliability expectations).

ON MARKET

Product launch after regulatory approval is a key milestone for patients to have a new medicine for the improved therapy. Healthcare providers and patients provide feedback to medical device and pharmaceutical companies. This includes their product uses in terms of the field experiences and observations of drug products, medical device for the drug delivery systems, and/or combination products. Reliability monitoring is continued from the scale-up to the technical transfer of mass production at a commercial manufacturing line.

The data from the field feedback and commercial-scale manufacturing can be used to assess both patient complaints and product failure rates. The reliability study at the on-market stage is not only to provide reliability growth assessment, but also to offer continuous improvement opportunities. The reliability outcomes of the on-market stage are the valuable knowledge and foundation that can be used to identify the critical subjects and processes for the manufacturing yield improvements and patient complaint mitigation.

CONCLUSION

A structured approach is essential to ensure a reliable combination product. Reliability begins with understanding the needs and establishing requirements. Reliability then gets embedded into planning and it should be characterized analytically and experimentally to fully understand the physics and the robustness of the design and manufacturing processes. Reliability to meet essential performance is demonstrated with preconditioned parts and assemblies.

Margin is shown by testing to end of life for multiuse drug delivery systems. Control strategies include those parameters necessary to meet reliability requirements and the risk management file contains the failure modes and probabilities of failures that are assessed throughout the product life cycle.

Reliability is more than testing or a demonstration; it is an approach that impacts patients, product performance, and business success. The goals of reliability deliverables and reliability engineering are to consistently assure trustworthy medical devices and robust combination products via drug-device delivery systems for targeted therapies.

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EMBRACING THE UNKNOWN:
QRM Strategies for Cell and Gene Therapies Facilities

By Barbara Vidière, Stephanie White, and Nicholas R. Haycocks

The pharmaceutical landscape is rapidly evolving, and cell and gene therapies (C&GT) are at the forefront of this transformation. These therapies are revolutionizing how we approach patient care, particularly in the realm of personalized medicine. However, this innovation has also introduced challenges, especially when establishing new manufacturing facilities.

One such challenge is qualifying equipment and utilities for drug manufacturing when critical quality attributes (CQAs) and the associated critical process parameters (CPPs) are not clearly defined and the relationship between quality attributes and process parameters is not yet fully understood due to an early development stage. This is a common scenario in multipurpose and new modalities facilities where future products are unknown. This raises the question: How can we ensure product quality and patient safety in such a dynamic and uncertain environment?

WHAT ARE NEW MODALITIES?

Traditional drug platforms such as small-molecule therapies and monoclonal antibodies are now established in the health care industry; new modalities that have emerged in the past 20 years include C&GTs, RNA drugs, and complex biologics [1]. C&GTs cover a broad spectrum of therapies (see Figure 1).

Cell-Based Therapies

For autologous therapies, cells are taken from the patient and genetically altered outside of the human body (in vitro) and then usually cultivated. Those cells are then reintroduced into the patient's body. These products are characterized by a one-patient, one-batch relationship (single-patient therapy). The facilities

Figure 1: Definition and pipeline snapshot by modality [2].

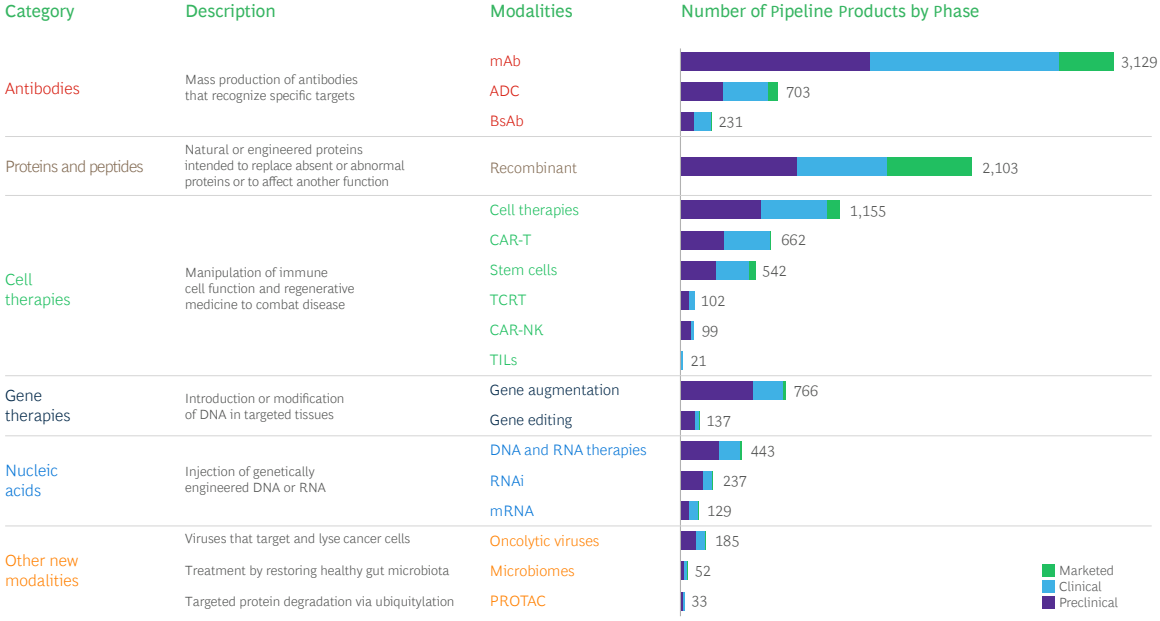
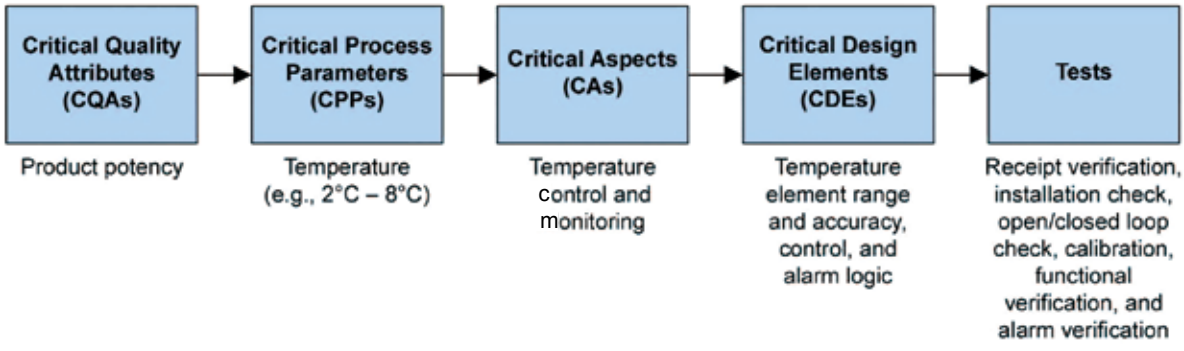


Figure 2: Relationship between CQAs, CPPs, CAs, CDEs, and associated testing [6].



are for small batch sizes and more "lab type" with small size and tabletop equipment. Also, the manufacturing facilities can be distributed (e.g., in hospitals).

For allogeneic therapies, cells are derived from human donors or other cell lines (such as induced pluripotent stem cells), with or without in vitro genetic modification, and the final cell therapy can be used to treat many different patients. Facilities for such therapeutic products consist of several small-scale operations (cell isolation, centrifugation, expansion, etc.). After cell preparation, the production process at scale starts as known from biotechnology product manufacturing.

Gene Therapies

For gene therapies, functioning genetic material is delivered, for example, with a viral vector into the human body to treat or prevent diseases. Facilities for such therapeutic products allow for bigger batch sizes and one batch is used for multiple patients. These kinds of facilities can consist of equipment or systems known from mature modalities for producing drug substances and equipment for the formulation, known as fill and finish [3].

UNKNOWN PRODUCT AND PROCESS REQUIREMENTS

Pharmaceutical companies need to get ready for their clinical/commercial manufacturing at an early stage of development when it is not clear which product or therapy will make it successfully out of the development pipeline.

A platform approach can help companies target multiple modalities. Platform facilities are adaptable to various processes and products. This is to support the production of new modality products or therapies and offer flexibility and a faster response to pipeline demands and changing market demands.

System, product, or process requirements are often not fully established, particularly in cases like ongoing development, multiproduct/platform approaches, and contract manufacturing facilities, as well as research and clinical manufacturing settings. With new modalities, further challenges arise with new or non-standard equipment. In these instances, a foundational design is often based on a set of general process requirements or performance criteria, which are shaped by both the user's needs and regulatory standards, such as ISO 5/Grade A conditions for aseptic filling with unidirectional airflow.

IDENTIFYING CRITICAL PARAMETERS

ICH Q8(R1), ASTM E2500-20, and the *ISPE Baseline® Guide Volume 5: Commissioning and Qualification (Second Edition)* describe how quality aspects from pharmaceutical development, or defined CQAs, are translated into the requirements of a manufacturing process, with the associated CPPs, to consistently deliver quality products [4–6]. Those requirements are an integral part of the quality risk management (QRM) application, which forms the basis for commissioning and qualification (C&Q).

ICH Q8(R1), ASTM E2500-20, and the *C&Q Baseline® Guide* categorize these aspects into:

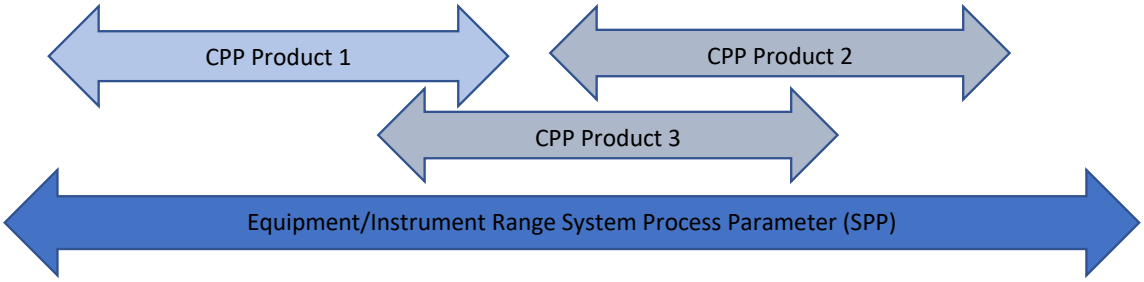
- CQA: A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality [4]
- CPP: A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality [4]
- Critical aspects (CAs): Functions, features, abilities, and performance characteristics necessary for the manufacturing process and systems to ensure consistent product quality and patient safety [5]
- Critical design element (CDE): Design functions or features that are necessary to consistently manufacture products with the desired quality attributes [6]

The *C&Q Baseline® Guide* illustrates the relationship between these aspects using automated temperature control and monitoring of process steps as an example (see Figure 2).

FROM UNKNOWN CQAs AND CPPs TO GENERIC SYSTEM QUALITY ATTRIBUTES AND SYSTEM PROCESS PARAMETERS

In scenarios where traditional CQAs and CPPs are not defined,

Figure 3: Establishing SPPs.



it may be beneficial to use a more generic term than CQA or CPP. The concept of system quality attributes (SQAs) and the associated system process parameters (SPPs) offers a strategic alternative. SQAs are the physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired system product quality. The system product is the output from that system. SPPs are the parameters whose variability has an impact on an SQA and therefore should be monitored or controlled to ensure the process produces the desired quality.

The SPPs represent the full instrument and equipment range and are not specific to one product or manufacturing process. SQAs and SPPs are derived by gathering and analyzing a range of information, including data from existing documentation and the insights of subject matter experts (SMEs). An alternative terminology would be equipment quality attribute and equipment process parameter.

A foundational design is often based on a set of general process requirements or performance criteria, which are shaped by both the user's needs and regulatory standards, such as ISO 5/Grade A conditions for aseptic filling with unidirectional airflow.

Also, where the equipment maybe be used for multiple products, there may be variation in the specific CQAs and CPPs for the products. The use of the broader terms SQA and SPP, which can encompass all the CQAs for the products that will be processed on the equipment, is then beneficial. This can also help explain why there may be more attributes or parameters used for equipment qualification than there are in a product filing, for example.

Figure 3 illustrates the establishment of SPPs where development and process SMEs provide expected or likely CPPs while going through different steps of a system risk assessment (SRA). In the absence of a CPP system, qualification will cover the full equipment/instrument range.

SYSTEM RISK ASSESSMENT

The process of identifying and validating SQAs and SPPs is greatly enhanced by using risk assessment methodologies, as detailed in the *C&Q Baseline® Guide*. This framework provides a structured approach to assess and document the SQAs and associated SPPs, assessing the potential impact of each SPP on the overall process and product quality. This approach is especially valuable when we deal with new technology or with complex systems, which is a challenge often associated with C&GT facilities.

Developing an understanding of the operational sequence of the process helps identify the SQAs and SPPs. It also helps build the knowledge of processes, systems, and equipment. By employing this method, manufacturers can ensure that even in the absence of traditional CPPs, the manufacturing process remains robust, controlled, and capable of producing high-quality products. This adaptation not only aligns with regulatory expectations but also facilitates a more agile and responsive manufacturing environment. The SRA methodology is demonstrated in the following example. We have picked this example because everyone might know washers and therefore can easily follow the concept.

As shown in Table 1, the SQA is general in the example—as the C&Q of the washer confirms that the system delivers the specified requirements. Cycle development and cleaning validation will confirm that the system is fit for its intended use. The same strategy can be used for process equipment with general parameters applied; these may apply to all utilization of the system or be specific to individual products.

The SRA considers the risks to the output of the system based on the proposed design and anticipated controls (design and procedural). The SRA then determines if the controls are adequate to provide an acceptable risk profile for that system.

EFFICIENT USE AND APPLICATION OF THE SRA

The process suggested to ensure efficiency is as follows. First, develop the initial draft of the SRA with a small group—system/process SME, facilitator, and quality; this makes the process quick. Then review the draft with a larger team, including operations and maintenance. This provides the benefits of letting the site staff get an understanding of the equipment and associated process early and ensuring that their localized experiences with similar systems/controls are incorporated.

Next, the project team can agree on the timing of this initial assessment. For a novel design or site-built system, it may be useful to do this early. It can be done later for established designs. The initial assessment is an engineering tool that may be reassessed if the design changes. It can only be completed when the design is

Table 1: Washer SRA example based on *ISPE Baseline® Guide Volume 5: Commissioning and Qualification (Second Edition)* template [6].

Row No.	Operational Sequence	Process Description	SQA/Regulatory Requirement	SPP	Impact on SQA	How SQA Can Be Impacted	Design Controls	Recipe Parameter	Associated Alarm	Procedural Controls	Comments	Residual Risk
1	Pre-loading inspection	Check to ensure unit is visibly clean and dry	N/A	N/A	None	N/A	N/A	N/A	None	The operational procedure will describe how to conduct the preoperational checks	None	N/A
2	Prerinse	Initial rinse to remove bulk residue and wet dry materials	No loose material, surface wetted	Temperature, flow rate/time (volume/pressure)	Direct	Particulate not totally removed	The system has low flow rate and high and low temperature alarms; the system will only move to the next step after the process has been completed for the defined time with no alarms, trend pressure/flow rate data	Yes	Low flow rate and high or low temperature	The operational SOP will describe the action required in the event of an alarm	None	Low
3	Detergent wash	Initial cleaning stage	Purity (loosening and putting material into suspension/solution with the cleaning material)	Detergent concentration (conductivity), temperature, flow rate/time (volume/pressure)	Direct	Variation from the validated cleaning process	The system has low conductivity, low flow rate, high and low temperature alarms; the system will only move to the next step after the process has been completed for the defined time with no alarms, trend pressure/flow rate data	Yes	Low conductivity, low flow rate, and high or low temperature	The operational SOP will describe the action required in the event of an alarm	Conductivity is used to determine the detergent concentration	Low
4	Interim rinse	Rinse to remove detergent and removed surface contamination and particulate	Purity (rinsing the wash solution from the unit)	Temperature, flow rate/time (volume/pressure)	Direct	Remaining surface material contamination of particulate	The system has low conductivity, low flow rate, high and low temperature alarms; the system will only move to the next step after the process has been completed for the defined time with no alarms, trend pressure/flow rate data	Yes	Low conductivity, low flow rate, and high or low temperature	The operational SOP will describe the action required in the event of an alarm	Conductivity is used to determine the detergent concentration	Low

SOP: standard operating procedure

approved (ready to be constructed) to ensure that the final proposed design is assessed.

The early risk assessment is essentially an engineering tool and may be stored in accordance with project documentation standards. The final assessment of the approved design is a quality document. It should be stored in a qualified document management system along with the associated summary report.

The benefits of this strategy are that a) if high risks are observed, the team has the right expertise to critique it and propose changes to reduce the risks; b) following this approach simplifies a complex

process into an easier step-by-step process; c) upon completion of the SRA there is a better understanding of how the system works and the associated risks; and d) there is a list of quality-critical alarms and instruments with the supporting rationale for their categorization.

FACILITY FIT TO PRODUCT

Upon completion of the development phase and finalization of the product and process requirements, it is crucial for the project team to review the initially defined generic requirements. This is to ensure that they align with the final requirements. This also includes an assessment of whether the actual CQAs are included in the SQAs and the SPPs include the CPPs. If there is a gap, an update of the SRA with the confirmed CPPs and CQAs added will be required, including any additional qualification required.

The process of verification relies heavily on engineering specifications and is executed by experts in the field. This includes conducting engineering runs and assessing the operational range and precision of equipment, ensuring it can meet future product and process demands. Evaluating equipment suitability often involves two key aspects: confirming that risks to product quality are sufficiently managed and determining equipment performance levels that are acceptable to both the user and the SME.

Should there be any discrepancies between the initial design and the final requirements, adjustments are made under change control and subsequently qualified. This ensures that the system remains compliant and effective [6].

CONCLUSION

In scenarios lacking defined product and process requirements, a generic set of process requirements is used as a design basis, aligning with regulatory expectations. Verification is performed by experts, focusing on equipment performance capabilities and risk to product quality. As per the *C&Q Baseline® Guide*, equipment qualification covers the operating capabilities of the equipment—these must be assessed against finalized product and process requirements once they are defined to confirm that the equipment is suitably qualified.

In conclusion, the qualification of equipment and utilities in the absence of defined CQAs and CPPs demands a flexible and knowledgeable approach. By leveraging existing data, engaging with experienced SMEs, and focusing on patient safety and product quality, the pharmaceutical industry can successfully navigate the uncertainties associated with the manufacturing of C&GTs and other drug modalities. This approach not only ensures compliance with regulatory standards but also upholds the commitment to delivering safe and effective therapies to patients.

The qualification of equipment and facilities in the absence of defined CQAs and CPPs demands a flexible and knowledgeable approach.

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INDEX

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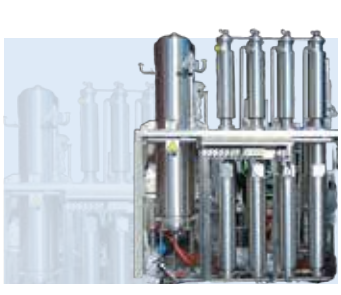

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