PHARMACEUTICAL ENGINEERING®

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MULTIPLE MODALITIES IN MANUFACTURING

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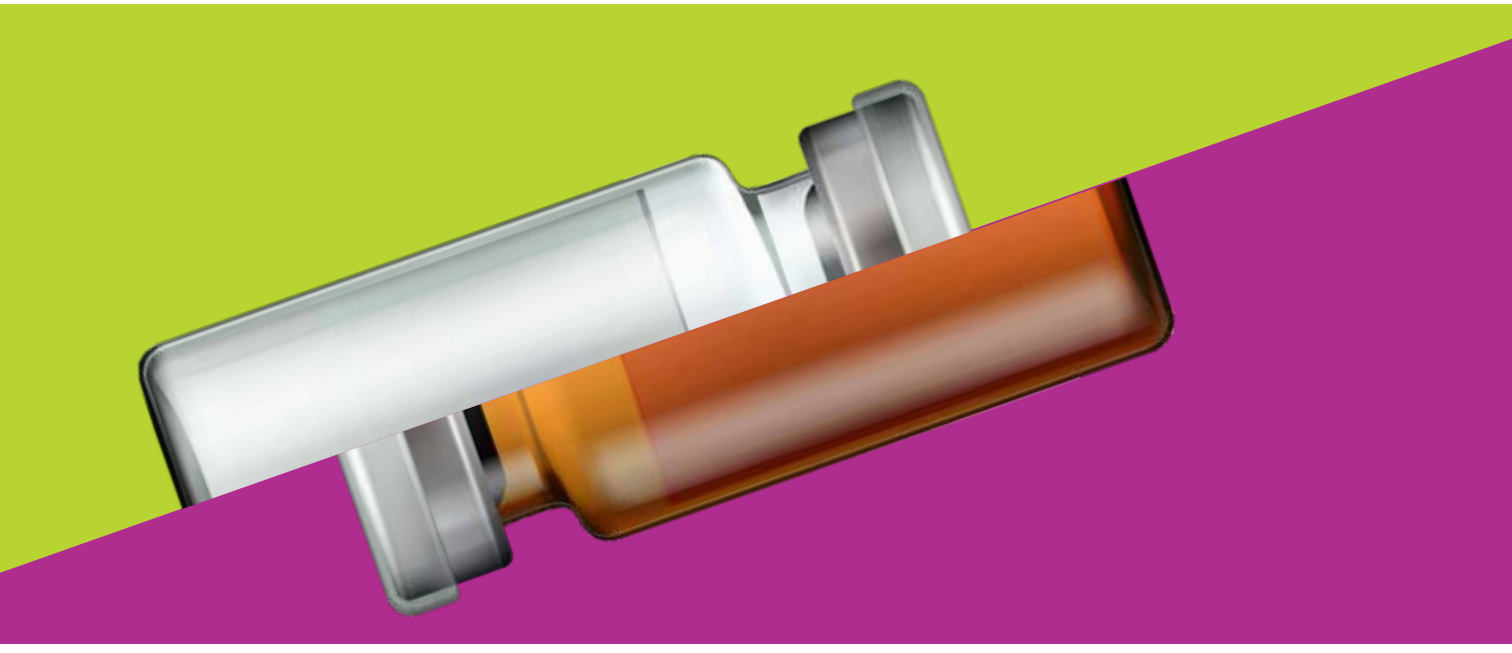

ON THE COVER Multiple modalities and flexible manufacturing for biopharmaceuticals are represented by the two sides of the cover—and the two cover stories that address these key topics.

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By Jörg Zimmermann


Jörg Zimmermann

An Exciting Year

Has it really been a year since I began my term as Chair of the ISPE International Board of Directors? It seems like yesterday, and now the 2022 ISPE Annual Meeting & Expo in Orlando, Florida, has come and gone, and Mike Rutherford is the 2022–2023 Chair.

It has been an honor for me to serve our Society and membership in this position, and we have progressed a number of important initiatives.

ONE ISPE AND STRATEGIC PLAN REFRESH

A lot of effort went into the One ISPE initiative, which defines the relationship between ISPE international and the Chapters and Affiliates. Eighty percent of Chapters and Affiliates have embraced the concepts that improve the interactions, promote growth of membership, and incentivize the involvement of students in ISPE, which is a topic that is very close to my heart. Reintroducing the liaison role of International Board members with individual Chapters and Affiliates has given us direct lines of communication to the mutual benefit of the International Board and the local groups. This interaction was used to further improve the ISPE Charter, and the proposed changes will be implemented into the 2023 version. We are confident that this will be accepted by all Chapters and Affiliates. Thank you very much to all involved: this was not an easy task!

The Board embarked on a refresh of the strategic plan with a hybrid workshop following the ISPE 2022 Facilities of the Future Conference in February. We defined the path forward for 2023–2025 after a final round of consultations with the Board advisors in July. Tim Howard, who was Chair of the International Board from 2017–2018, helped

ISPE is shaping the future of our industry to the benefit of patients.

by moderating the sessions. Thank you, Tim! As you could see in the overview that we gave at the Annual Meeting, ISPE is taking a much more confident position, moving from "connecting pharmaceutical knowledge" to "shaping the future of the pharmaceutical industry." ISPE is a true independent voice of the industry, accepted by the regulators worldwide, and as such, we are shaping the future of our industry to the benefit of patients.

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Figure 1: Board dinner on Castle Waldburg near Ravensburg. From left to right: Mike Rutherford, Vivianne Arencibia, Beth Billman (Scott's wife), Scott Billman, Jeff Biskup, Joanne Barrick, Nina Cauchon, and Jörg Zimmermann.

Figure 2: ISPE Board members visiting Vetter: pictured is a robot application for adding syringes to trays in secondary packaging. From left to right: Vivianne Arencibia, Chris Chen, Scott Billman, Dirk Margosch, Georg Singewald, Christian Herrmann, and Joanne Barrick.

AN EXCITING YEAR

What else did I do as Chair this year, in addition to running the Board and its meetings plus sitting on numerous committees? I started the year by attending the ISPE Ireland Affiliate's Annual Event and gave the 2020 ISPE Member of the Year award to Eamon Judge from Eli Lilly. Shortly after that, I spoke for ISPE at an event in Italy.

2022 brought back in-person international conferences, starting with Facilities of the Future in February, followed by the 2022 ISPE Aseptic Conference in March, which I have been deeply involved with for almost 15 years.

Everybody has been saying it, but it is true: it was wonderful to be back in person and to interact face-to-face, not just listen to presentations online. The buzz continued with the 2022 ISPE Europe Annual Conference in Madrid, which saw excellent discussions with regulators from around the world. I participated virtually in the ISPE Japan Affiliate Annual Meeting in May, spoke at the "Developments and Innovations in the Pharmaceutical Industry During the Pandemic Period" seminar of the ISPE Turkish Affiliate in September in Istanbul, and attended Board meetings both at the ISPE Germany/Austria/Switzerland (D/A/CH) and the Netherlands Affiliates. Within the D/A/CH Affiliate, the local community of practice for sterile products and processes (which I belong to) organized a workshop on ATMPs in Leipzig. We had a very intense interaction, including participation from the Paul Ehrlich Institute—a German federal agency, medical regulatory body, and research institution for vaccines and biomedicines—and had the unique opportunity to make site visits to view two commercial cell-based products: autologous cartilage cell therapy at Co.don AG and CAR-T cell therapy at the Fraunhofer Institute for Cell Therapy and Immunology IZI.

The highlight for me was the Board meeting that we held at Vetter in Germany. Most Board members were able to attend in person, and we had very productive Board and Executive Committee sessions. In addition, we took the Board on tours of Vetter's facilities for sterile products and through all the production steps: compounding to fill-finish to automated visual inspection and secondary packaging. Board members were most impressed by the state-of-the art technology and the use of robots in the processes. Of course, there was also time for some sightseeing, including the Zeppelin-Museum in Friedrichshafen and a dinner on a historic boat on the Bodensee.

LOOKING AHEAD

What I could experience first-hand in all these interactions is the great collaboration between ISPE members from around the globe, all bringing their unique viewpoints, perspectives, and cultural backgrounds. This almost limitless networking is what has motivated me in my time as Chair, and I thank you all for this. I also thank my fellow Board members and the fantastic ISPE staff that is making sure that our Society is functioning, striving, and growing.

What lies ahead for ISPE is another year of great conferences that will help shape the future of the pharmaceutical industry, including the Aseptic Conference in March, the Europe Annual Conference in Amsterdam, home of the European Medicines Agency, and the 2023 ISE Annual Meeting & Expo in Las Vegas. For me, it is not time to say goodbye, as I continue as past Chair during 2022–2023 and in various other functions within ISPE from chairing the program committee for the Aseptic Conference, as a reviewer for PE magazine and member of the *Pharmaceutical Engineering*® Committee (PEC), and many more activities.

It has been a great honor for me to serve as Chair and certainly a highlight in my professional career. And on top of it, it has been fun, following my credo: the more you put in, the more you get out of it. I know that the Society is in good hands, and I wish us all the success that we as ISPE deserve. Stay safe and stay in touch.

Jörg Zimmermann is Vice President, Vetter Development Service, External Affairs, at Vetter Pharma-Fertigung GmbH & Co., and the 2021–2022 Chair of the ISPE International Board of Directors. He has been an ISPE member since 2006.

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By Heather Bennett-Kelley


Heather Bennett-Kelley

TIMES OF TRANSITION

We don't often take time for reflection, except when in times of trial or transition. I recently needed to update my resume, which forced some reflection on what I had done of note since my last update. This reminded me that we are coming up on the end of the year, a transition to new leadership and new goals, and maybe even cleaning up our toolboxes.

Over the last year, we have been getting used to a variety of ways of getting back to "normal" and what they look like, though in some ways we may be forever changed. Our students have had a mixed bag of experiences. Online exams might be easier for some classes, but how does an online laboratory for engineering or science compare to the hands-on experience?

With 2,279 student members in 2022 and 667 recent graduates, there may be an unknown gap to fill with experience and team interaction. The workforce gap will initially be the responsibility of managers and mentors: they must pay attention to the needs of those they shepherd into the future and help build a bridge so those future industry leaders can get to the knowledge they need. The Emerging Leaders (EL) Community of Practice (CoP) will also be here to help with the identified knowledge gaps with tools, sessions, and reengagement for recent graduates. Those graduating need to keep eyes and ears open and ask lots of questions. I have learned a lot just by absorbing information from the environment around me.

GLOBAL SUPPORT

As an international organization, ISPE tries to support all corners of the globe, although there are still improvements to be made. ELs are in every region, with most of our Chapters and Affiliates having student members. Historically, many ELs have been active in the Americas (North America and South America) and in the European Union (EU). Both regions have formal ISPE EL leadership, and starting this year, we have official regional leadership for our EL groups in Asia Pacific (APAC). Welcome and thank you to those EL leaders who are stepping up: Jaywant Pawar, Wong Jianwei, Raine Fernandez, and Onwara Wongwatcharamongkol! I want to bring special recognition to Canada, as ELs there have been more active and stronger in the last couple of years. Nice job, Diego Legrand and Amanat Kaur! In North America and South America, there is continued growth and reinvention with the Annual Meeting Hackathon, initiatives to connect Chapter and Affiliate EL leaders, and new programs to reach future members. Our EU EL group continues to be a source of inspiration, with the in-person Hackathon at the ISPE Europe Annual Conference in Madrid, Future Leaders Day, and more to come. Great energy leading the charge, Emer Somers and Robin Schiemer!

As an industry, we are ever evolving, improving, and innovating. These are all helped along by our continued collaboration.

COLLABORATION CONTINUES

As an industry, we are ever evolving, improving, and innovating. These are all helped along by our continued collaboration. With the local, regional, and international Hackathons, best practices are shared to better serve the coaches and participants in ones that follow. The latest Hackathon took place at the ISPE Annual Meeting & Expo in Orlando, Florida, on 29 October. We also have global initiatives like those to get more EL representatives writing articles for *Pharmaceutical Engineering*®.

Our younger members are the future of our industry, so we need to support and start listening to them now to help shape the future for the better. I have been honored over the last year to serve as the International EL Chair and help push some of these ideas along. I look forward to what we will accomplish in the next year with Zen-Zen Yen from the D/A/CH Affiliate as our EL chair for 2022–2023.

Heather Bennett-Kelley is Project Manager/Engineer at ACCO Engineered Systems and the 2021–2022 International Emerging Leaders Chair. She has been an ISPE member since 2007.

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By Vivien Santillan


Vivien Santillan

WOMEN IN PHARMA® EXPANDS IN ASIA

The inclusive nature of ISPE promotes diversity in thought, providing pharma professionals of all levels, geographic, and cultural backgrounds the opportunity to share their knowledge and collaborate across borders. ISPE's Women in Pharma® (WIP) is a testament to this.

Over the past few years, we've seen this professional community deliver quality programming for personal and professional growth, creating social impact opportunities as we work collectively without biases to shape the future of the pharmaceutical industry.

GROWTH IN ASIA

After more than two years of online conferences, meetings, and webinars, Asia is slowly opening its borders once again and seeing a growth in WIP initiatives. ISPE's Malaysia Affiliate launched its WIP group on 29 July 2022. It was the first in-person gathering for the Affiliate since the pandemic began in 2020. For many, it was an opportunity to reestablish personal connections and dive back into traditional networking. To add to the excitement, the launch coincided with ISPE Malaysia's General Membership Meeting and the celebration of the Affiliate's tenth anniversary.

The event introduced attendees to the WIP community, including an outline of the mission and a lineup of upcoming WIP activities for the local community. ISPE Malaysia hosted a WIP Workshop on 9 October that focused on personal development and roundtable discussions for thought exchange and networking. The Affiliate is committed to growing this initiative and helping women develop the confidence to push past geographic and cultural barriers as they pursue excellence within their careers.

The ISPE Singapore Affiliate's conference has always proved to be an anticipated event in the Asia-Pacific pharmaceutical industry, with over 1,000 participants attending virtually and in person. WIP again was present at the conference, hosting a lunch and roundtable discussion. Present at each table was a WIP leader from the Asia-Pacific region who facilitated the conversations and allowed time for each participant to share their experiences on assigned table topics.

The presence of WIP in every ISPE Affiliate and Chapter helps us bridge gender, cultural, organizational, and geographic boundaries.

The ISPE Asia-Pacific Council, which represents leaders of all ISPE Affiliates in that region, and its WIP community leaders staged its first Think Tank webinar in November, a concept initiated by the ISPE Women in Pharma's International Steering Committee. Industry professionals discussed how Asia can equip its workforce to embrace and influence trends and evolving technologies in the pharmaceutical industry.

ANNUAL MEETING AND BEYOND

At the 2022 ISPE Annual Meeting and Expo in Orlando, Florida, WIP welcomed members and other attendees on 30 October with a workshop, "Career Connections—Developing Your Personal Brand." The immersive, hands-on event focused on evolving as a leader and taking LinkedIn profiles to the next level. A dinner on 31 October focused on networking and camaraderie, and a 1 November morning yoga session helped provide a refresh for the final full day of the conference.

The presence of WIP in every ISPE Affiliate and Chapter helps us bridge gender, cultural, organizational, and geographic boundaries, allowing us to enjoy a safe space to discuss our goals, aspirations, and ambitions. The global collaboration and reach of WIP allows our members to build important relationships that transcend the industry.

It's been a successful 2022, with various milestones worth celebrating and a growing community focused on grand breakthroughs and ideas adapted to a local mindset and needs. We look forward to what's in store next year and having continued conversations that will help "Women Shape the Future of Pharma." We'll see you next year!

Vivien Santillan is Regional Director for Asia, Novatek International; Immediate Past President and VP of the ISPE Philippines Affiliate; Past Chair of the ISPE Asia Pacific Council; and a member of the Women in Pharma® International Steering Committee. She has been an ISPE member since 2012.

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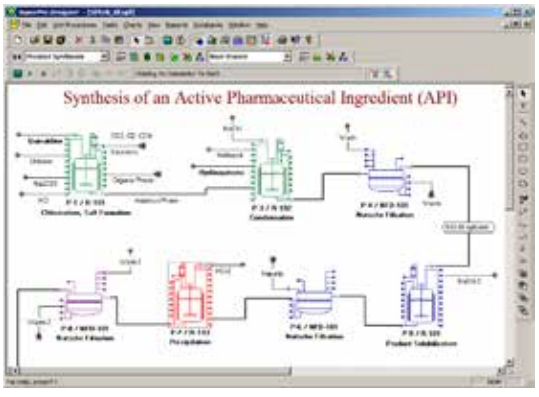

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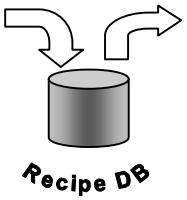

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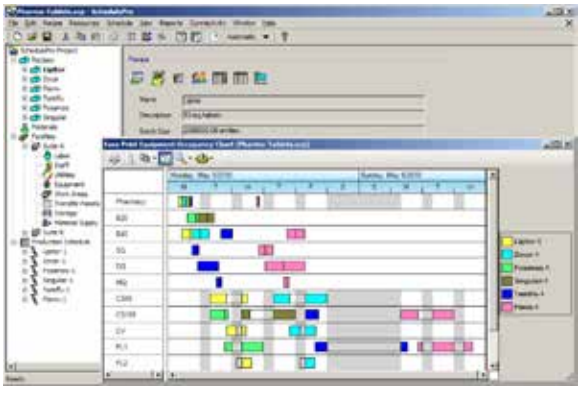

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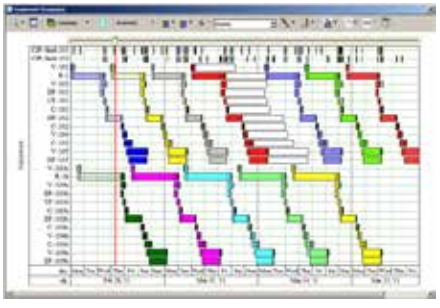

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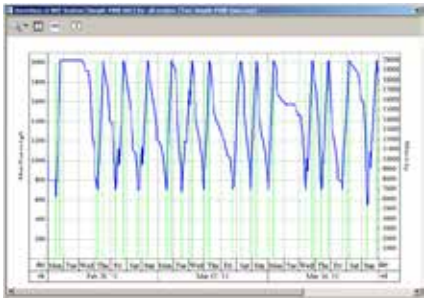

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ACCOMMODATING MULTIPLE MODALITIES in the Same Facility

By Tom Bannon and Alfred Penfold, MBA, CEng, MIET

Many organizations are evaluating how advanced therapy medicinal products (ATMPs) and other traditional modalities may be combined within the same facility or within a newly constructed agnostic building. This article outlines a broad framework to evaluate different types of modalities that may be accommodated concurrently in a new or existing facility and then uses a case study to explain how the approach may be applied to an existing facility.

ATMP facilities are different from conventional pharmaceutical facilities that process other traditional modalities, such as vaccines and monoclonal antibodies (mAbs), and often require heightened segregation and smaller footprints. A new framework is proposed to accommodate multiple different modalities, with six major steps: (1) identify the business need; (2) identify possible modalities and the scale of manufacturing; (3) complete data gathering, which includes outlining segregation principles and reviewing GMPs and industry best practices; (4) develop a risk profile, which includes developing viral and toxicity risk progression, a risk matrix, and a facility features matrix; (5) perform risk assessments, and then update the risk profile and facility features matrix as needed; and (6) complete a segregation strategy for a future multimodality facility.

BUSINESS NEED, POSSIBLE MODALITIES, AND MANUFACTURING SCALE

When a business need is being developed, it must be determined which modalities are of interest to the organization, how their manufacturing might be accommodated, and at what scale they should be manufactured. These modalities may include cell therapies, gene therapies, tissue engineering, nucleic acid synthesis, vaccines, and mAbs.

COMPLETE DATA GATHERING

Outline Guiding and Segregation Principles

Next, broad guiding principles and key segregation principles should be determined as part of the data-gathering step. Key segregation principles are required for existing, proposed, and potential new modalities. Some example principles and assumptions that should be determined and agreed upon relate to facility design, manufacturing area capacity, defining process steps, safety requirements, and infrastructure.

Facility design: All new facilities will be designed and built to current industry best practices using the latest available technology. More specifically, closed systems, isolators, and single-use technology are to be adopted as appropriate. Alternatively, an existing facility will be agile and can facilitate early-stage processes received through acquisition. These processes may still have open aseptic steps. The manufacturing spaces should be able to accommodate the full journey through to process closure.

Manufacturing area capacity: The capacity of the individual manufacturing areas should be established. This may include answering questions like: Is the facility aimed at commercial manufacturing? Is the facility designed only for volumes to support clinical trials?

Defining process steps: The core processing steps for each modality should be defined. If processes are not already fully defined, the assessment will need to make broad assumptions in terms of processing steps and possible technologies to be used. However, future assessments will be required to either confirm or modify some of the assumptions based on actual product and process information. Any decisions or recommendations are ultimately determined by quality risk management (QRM) principles and practices, as well as relevant GMPs.

Safety requirements: Similar to GMP requirements (see next section), all safety requirements should be agreed upon. This should include biosafety, hazardous agents, and any occupational hygiene considerations. This will require broad assumptions and understanding of some of the modalities being considered. For the purposes of brevity, this article doesn't discuss safety. However, it is noteworthy that often safety and GMP requirements drive complementary results.

Infrastructure: All available infrastructure that will be used should be considered; for example, shared quality control laboratories, utilities, and waste handling.

Review Guidance

Regulations

The assessment must outline which GMPs are being used. For example, an assessment for a facility primarily focused on US and EU markets would only consider GMPs and regulations from EudraLex and the FDA. However, with an agnostic building, the breadth of regulations that must be considered can be extensive.

The following list includes regulations that can be considered, but it is by no means exhaustive: EudraLex Volume 4 Parts I, II, and IV and Annexes 1 and 2 [2–6]; EU human tissues and cells directive 2004/23/EC [7]; FDA CFR Title 21 Parts 211, 600, and 1271 [8–10]; FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing–Current Good Manufacturing Practice [11], and Guidance for Industry: Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues and Cellular and Tissue-Based Products (HCT/Ps) [12]. Also, regulatory agencies may refer to a corresponding pharmacopeia such as USP 800 [1].

These regulations contain some requirements that relate to specific modalities. For penicillins and cephalosporin (highly sensitizing materials) and for pathogenic organisms (i.e., Risk Group 3 or 4), dedicated and self-contained facilities that include air-handling equipment and process equipment should be employed [3]. In addition for penicillins specifically, air-handling systems for manufacture, processing, and packing shall be completely separate from those for other drug products for human use [8].

> It is possible to develop a basic set of guidelines to accommodate multiple modalities within the same facility once that facility's main purpose has been established. But to do so, it is important to understand what boundaries may exist.

For materials of an infectious nature (Risk Group 1 and 2) or with high pharmacological activity or toxicity (such as certain steroids or cytotoxic anti-cancer agents), dedicated facilities are not required. However, these do require that validated inactivation and cleaning procedures able to reduce product residues to amounts below defined safety thresholds are established and maintained [3]. For live vaccines, manufacturing in a separate wing of a building is acceptable, with the appropriate controls to prevent cross-contamination of other products within the building [9].

If the manufacturing site produces medicinal products other than ATMPs, based on a risk assessment, ATMP manufacture may need to take place in a dedicated area of the facility. Special precautions should be taken in the case of manufacturing activities involving infectious viral vectors (e.g., oncolytic viruses): these activities should take place in a segregated area [4].

Industry Best Practices

In addition to regulations, there are many industry best practices that further interpret GMPs. Some practices are recorded in industry best practice guides and can include ISPE Guides, Baseline Guides, and Good Practice Guides, and Parenteral Drug Association (PDA) technical reports [13–15]. Other industry best practices may not be formally documented in regulations or industry best practice guides, but should also be investigated as part of the assessment.

The assessment may also identify perception concerns. Owner companies—they own both the product and the manufacturing facility—will have freedom to set their own segregation principles. For example, a contract manufacturing organization (CMO) that may have differing client modalities adjacent to each other will want a segregation policy that is acceptable to a wider customer base.

Table 1: Levels of potency and toxicity risk.

Low Risk	Medium Risk	High Risk	Very High Risk
Caustic, acids, medias, salts, and other commodity chemicals (< OEB 2) For example: • Chemical involved in mammalian bioprocessing • Formulation buffers for therapeutic proteins	Manufacture of cytotoxic products (≤ OEB 3)[2] For example: • Vial or syringe filling of an ADC These cytotoxic processes have specific guidelines within regulations	Manufacture of cytotoxic products (> OEB 3)[1,2] For example: • Conjugation of ADCs These cytotoxic processes have specific guidelines within regulations	Sensitizing agents with specific requirements mentioned in regulations For example: • Beta-lactams • Penicillin • Cephalosporin • Hormones (high potency)

[1] Carcinogenic, mutagenic, and teratogenic materials need to be considered on a case-by-case basis. In general, any use of these materials will be in small volumes and will receive dedicated risk assessments.

[2] OEB classification to include assessment of carcinogenic, mutagenic, and reproductive (CMRs) toxic substances.

Internal Corporate Standards

The manufacturer may have internal corporate standards that address how any manufacturing asset should be designed and operated irrespective of location or markets served. These standards should be listed prior to commencing this exercise.

DEVELOP A RISK PROFILE

It is necessary to develop a risk profile for different modalities to establish some key segregation principles. The risk profile should also be based on regulations, industry best practices, and the company's own risk profile and practices. In this article, two separate risk profiles have been developed: chemical potency and toxicity risk, and biological (viral and microbial) risk.

In both cases, the category of risk ranges from low to very high. Each risk profile category contains a definition with examples. Profiles also form the basis for the proposed segregation principles in the case study. Very-high-risk profiles align with clear regulatory expectations for dedicated manufacturing facilities.

Chemical Potency and Toxicity Risk Progression

In Table 1, the authors have captured some types of biotechnology modalities that relate more specifically to potency and toxicity with respect to risk profile: low, medium, high, and very high risk. The potency ranges from occupational exposure band (OEB) 1 to 5, with 5 being the highest potency. The final risk profile is determined by the toxicity and potency data, containment strategy, and technology used.

Cleaning of shared equipment for multiproduct facilities is a major concern in GMPs. In addition, the HVAC, utilities, material, waste, and personnel flows all must be assessed. The toxicity assessment feeds into all of these considerations. The QRM approach focuses on how cross-contamination can occur across modules through HVAC, utilities, material, waste, and personnel flows. For example, if an isolator is capable of containing an OEB 5 process, the operator may only be exposed to microgram levels. Therefore, a risk assessment will look at how many micrograms of material can contaminate a different process. More specifically, it will ascertain if the level of theoretical cross-contamination exceeds the permitted daily exposures (PDE) for a product in another module.

Risk-Based Manufacture of Pharmaceutical Products

A useful guide for performing the risk assessments is the ISPE *Risk-Based Manufacture of Pharmaceutical Products Baseline Guide,* often referred to as Risk-MaPP [13]. The second edition of the ISPE guide received regulatory input from the FDA and other agencies and was published in 2017. The guide has a useful workflow for assessing multiproduct manufacturing and advocates the QRM approach. The four key areas in the Risk-MaPP approach, in the order of decreasing risk, are as follows: mix up, retention (carryover), mechanical transfer, and airborne.

Mix up: Mix up refers to the general tracking and control of materials. For example, materials may be closed on delivery to dedicated suites, i.e., not opened adjacent to other materials. Robust wipe-down procedures and industrial hygiene practices apply at all times. Control storage may be necessary in the warehouse, along with segregated waste flow as required.

Retention (carryover): Modules and associated equipment may be dedicated to a product with no carryover risk from equipment cleaning. If using single-use technology, then there is minimum risk from cleaning. In-suite cleaning facilities may be required. Inactivation methods for active pharmaceutical ingredient (API) and organisms or DNA and RNA may also be required in the suites. All potential leaks, spills, and material air lock (MAL) operations will need to be risk assessed.

Mechanical transfer: Mechanical transfer often refers to operators and how they may become contaminated with product and then inadvertently contaminate another person, product, or both. The use of isolators and/or closed processes—along with a suitable gowning policy and layout (e.g., unidirectional flow of personnel, product, and waste, as required)—helps reduce the risk of contamination. Dedicated procedures for spills or deactivating an operator gown when soiled may be required.

Airborne: A "sink" or "bubble" concept for airlocks will limit the airborne transfer to corridors. There may also be a requirement for a segregated HVAC unit with or without terminal HEPA filtration on the supply and return.

The Risk-MaPP approach is a useful guide that will help risk assess products and processes based on QRM principles.

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High-Potency and High-Toxicity Products to Be Excluded

From a regulatory perspective, the only products that are to be excluded are sensitizing agents, including penicillins and cephalosporins (beta-lactams); potentially genotoxic compounds; and potentially OEB 5 compounds where the risk assessment indicates the compound cannot be adequately controlled. Manufacturing of (or with) high-potent compounds in adjacent suites may be possible with the appropriate engineering controls and risk assessments based on toxicity data.

Biological (Viral and Microbial) Risk Progression

There is not a single document for assessing different modalities where varying levels of viral and microbial risks are present equivalent to the ISPE Risk-MaPP guide for chemical potency and toxicity risk. The PDA publications "Virus Contamination in Biomanufacturing: Risk Mitigation, Preparedness, and Response" [14] and "Points to Consider for Microbial Control in ATMP Manufacturing" [15] are very useful publications that should be read as part of this exercise.

These documents outline practical engineering and procedural controls, which need to be used for mix modality manufacturing; however, these documents are written from the perspective of an adventitious viral or microbial contamination from external environments and raw materials. Similarly, closed processing risk assessment methodologies are available (such as the ISPE *Biopharmaceuticals Manufacturing Facilities Baseline Guide*), but these are written in the context of multiproducts within mAb or therapeutic protein where viral risk is uniform across the processes considered.

Therefore, a science- and risk-based approach from first principles must be taken to assess biological risk. QRM tools commonly used in the biopharma industry should provide good guidance on what is acceptable. Table 2 captures the types of modalities that relate more specifically to viral and microbial organisms with respect to risk profile, and provides an approximate risk ranking of viral and microbial risks. It can be used as an initial guide until the actual level of risk is determined by a more comprehensive risk assessment. A site biosafety committee will be required to help categorize the risk grouping of hazardous organisms.

Table 2: Levels of biological (viral and microbial) risk.

Low Risk	Medium Risk	High Risk	Very High Risk
1. Risk Group 1 (biosafety) organisms 2. Processes in which the likelihood of the presence of viruses or propagation of viruses is low For example: • Mammalian cell culture using characterized non-human cell lines This includes established and controlled practices, including the use of controlled animal-derived media components	1. Risk Group 2 (biosafety) microbial organisms 2. Processes in which the likelihood of viruses or propagation of viruses is increased For example: • Allogeneic cell therapy (prescreened cell stock) • Replication incompetent viral vector/gene therapy • Viral antigen vaccines • Animal tissue These processes have specific guidelines within regulations	1. Risk Group 2 (biosafety) viral organisms 2. Processes in which human virus are likely to be present For example: • Live vaccine manufacturing • Autologous cell therapy • Replication competent viral vector/gene therapy • Blood/plasma processing These processes have specific guidelines within regulations	1. Risk Group 3 and 4 (biosafety) organisms 2. Processes in which particular pathogens are produced 3. Bioprocessing spore-forming organisms For example: • Live BSL-3* or BSL-4 organisms These processes have specific requirements within regulations

* BSL = Biosafety Level

Understanding the Biological Risk Categories

Viral and microbial products have been classified into the following broad categories (excluding very high risks that are not in scope): low, medium, and high risk (very high risk is not discussed here). Low risk includes mAb processes where characterized murine cell banks are used, BSL-1 bioprocesses, and fill finish of traditional therapeutic proteins. These are low-risk processes because the presence of viral material is low and if it is present, it is likely to be of animal origin and are not known to propagate in humans. Medium-risk processes include those that use viral vectors, human cell lines where an adventitious human virus will replicate, or animal tissue that may have viruses but those that are not known to propagate in humans. High-risk processes are typically those where human viruses may be present. These include human-donated material and culturing of live human viruses.

Based on this risk categorization, the low-risk and high-risk processes are easier to distinguish. Medium-risk processing covers a broad middle ground and careful consideration of the underlying science will be needed in the corresponding risk assessments. It may result in the process being reclassified as either low or high risk. In general, it is possible to conclude that medium-risk viral and microbial processes may be accommodated within the same facility, provided there is data to support a comprehensive risk assessment.

The following have been categorized as medium-risk processes: human cell lines, allogeneic cell therapy (screened cell stock), processing of proteins extracted from animal sources (e.g., heparin, insulin); replication incompetent viral vector/gene therapy; and viral antigen vaccines. The overarching principle is that although human cells are often being cultured, their origin is known or, better still, characterized. Therefore, in principle, there are no viruses present, but care is taken for adventitious viruses. The level of screening of donors will be key to the risk characterization of this type of processing. If inadequate screening is performed, this may be recategorized as high risk. Similarly, viral vectors, gene therapies, and viral antigen vaccines have viral

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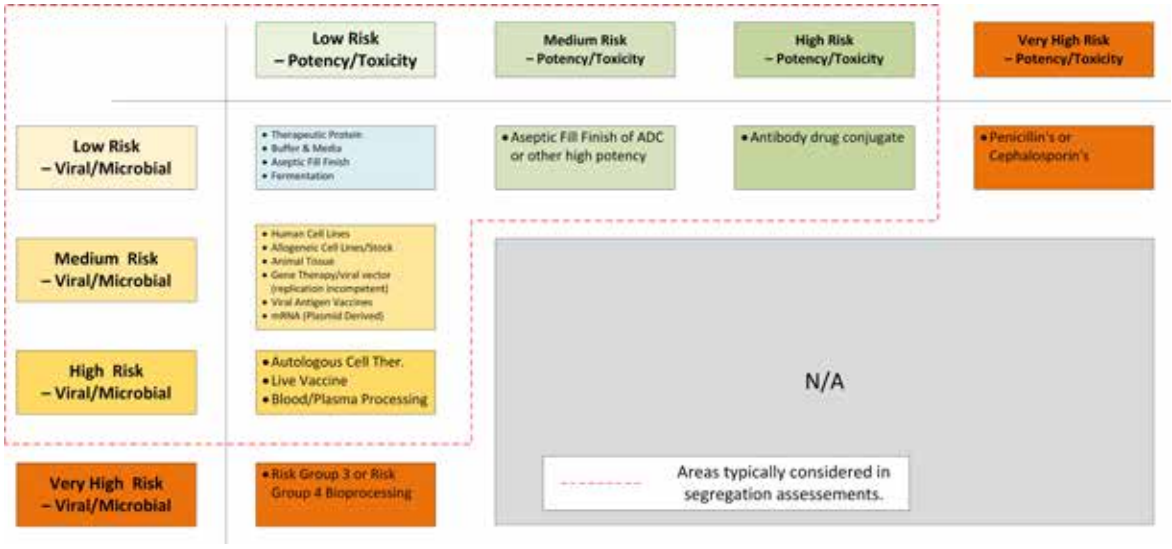
Figure 1: Risk matrix showing the risk hierarchy for potency and toxicity risks and viral and microbial risks taken together.



properties. However, they have been genetically engineered to be replication incompetent outside of the bioreactor environment. Many of these examples fall into the category of ATMPs. Similar to the high-potent compounds, there may be different and conflicting perceptions that will need to be managed. It may be more prudent to consider fully segregating these types of processes.

High-risk viral and microbial processes will invariably face regulatory or perception concerns. For example, CAR-T manufacturing acknowledges that patient cells arriving into the facility may harbor infectious biohazardous organisms. As a result, dedicated material flows for patient material arriving and leaving the facility is common. This will be difficult to achieve in many facilities unless it is initially included in early design stages. Similarly, live vaccine manufacturing and any blood processing would require the acknowledgment of a high possibility or intentional presence of human viruses.

Biological Products to Be Excluded

From a regulatory perspective, the only products that should be excluded are spore-forming microorganisms, due to their persistence in the cleanroom environment. Processing products at BSL-3 and BSL-4 should be excluded and there is strong consideration against manufacturing of live vaccines.

Develop a Risk Matrix

Once the risks for each category have been determined, a risk matrix should be completed to align the team with the escalating risks from differing modalities (see Figure 1). Although this is an important step in the mix modality risk assessment and the risk matrix is a useful guide, the assessment team must evaluate it themselves to calibrate their own risk appetite and ensure that particular modalities of interest are properly characterized. It cannot be sufficiently stressed that the underlying science of a particular modality should be understood when characterizing the matrix info. New modalities or variations of existing modalities are constantly appearing, so evaluating the matrix for each new project is important.

Develop a Facility Features Matrix

An agnostic facility is a pre-invested facility that has been designed to accommodate a range of manufacturing processes. It is typically constructed with the core internal process area left unconstructed. This allows a rapid buildout of the manufacturing area once a business need is identified and greatly reduces deployment times.

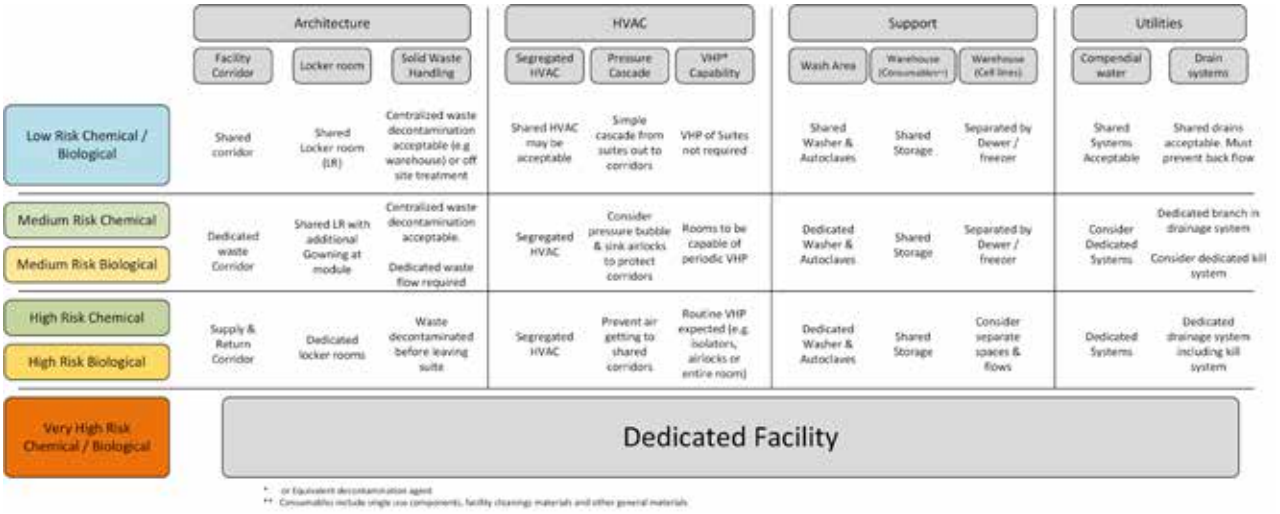
Because of this, an agnostic facility may have multiple manufacturing spaces, each capable of being fitted out for working with a particular modality. These spaces may be spread across a specific manufacturing level or across multiple floors.

When assessing the adjacency of different modalities, key considerations will include the equipment and closure design (primary containment), whether a single or separate supply and return corridor is required, and whether physical or temporal product segregation is needed. Secondary containment factors such as the HVAC design, pressurization regime, and airlock design will also need to be considered. The segregation of air between manufacturing spaces will be input into any analysis.

It should be noted that if one of the spaces is assigned a high-risk modality and the others are low risk, many of the engineering and architectural controls to minimize cross-contamination will be driven by the highest risk modality.

As a generalization, the following will apply when choosing to add a higher-risk modality: increased secondary containment

Figure 2: Sample facility features according to risk group.



(e.g., airlocks and pressure cascades); progressively stricter personnel, material, and waste flows with consideration for supply and return corridors; potential for dedicated locker rooms; increased reliance on closed processing, barrier technology for open steps, and physical segregation compared to temporal segregation; and less reliance on procedures and training.

Determine Requirements by Risk Group

Once the core risk groups have been developed, the assessment team must now assess the corresponding facility features for each risk group. This exercise should propose the various facility features. Figure 2 outlines a high-level example, giving some cases of escalating design features and possible inflection points where facility systems can no longer be shared.

Figure 2 is simply the starting point for a GMP risk assessment for the proposed modalities the manufacturer intends to operate adjacent to each other. Once this matrix has been developed, GMP risk assessments should be performed with a cross-functional team to ensure that the level of segregation is sufficiently robust.

PERFORM RISK ASSESSMENT AND COMPLETE SEGREGATION STRATEGY

Risk assessments should be performed for potential failures that may occur in various manufacturing areas and any connected pieces of infrastructure (e.g., corridors, utilities, and HVAC). These risk assessments should be supported with typical process descriptions and a very high-level layout based on the features described previously. The study should perform risk assessment on possible failures that may lead to cross-contaminations in the manufacturing spaces. The following are examples of typical failures:

Failure 1: Operator wearing a soiled gown, after a spill, is returning to the locker room and passes by personnel entering other manufacturing spaces.

Failure 2: Waste containers are not sealed correctly and leak waste material onto the floor of the corridor.

Failure 3: HVAC failure in manufacturing space #3 causes risk of air mixing between manufacturing spaces, which leads to a cross-contamination.

There are many failure modes that can be considered and these examples represent only a selection. The risk assessment may conclude that some of the escalating features outlined in need to be adjusted to reduce the risk associated with various failure modes.

Once the risk assessment is complete, the risk profile and facility features matrix should be updated as needed, with this process being repeated as appropriate. Finally, a segregation strategy for a future multimodality facility should be completed.

BIOLOGICAL MANUFACTURING CMO CASE STUDY

This case study references a CMO whose primary business is focused on biological products. This CMO has constructed a large agnostic facility with pre-invested infrastructure, e.g., clean utilities. The facility consists of multiple manufacturing floors with a just-in-time (JIT) warehouse and support areas, including waste management on the ground floor. Material is supplied to each floor via an elevator from the ground floor JIT warehouse, with further elevators included for separate waste streams. Each floor is designed to accommodate multiple modalities' manufacturing

Figure 3: Facility layout designed to accommodate manufacturing processes for multiple modalities.

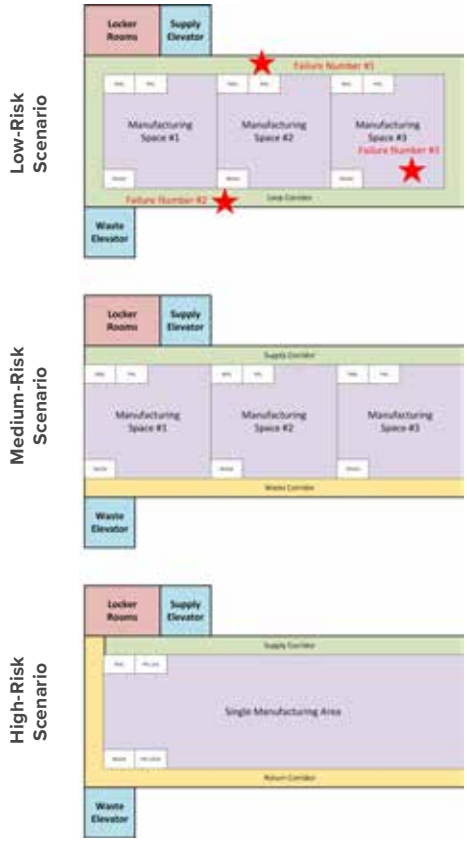
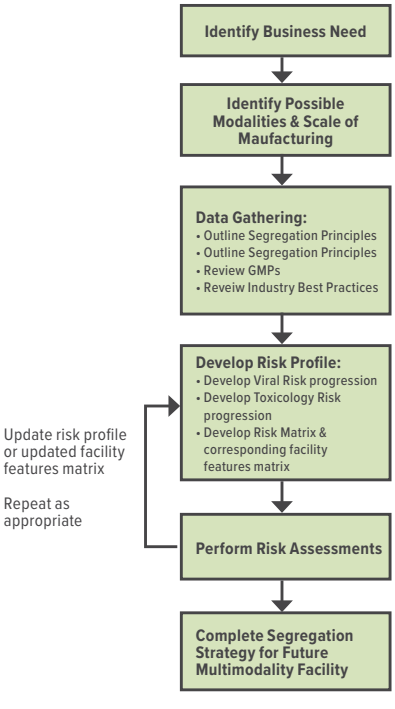


Figure 4: Multimodality segregation study process.



processes (see Figure 3). The manufacturer concluded that modalities of the same risk group will be shared within manufacturing floors. This will allow common approaches to personnel flows, gowning, and airflows.

For low-risk modalities, these can share a loop corridor because waste material can be easily contained prior to leaving the manufacturing space. It was determined that all manufacturing spaces should have unidirectional flow within the space, but the corridor can be one corridor. It must be noted that the loop corridor does permit the majority of waste and material flows not to cross due to the position on the corridor of the materials lift and waste lifts. Once personnel have entered a manufacturing space, they will not be permitted to enter other space without returning to the locker room (which is access controlled using swipe cards). The manufacturer decided that each room has its own dedicating air handlers with terminal HEPA filters and the common corridor has its own air handler. Because the risk is low, the pressure cascade is simply from the suites to the common corridor.

The medium-risk modalities considered (viral vector, viral antigen vaccines, and allogeneic cell therapy) will require a waste corridor because the risk of cross-contaminating with viral material was considered too high. Similarly, badge access control would limit personnel movement between areas. Each room has its own air handler dedicated to each suite. However, the pressure cascades: the supply-side airlocks operate as pressure sinks to prevent air getting to the common supply corridor where operators from different suites can mix.

High-risk manufacturing modalities are isolated and multiple higher-risk modalities do not share locker rooms. It was determined that one manufacturing process should use the entire floor and not have multiple higher-modality processes adjacent to each other. If the floor was too large for a desired modality (e.g., autologous CAR-T), then the process should be accommodated elsewhere in a dedicated building. As there is only one suite on a floor, the HVAC strategy can be simpler, with a dedicated air-handling strategy for this floor.

Naturally, the preceding overview is quite simplified for the purposes of this article, with many details excluded for brevity. The key point is noting which higher-risk scenario engineering controls must increase to mitigate higher risk. A completed assessment should conclude with architectural layouts, including area classifications, personnel, materials flows, and HVAC zone and pressurization drawings. The assessment must also include warehouse and quality control areas that will share areas and functions.

CONCLUSION

It is possible to develop a basic set of guidelines to accommodate multiple modalities within the same facility once that facility's main purpose has been established. But to do so, it is important to understand what boundaries may exist. For example, there is clear regulatory guidance on which modalities require separate facilities. The approach outlined in this article identifies some

basic guiding principles, working within the regulations that apply, and develops a basic risk profile to determine how best to accommodate the different modalities given any facility constraints that may exist (see Figure 4).

The proposed six-step approach is designed to help understand which modalities may be suitable for a given facility, and how those modalities may be accommodated. Although each facility may be different, with a different set of recommendations, the described approach can be used during early feasibility. It is worth noting that, as with all early feasibility studies, it is important to reassess the outcome and recommendations as more concrete process information becomes available and as QRM is applied.

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SUPPORTING CELL AND GENE THERAPY

Through Multimodal and Flexible Facilities

By Stephen Judd and William Whitford

Cell and gene therapies (C&GT) have unique needs in manufacturing suites that differ from those for classic product biopharmaceuticals. Facilities must be created with flexibility in mind, able to run multiple products and production types to remain viable.

Cell and gene therapies are part of advanced therapy medicinal products (ATMPs) and offer great potential for regenerative medicine, including ways to treat and cure a variety of acquired and inherited diseases. C&GT sponsors currently address numerous emerging pharmaceutical entities, as well as manufacturing platforms, modes, and scale. This can require special manufacturing considerations less common in well-established biopharmaceuticals, such as enzymes or monoclonal antibodies (mAbs).

These considerations include processing safety (e.g., levels of biological, chemical, and solvent handling safety), multiple scaled-out batches, and the requirement for end-to-end aseptic processing. C&GT is still a relatively young field and therefore continually evolving, which has resulted in diverse research pipelines, entity types, manufacturing technologies, clinical trials, and commercial scale facility designs. For all these reasons, C&GT have unique needs or require special considerations in manufacturing suites beyond those for classic products. This article discusses types of facilities and design considerations for C&GT.

FLEXIBLE FACILITIES

In many C&GT processes, success is dependent on the ability to efficiently deliver new genetic material to the target cells. This can be challenging for many reasons: it can be difficult to estimate the size and number of polynucleotides to transfer, the efficiency of the vector in the particular cells addressed, the scale of production required, and whether a patient's immune system will respond to vector particles as a microorganism. For such reasons, a number of viral vector (VV) systems are currently in place, with many other gene-vector systems in development.

This diverse landscape and process-specific supply-chain issues are driving the need for highly flexible facilities that may run multiple products and/or production modes. The traditional, rigid facility design approach associated with the well-defined processes of classic products are not meeting the needs of the C&GT manufacturing field. Tables 1 and 2 exemplify an aspect of this diversity in only the most popular current VV methods. Each vector modality presents distinct values in the current range of therapeutic entities, clinical indications, cells to be modified, and evolving manufactur-

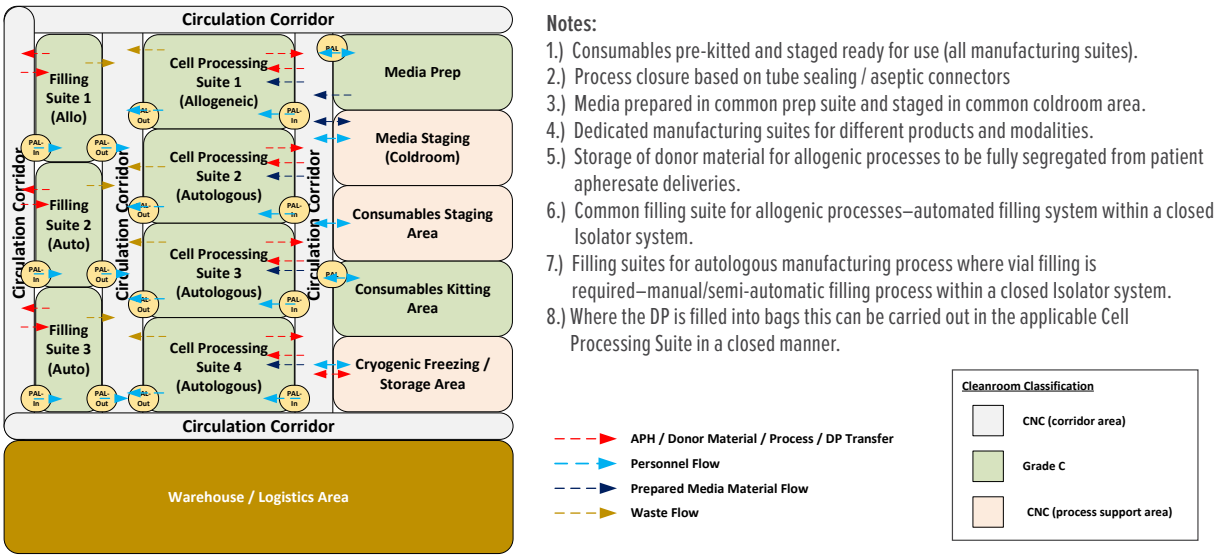
Table 1: Viral vectors by type in percent of worldwide assets (c. 2021) [1].

Viral Vector Modality	Percentage of Worldwide Assets (%)
Adenovirus	5
Adeno-associated virus	82
Lentivirus	10
Other	3

Table 2: Summary of viral vectors currently being used in clinical trials (c. 2021) [2].

Viral Vector Modality	Number of Clinical Trials	Percentage of Total in Use (%)
Adenovirus	575	50
Adeno-associated virus	315	28
Lentivirus	250	22

Figure 1: Adjacency diagram for an autologous and allogeneic multimodal facility.



ing methods. The most successful vectors to date have been adeno-associated virus (AAV), adenovirus (AdV), and lentivirus (LV). AAV vectors are commonly associated with in-vivo gene therapies; AdV vectors show promise for vaccine applications including oncolytic virotherapy; and LV vectors are commonly associated with such ex-vivo approaches as CAR-T cell therapy.

The two sources cited for Tables 1 and 2, while contemporary to each other, show a slightly contrasting view of the current VV landscape. This highlights yet another of the challenges for sponsors of new C&GT products: The facility and suite design must be flexible to support many existing future unknowns, including the following:

- Particular products successfully licensed
- Number and type of processes validated
- At-scale manufacturing operations and flow
- Timeframe of launch and capacity demand

MULTIMODAL FACILITIES

The requirements for a multimodal facility can be complex and variable. They depend on such factors as the particular focus of the manufacturing company and whether that company is an owner-manufacturer or a contract manufacturing organization (CMO). Multimodal C&GT facility designs are outlined next, followed by an overview of flexible facility design criteria.

CAR-T Manufacturing Facility

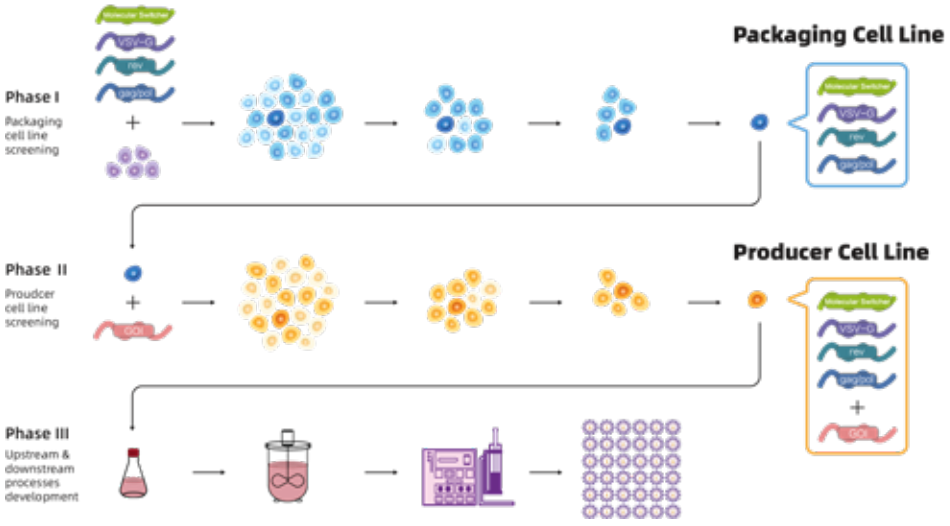
Although there is significant and exciting progress in a variety of cellular therapy designs, all those currently approved for commercial production involve autologous (cells from the patient) CAR-T cells. Autologous therapies are effective, but present significant limitations in sample logistics, manufacturing facility throughput capability, and variability in the performance of cell samples from different patients. Allogeneic therapies (employing a master cell bank from donor cells) offer the greatest potential for a scalable, off-the-shelf solution, provided that the risk of identified complications can be overcome.

Although there are many advances in cell isolation, activation, transduction, and expansion technologies, currently popular autologous approaches demand a significant footprint for the manufacturing facility. Production of ~3,000 patient batches per year using in excess of 100 pieces of specialist equipment requires a facility of ~4,500 m² for an autologous therapy [3]. In comparison, Allogene Therapeutics, for example, has indicated that their lead candidate for an allogeneic therapy (ALLO-501A) may produce up to 20,000 patient doses annually for a fraction of the equipment and manufacturing batches required for an autologous equivalent [4].

This potential inspires many CMOs and owner-manufacturers with multiple candidates in clinical trials to maximize the potentials for their facility by engineering the ability to manufacture either autologous or allogenic therapies, or both in parallel. The current basis for design requires all individual therapies (each having a distinct gene vector component) to be manufactured in dedicated suites. To reduce risk of product cross-contamination and protect chain-of-identity requirements, suites associated with autologous operations also require segregation from allogeneic operations. However, support functions such as consumables kitting and media preparation can be shared across such multimodal facilities.

The adjacency diagram in Figure 1 illustrates one potential layout approach for this type of facility. Unidirectional personnel flow should be maintained through the BSL-2 (or higher) spaces to ensure containment of the suite through a bubble/sink arrangement on (personnel airlock) PAL-In/PAL-Out. Product and waste flows should be separated with dedicated transfer

Figure 2: Development of a stable producer line for lentivirus production. (Source: Eureka Biotechnology [6]. Reprinted with permission.)



routes to prevent risk of cross-contamination. However, dedicated supply and return corridors are not required. The circulation corridors can be designated as bidirectional common spaces, provided that procedural controls are in place to ensure that all in-process product and biohazardous waste materials are properly contained before transfer.

Viral Vector Manufacturing Facility

Both CMOs and owner-manufacturers with different production modality candidates under consideration require maximal flexibility to facilitate manufacturing of the different modalities without the need for expensive and continued facility modifications. Although there are a number of new gene transfer technologies in development, current factors in flexible facility design requirements for VV manufacturing include the following:

- Production batch strategy: Will the facility operate on a campaign basis with only one product manufactured at a time, or will different products be manufactured in parallel?
- Production modalities: Will there be distinct, unique production processes and equipment employed either sequentially or concurrently?
- Host cell line requirements: Will the manufacturing processes all be based on mammalian cell lines or will insect cell lines also be employed?
- Cell culture mode: What are the requirements for adherent, suspension, and/or continuous culture?
- Method of production: Will the manufacturing operations support the popular transient transfection (TT), the newer stable producer lines (SPL), or both?
- Yield vs demand vs capacity: Will the culture volumes and bioreactor style be similar or divergent between products/modalities?

If manufacturing will operate on a campaign basis, then many aspects of facility design can potentially be comparable to those of a single product facility, with a rigorous changeover protocol required to sanitize manufacturing areas. If the manufacturing operations are to include both insect and mammalian cell lines, and it is only feasible for the company to construct a single manufacturing train, then such a campaign-based approach is required.

If manufacturing with different modalities is to occur concurrently, in parallel, then segregation requirements will depend on whether the approach to viral production follows a TT or SPL approach. Figure 2 depicts the process development roadmap associated with an SPL. It is a regulatory requirement that different VV types are manufactured in segregated manufacturing suites [5]. The TT approach requires introduction of plasmids to the N-stage production bioreactor to produce the loaded viral particle. For an SPL, the vector and transgene instructions are integrated into the host cell genome, allowing induction of the complete viral product once the required host cell density has been achieved.

With the TT approach, where different products employ a similar host cell line, it is possible to operate the host cell expansion train as far as the N-1 stage in a ballroom area, with multiple batches being manufactured in the same manufacturing suite in parallel on the basis of closed processing. The product-specific aspect is introduced at the N-stage bioreactor step through the addition of the plasmid cocktail. Segregation of the manufacturing suites from this step forward is required for parallel manufacturing of the different products. With an SPL, as both the vector instructions and new genetic material are already present in the host cell seed stock, end-to-end segregation of the manufacturing process is required for the parallel manufacturing of different products.

Another factor to be considered is the design of downstream processing (DSP) suites and spaces. Maximizing the throughput of a multi-train upstream processing (USP) area will likely result in the USP trains operated in a staggered fashion. The DSP operations

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here often take between four and seven days and, if the Takt (cycle) time associated with the USP operations is greater than this, then only one DSP train will be required to ensure full "temporal segregation" between batches. A rigorous changeover protocol will then be required to sanitize the DSP area before processing of the next batch. However, the most flexible and streamlined design of the DSP area is to have the full DSP train in a single ballroom suite. This approach can be facilitated by ensuring that, through one of a variety of means, fully closed process operations are maintained throughout the DSP train.

An additional factor to consider is adventitious virus safety; closed processing will guard against the potential ingress of other product- or process-related agents. This is an important factor in many cases because, due to the size of the viral particle, only an AAV process can include a virus filtration step. Therefore, if a multi-vector mode facility will potentially be manufacturing AAV in a process that includes a virus filtration step, it may not be practical to segregate the pre-viral and post-viral areas.

The risk mitigation measures here therefore need to be designed into the manufacturing operations, and not based upon their physical segregation. Figure 3 presents a series of adjacency diagrams that depict the potential approach to multimodal facility design based on the preceding discussion.

Viral and Non-Viral Modalities Facility

Critical preprocessed ingredients associated with C&GT manufacturing operations, such as plasmids for TT processes and LV for CAR-T cell therapies, can present supply-chain issues if provided by third-party vendors.

One approach to protecting the integrity of this supply chain is to bring the operations for these key modalities in-house. For example, if the therapeutic product is a CAR-T cell therapy based on a TT modality, then having a facility supporting plasmid and lentivirus vector manufacturing, as well as the cell therapy process, would provide significant advantages.

Such a facility would require three defined and fully segregated manufacturing areas: plasmid manufacturing is E. coli, microbial fermentation based; LV vector manufacturing is animal cell, virally positive based; and autologous cell therapy (CT) processes involve blood product directly from the clinical patient. Designs ensuring the lowest risk of cross contamination between these different manufacturing areas are essential, and achievable, provided there is sufficient space associated with the new facility.

The approach to segregating the different areas may be through either vertical or horizontal integration. Having a vertically integrated facility, with the different manufacturing areas on different floors, has the advantage of requiring a smaller overall footprint, which can be beneficial if the site boundary area is limited. A horizontally integrated facility, with all manufacturing on the same floor, can potentially optimize the material, product, and waste flows.

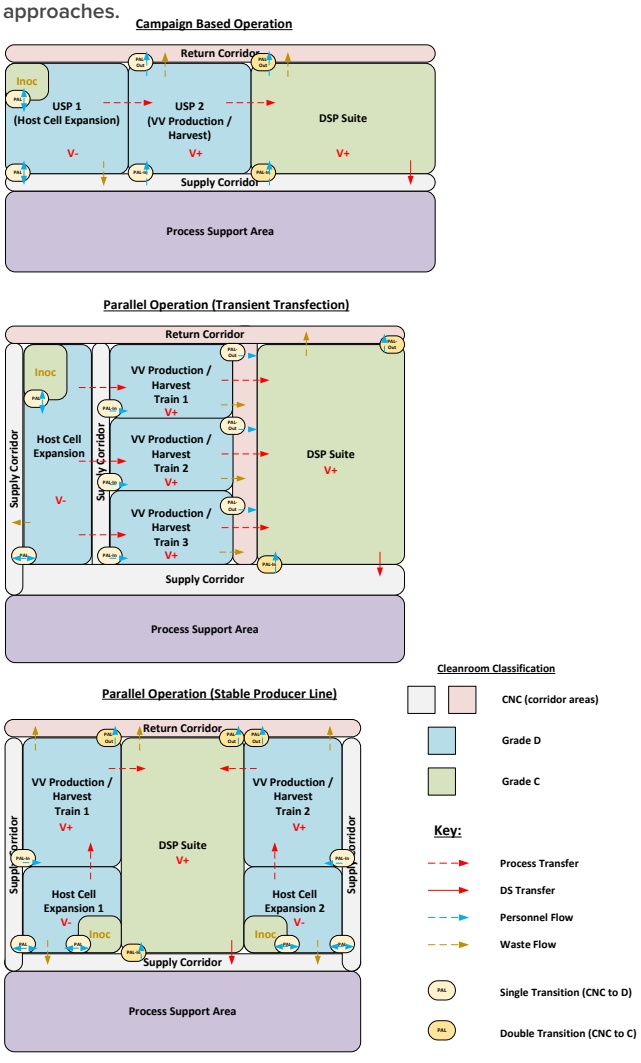
FLEXIBLE FACILITY DESIGN CONSIDERATIONS

Demands for flexibility derive from requirements to support diverse or emerging therapeutic entities, processing modalities, equipment design, security of supply, and manufacturing scales. Some key factors associated with the design of such a flexible facility include:

- Suite design for multiple process train support
- Suite design for modular and smart automation [7]
- Equipment capable of multiple, diverse applications
- Manufacturing train design for ease of modification and changeover
- Minimization of cleanroom grading, supporting ease of operation, divergent closed operations, and streamlined activities when relocating equipment
- Facility design to support compliance of the most stringent biological, chemical, and solvent handling safety requirements of the modalities envisioned

Beyond facility design and process flows, C&GT production equipment is becoming commercially available to support the development of multimodal and flexible facilities. Both systems

Figure 3: Adjacency diagrams for VV multimodal facility design approaches.



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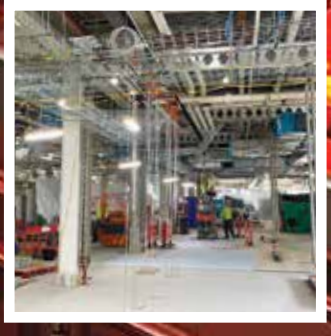

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and equipment are emerging to support modularity of operations; ballroom application; and ease of scale-up/down and scale-out/in. Respective equipment is engineered with sample number, production volumes, flow rates, and/or turndown ratios to enable variability in capacity.

Single-Use Technology

Single-use technology (SUT) is typically used across C&GT facilities, and it offers many advantages that support process/product flexibility. These advantages include inherent process closure, as well as reduced cross-contamination risk, suite classification, service requirements, and time in changeover.

Product contact components associated with SUT are disposed of after use, eliminating the requirement for the cleaning and sterilization of equipment, as well as for related validation studies. SUT facilitates fully closed process operations using aseptic connectors, tube welding, and aseptic disconnect methods (i.e., tube sealing or crimping). Fully closed operations enable the downgrading of cleanroom classifications, concurrent disparate manufacturing processes, and streamlined equipment move in/move out activities.

Unidirectional personnel, in-process product, and waste flows are required for the V+ (BSL-2 or greater) areas, illustrated in Figure 3. Transfers between single-use systems (SUS) require specific suite adjacencies compared to stainless steel facilities, where hard piped transfer lines can potentially be run indefinitely across a facility. These unidirectional flow demands, combined with SUS suite adjacency requirements, can add complexity to facility layouts when considering how transfer tubes need to run between suites, particularly where multiple USP suites all feed into a single DSP suite. Ideally, a transfer tube should run through the wall between directly adjacent suites. Where this is not possible, the transfer tubes can potentially be brought at a high level over short distances through a transition corridor, with isolatable tubing pass-throughs installed in each cleanroom wall.

Emerging Standards and Equipment

Emerging standards in design elements, such as physical connectors and service specifications, are occurring in such areas as data transmission and curation that support process-related analytics, equipment maintenance, and process monitoring and control. Although more can certainly be done, a growing number of equipment and instrumentation specifications can be vendor agnostic. Intra-vendor plug-and-play equipment connectivity is currently available for some processes, and there is less need for customization of some assets.

Equipment is being designed to support flexibility in the scale-out or reconfiguration of a process. Individual components, skids, and modules can be added, removed, or rearranged with minimal customization. These equipment design elements also allow a system to operate in a different geographic setting or service conditions than its initial establishment and validation. Especially when employed in the growing number of podular suites, this promotes ease of the worldwide transport of such processes.

Utility Panel Design and Optimization

Partially automated SUT-based equipment is "plug-and-play" and relatively straightforward to move in and out of a manufacturing suite as equipment train modifications are required. Ease of equipment changeout without the need for suite modifications is supported by the design and set-out of utility panels (UPs) and access supporting such equipment.

UPs provide the services required to operate relevant SUT and semi-automated equipment, including power, data connections, process control systems (PCS), process gas supplies, jacket service connections, and liquid waste connections. UPs can be wall- or ceiling-mounted. Example determining factors for UP location are that ceiling-mounted panels allow flexibility in the equipment layout without the need for long, trailing cables, but equipment requiring drain connections should be associated with a wall panel. Key features maximizing the flexibility of the UPs include maintaining a common design approach, and ensuring that the process automation design associated with such equipment as customized SUT cell-processing carts and mixers is related to the UPs, as opposed to the individual equipment.

Common design approach:

- Avoid unique UPs designed specifically for an individual piece of equipment
- Limit the number of different UP types, and select the most appropriate type for each manufacturing area/operation
- Accept that the full range of services associated with each type of panel need not be required for each piece of equipment potentially connected

Relate PCS connections to the UP:

- Process automation is associated with the UP, not the equipment connected to it (standardized instrument transmitter connections at each UP)
- Single-use mixers (SUMs) and custom-designed process carts will bring the instrument connections to the UP with a heavy duty, plug-and-play electrical connector
- The specific SUM or cart will be recognized by the PCS through an automated signal or scanning of a quick response (QR) code on the equipment frame
- Different SUMs and carts will have different instrument requirements and the PCS will recognize the equipment currently connected

A thorough assessment is required to determine the necessary level of flexibility across the manufacturing area. The number of services associated with each panel are factors in their size and cost, and there should be a trade-off between the maximum possible level of flexibility and what is sensibly required.

Cleanroom Grading Approaches

Early commercial-scale C&GT facilities favored a conservative approach to cleanroom grading, whereas processes that involve open handling of sterile operations are now commonly performed

in a biosafety cabinet (BSC). Grade B cleanrooms are therefore relatively commonplace, yet these tend to limit flexibility due to the constraints around maintaining the associated stringent environmental controls. Operating a C&GT facility, such as a VV manufacturing facility, with Grade C or potentially even Grade D manufacturing suites is a viable option when using SUT (and closed-process operations), as described above and highlighted in Figure 3.

For the smaller-scale cell therapy operations, the transition away from the use of BSCs in Grade B suites can be achieved using isolator technology, such as custom isolator systems designed around the specific process. These may include cell culture operations such as cell factories and incubators, or filling operations carried out using automated and semi-automated systems. The ergonomics of the isolator systems can be optimized through effective selection of the glove material, with thinner and more flexible materials now available for undertaking the delicate tubing manipulations associated with CT processes.

An isolator can be categorized as providing full aseptic segregation of the operations inside the unit, reducing the required environment classification, as compared to operating a BSC. Isolator technology can facilitate different products or platforms being operated in the same area in parallel by installing multiple isolators in a single ballroom suite, potentially operated as a Grade D environment. This approach will maximize the flexibility of the area by minimizing the operational footprint from walls and airlocks.

A recent industry survey conducted on the C&GT marketplace indicates that only around 25% of CT companies currently operate Grade C cleanrooms with such closed-process operations [8]. However, based upon the continually advancing manufacturing technologies, it is expected that there will be a significant shift toward reduced suite classification in the future.

Biosafety Design Considerations

Biosafety plays another key role in the design of a multimodal facility. As mentioned, designs must comply with the most stringent biosafety product and production requirements anticipated. Furthermore, geographic regions and internal company standards impose different biosafety requirements. Corporate strategies have often been based upon the regulations of the most stringent region that the company operates in, regardless of where a particular facility is located.

Examples of regional differences:

- The BSL associated with genetically modified HEK293 (or equivalent) cell lines used in TT processes are classified as BSL-1 in the EU and BSL-2 in the US.
- Third-generation lentiviral vector systems have recently been downgraded to BSL-1 (ML-I) in the Netherlands, but remain a BSL-2 material in other regions [9].

One common approach is to use the classification BSL-2+, which is a risk-based approach that implements certain BSL-3 requirements above a BSL-2 baseline. As the majority of C&GT modalities fall within the BSL-2 category, BSL-2+ provides a robust strategy to ensure the facility will be suitable for a wide range of modalities. The nature of VVs puts them among the more biohazardous materials in C&GT operations, and a guideline for their BSL classification is outlined in Table 3.

Table 3: Guidelines for the classification of VV materials [10].

Viral Vector Type	BSL	Comments
AAV	BSL-1	Based on the use of a helper plasmid
AAV	BSL-2	Based on the use of a helper virus
AdV	BSL-2	Replication incompetent systems reduce risk, but are more challenging to process
LV	BSL-2 / 2+	Recently reduced in the Netherlands
Retrovirus	BSL-2 / 2+	
HSV-1	BSL-2	

To ensure containment of the suites to surrounding corridors, either recirculation or once-through air design can be considered in heating, ventilation, and air conditioning (HVAC) associated with higher biosafety levels. A recirculation approach requires an individual air handling unit (AHU) per manufacturing suite and may increase cross-contamination risk for multi-product/modality operations. A once-through air design can facilitate a single, larger AHU supplying multiple manufacturing suites, but may increase the utility demand compared to the recirculation approach.

High-efficiency particulate air (HEPA) filtration on the exhaust air from a facility is not typically included with lower BSL or non-biohazardous operations. The risk of exhausting biohazardous material via the exhaust air from a facility supporting closed process operations is negligible. It therefore follows that HEPA filtration is not required for the exhaust air on such a room or facility.

Product or equipment changeover for a manufacturing suite should be a repeatable and validatable process. Suitable methods include a vaporized hydrogen peroxide (VHP) fumigation of the suite. VHP can be supplied by mobile generators within the suite itself, or introduced to the suite via an inlet point in the supply ductwork. Either approach necessitates full isolation of the manufacturing suite from the surrounding area. This is achieved using such measures as isolation dampers on ductwork and interlocked airlock doors with gas tight seals to isolate the VHP vapors. VHP fumigation of a suite is an example of a BSL-3 requirement that may be implemented as part of a BSL-2+ strategy.

Waste Handling Considerations

Single-use consumables used in the main manufacturing operations of any C&GT process require handling as biohazardous waste following the BSL classification of the particular process. Decontamination / disposal methods vary, and they can have significant implications for the facility design and operation. The principal method employed is through the use of an onsite

decontamination autoclave. These units can be large and have significant utility demands and lengthy cycle times, but the waste can be subsequently disposed of as inert plastic waste.

An alternative is to transfer the functional responsibility for decontamination and disposal to a specialist waste management contractor. Factors affecting the choice of approach include consideration of the legal or regulatory responsibilities, decontamination of reusable gowning materials, the volume of waste being handled, and the available frequency of collection by the contractor. If genetically modified organisms containing biohazardous materials require prolonged storage before collection, a temperature-controlled waste staging area is likely to be required.

If onsite decontamination is employed, the location of the required facilities can impact the flexibility of the site. Lower BSL ratings (BSL-1) indicate the decontamination facilities must be available somewhere at the production site. More stringent guidelines (BSL-3, and potentially BSL-2+) state that the decontamination facilities are at the boundary of the specific BSL zone. How the specific BSL zones are defined, e.g., whether there are multiple segregated manufacturing areas in the same facility, can dictate where the decontamination facilities should be installed to promote flexibility. Examples of this include facilities for the manufacture of both viral and non-viral modalities, and how a facility is operated with respect to the common support areas and circulation spaces.

Installation of a decontamination autoclave at the boundary of a specific manufacturing area, as opposed to installing in a common waste area, can increase flexibility. This approach provides robust protection against cross-contamination in other areas of the facility, but potentially necessitates additional decontamination autoclaves, increasing cost and spatial considerations. An alternative approach involves detailed procedures ensuring robust waste material containment before transport to a common area. The most suitable approach should be determined through a structured risk assessment during the facility design phase.

For a facility that includes multiple defined manufacturing areas, careful consideration is required in the design of liquid waste systems. Either separate biowaste waste systems must be provided for each area, or the piping design needs to guarantee no possibility of backflow or crossflow between waste headers from different areas. If a common waste system is desired, then separate headers should be run from each area that connect independently into the waste collection tank/treatment system.

Process Modeling and 3-D Design

Effective upfront planning is required to ensure optimal flexibility in a multimodal facility. Detailed process and structural models allow comparison of different manufacturing scenarios to determine the optimal approach for a particular site, while not limiting manufacturing capabilities or incurring excessive costs.

Process modeling software allows different processes to be built out and then scheduled in campaign or parallel manufacturing scenarios. This supports optimization of specific throughput requirements following each stipulated design constraint and priority rank. Such software can be used to not only model the known processes associated with the facility, but also to run theoretical scenarios to plan for potential or yet unknown future products. The outputs from these models will determine equipment requirements, identify bottlenecks, and "right size" utility and waste systems. Facility and equipment layout designs that support existing needs and outputs from theoretical scenarios guide proper sizing and spatial planning of manufacturing suites and support future changeout or expansion.

Advances in process modeling and building information management software now allow development of a true digital twin of a facility to be developed. Discrete event simulation (DES) software can model the suites and process flow of manufacturing operations as sequences of events over time. This provides an accurate picture of the equipment requirements and of how all the manufacturing and ancillary operations fit together to produce the desired throughputs and other goals for a facility. This is particularly powerful for more labor-intensive processes such as CT modalities. Planning the movement of operators through the facility brings significant benefit to spatial planning of both the manufacturing suites as well as such ancillary areas as airlocks, main gowning areas, and locker rooms.

When it comes to the design of the facility itself, this is almost exclusively now done using three dimensional (3-D) modeling software tools. Different engineering disciplines, such as architectural and process piping, may use different software packages, which can then be combined into a single coordinated model. The end result is a 3-D model of the facility in which people can "walk around" to get a feel for how each area will look and adjust spatial arrangements to optimize ergonomics. The output from the DES software is an animated model that uses 3-D objects to illustrate the orientation and placement of manufacturing and support equipment, as well as to show how the operators will interact and undertake their activities. The 3-D objects used in the model can be customized to show a true representation of the specific equipment and an actual 3-D model of the building can be imported into the DES model. The consequent amalgamated in silico model (a digital twin) then provides a precise virtual depiction of how the facility will both appear and operate. This very powerful tool can show how the introduction of different equipment, manufacturing modalities, and processes will affect requirements of the facility compared to the start-up conditions and enable companies to plan accordingly.

Digital Biomanufacturing

Finally, such comprehensive digital initiatives as Industry 4.0 are now making serious inroads to biopharmaceutical manufacturing. The digitalization of biomanufacturing is supporting flexibility in multiple product/process facilities. Structured, segregated, and distributed modeling of cell cultures and the hybrid (mechanistic and data-driven) model-based control of bioproduction is enabled by advances in culture omics, process analytics, and data science.

Edge computing, the Internet of Things (IoT), and machine learning (ML)-supported digital twins are advancing capabilities in plant maintenance and systems control, procurement, process scheduling, prediction and control, and changeover ease.

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OLIGONUCLEOTIDES: A Cornerstone for Therapeutics and More

By Brendan Nichols

Resounding clinical successes and maturation of extensive therapeutic pipelines have catapulted oligonucleotides from a fringe modality to therapeutic relevance in just a few short years. Oligonucleotides are a cornerstone of a burgeoning class of drugs classified as nucleic acid therapeutics. These therapies interact with DNA and RNA targets rather than traditional protein therapeutic targets. Oligo therapies offer access to gene regulation mechanisms that were previously inaccessible for treatment. Oligos are also a key component of gene editing systems, serving as the guiding instructions for DNA and RNA editing technologies.

The oligonucleotide therapeutics industry has been around since the mid-1980s but had a period of relative stagnation for years. Much of the 2000s and 2010s were fraught with clinical setbacks and companies exiting the space. A few innovators have shepherded this industry through these down years and managed to build impressive pipelines. Since 2016, drug approvals per clinical campaign have outpaced the average across all modalities, resulting in 11 FDA-approved therapies in that span. This platform technology is being adopted by growing ranks of large pharmaceutical manufacturers via licensure and acquisitions and by dozens of innovators. As of earlier this year, 80 molecules were in phase II and phase III clinical trials, with many more molecules in development [1]. There has been significant global interest in investment to rapidly expand commercial and clinical manufacturing capacity [2]. The industry is responding to the lack of manufacturing capacity with creative science and engineering solutions.

OVERVIEW

The oligo manufacturing platform has been developed based on solid phase synthesis, which consists of a series of chemical reactions that covalently link modified nucleotides to create a molecule of appropriate length, all while anchored to a solid support. Synthesis is typically followed by a cleavage reaction, which cleaves the molecule of interest from the solid support, and a subsequent deprotection reaction, which removes protecting groups and renders the molecule biologically active. Typically, the drug substance is then purified via one or more chromatography steps, concentrated via ultrafiltration, and isolated via lyophilization. The active pharmaceutical ingredient (API) drug substance (DS) from lyophilization is then transported to a fill/finish facility for final formulation and filling into vials for sterile injection. Figure 1 shows a typical block flow sequence of unit operations. In this article, we'll explore some innovations and improvement opportunities in the science, manufacturing processes, and facilities that produce these therapies.

Figure 1: Block flow diagram for a common oligonucleotide DS manufacturing process.

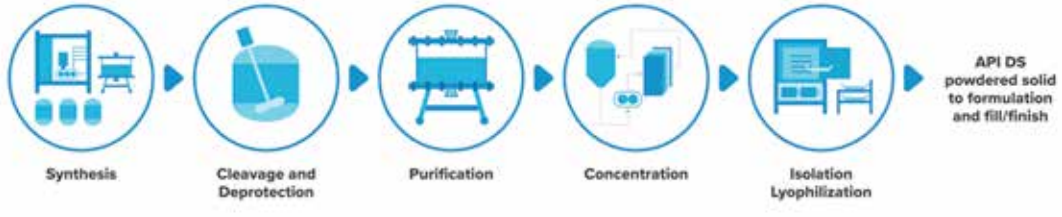
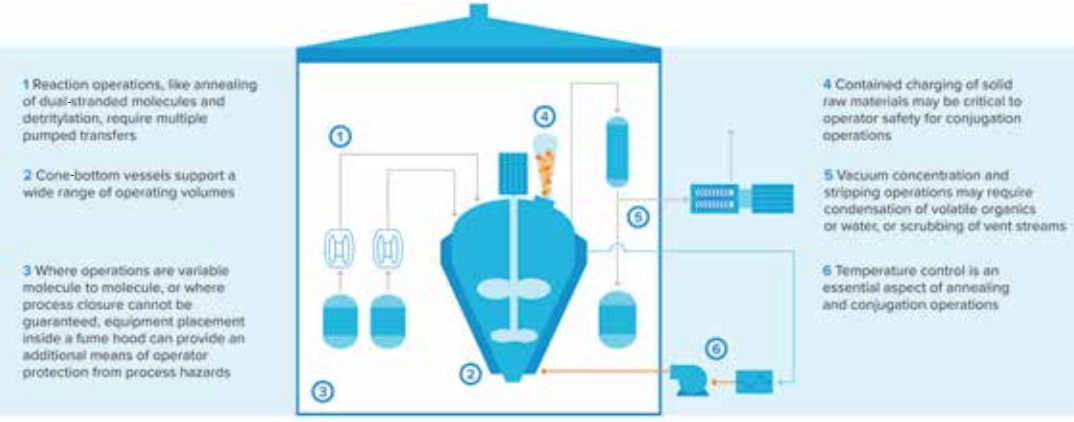


Figure 2: **Multipurpose reaction equipment: Features of a highly flexible reaction setup for oligo manufacturing.**



SYNTHESIS AND REACTION

The solvent burden in oligonucleotide production is significant, owing in large part to the solid phase reaction platform where reactants are repeatedly flushed from the synthesis column. Solvent usage per kg of API produced can easily exceed 3,000 liters, much of which is acetonitrile. The demand for acetonitrile from the oligonucleotide industry may soon outpace the global production capacity, so reduction of solvent usage is a point of emphasis.

One approach to reducing solvent usage is to reduce the dose size of therapies. There have been promising developments in the industry to maximize the effect of these molecules without parallel increases in toxicity. Nucleotide modifications, whether by alteration of synthesis starting materials or alternate reactive chemistries, can help achieve this goal. Experimentation with mesyl backbone modifications has demonstrated a significant broadening of the therapeutic index in preclinical studies [3]. Wave Life Sciences has likewise reported advantages with a nitrogenated backbone, and Alnylam has demonstrated promising results with (E)-vinylphosphonate backbones [4, 5]. Many innovations in base chemistry have been developed and implemented in recent years; a notable example is bridged/locked nucleic acids (BNA/LNA), which confer increased stability to molecules. The full clinical benefits of these chemistry advancements have yet to be realized, but there is tremendous promise.

For many of these cases, the production nuance all exists in the starting materials, where convoluted manufacturing processes drive up pricing but produce starting materials using classical reaction and isolation equipment via organic chemistry. These high-value molecules can then be integrated into a synthesis cycle with ease via a simple substitution of reactant solutions. However, the use of new base chemistries sometimes requires unique engineered solutions. In the case of mesyl azide, liberated nitrogen during the coupling reaction must be removed from a closed, pressurized system and excess reactant requires quenching prior to disposal, resulting in a need for specialized equipment upstream and downstream of the synthesis column.

Other work seeks to overcome drug delivery challenges to limit dose sizes. Significant investment has been made in expanding the targeted delivery of oligos to muscle, heart, lung, skin, and brain tissues, among others. Conjugation of oligos to targeting ligands such as peptides, antibody fragments, aptamers, and proteins can unlock these areas of disease relevance to access disease targets that were previously difficult or impossible to reach. Endosomal escape mechanisms are also being utilized to enhance bioavailability of these medicines. Studies have shown that a vast majority of an administered siRNA or antisense oligonucleotides (ASO) dose that is transported across the cell membrane is trapped and degraded prior to exiting the endosome, thus never reaching its target [6].

Engineered molecules with a knack for breaching endosomes are being developed to significantly increase the proportion of a dose that has therapeutic effect. These innovations require a diverse chemical manufacturing toolbox, elements of which are displayed in Figure 2. Stirred tank reactors are needed to forge covalent linkages between oligonucleotide and targeting ligands. Broad pipelines require facilities to be designed with a large degree of flexibility to support anything from mild reaction conditions to the use of potent or highly biologically active compounds. Large walk-in fume hoods are organized to support a variety of unit operations. Cone-bottom reaction vessels can provide the turndown required to process a variety of scales and handle different reactions.

PURIFICATION AND ISOLATION

Purification of oligonucleotides generally results in multiple eluate fractions of inconsistent purity and yield. As a result, analytical timelines to verify eluted purity and concentration of full-length product often bottleneck facility production. To combat this, facilities must be designed with appropriate capacity to handle the intensive analytical burden, and additional tankage is often required for simultaneous in-process storage of multiple eluate batches.

Many innovations commonly adopted in biologics production are starting to find footing in oligo facilities. Use of buffer concentrates combined with inline dilution allows a significant reduction

Figure 3: Optimizing chromatography.

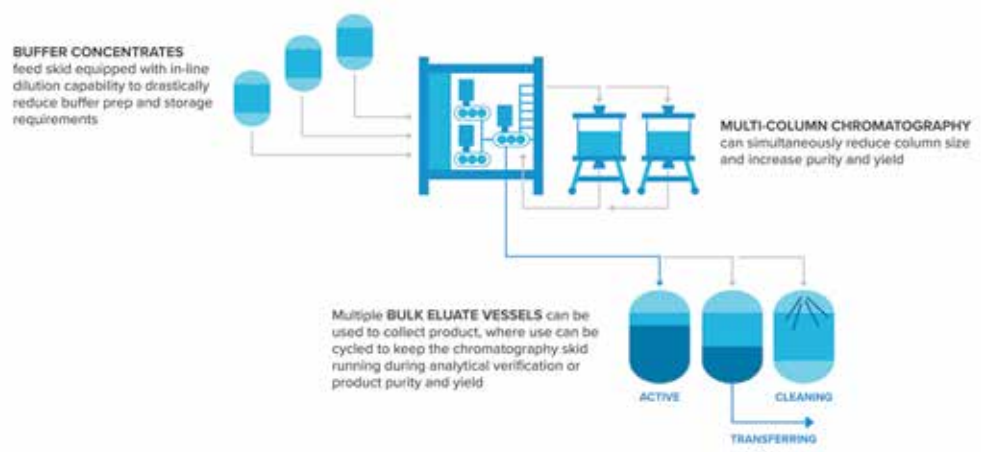
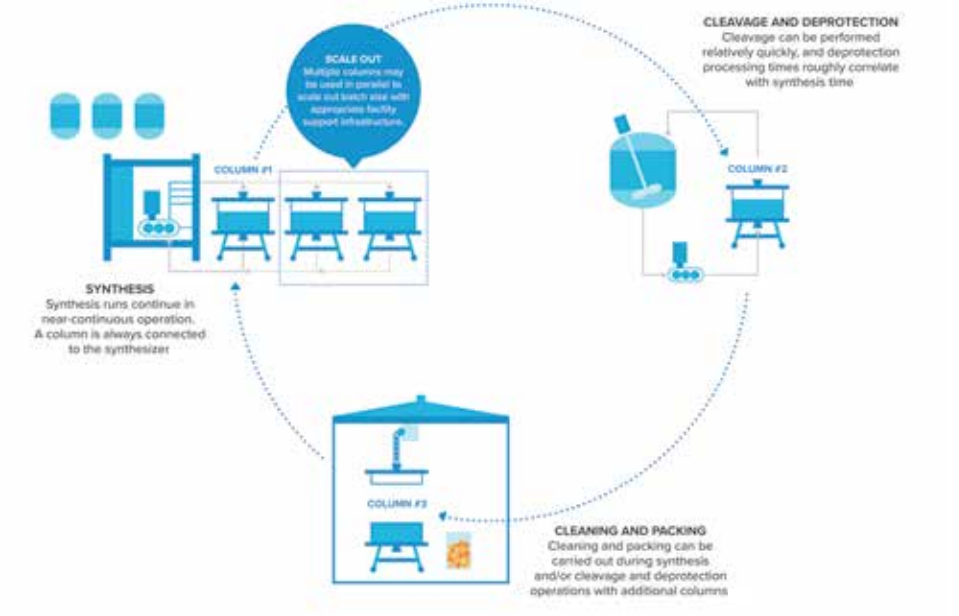


Figure 4: High-throughput synthesis operation.



in capital equipment to support high-throughput chromatography and ultrafiltration operations. Buffer tank sizes can be reduced significantly or eliminated entirely. Multicolumn chromatography systems are receiving increased attention to drive to higher purities and yields. Some systems are designed to recycle off-peak side fractions that are normally discarded, increasing yield [7]. Ultimately, focused process development is required to take advantage of these opportunities. Figure 3 highlights opportunities for optimizing chromatography.

LYOPHILIZATION

Lyophilization has been the classic unit operation of choice for isolation of oligonucleotides prior to formulation and filling. Unfortunately, lyophilization is energy intensive and time consuming, often requiring 3 to 5 days to complete a batch. Oligos generally have excellent stability in aqueous solutions, and lyophilized oligos are dissolved in aqueous formulation buffers for preparation of the final dosage form anyway. As a result, some companies have challenged the paradigm by forgoing lyophilization entirely, opting to provide solution phase API to drug product facilities for filling and packaging. Some regulatory hurdles remain around classification of solution phase oligo as API versus drug product intermediates [8].

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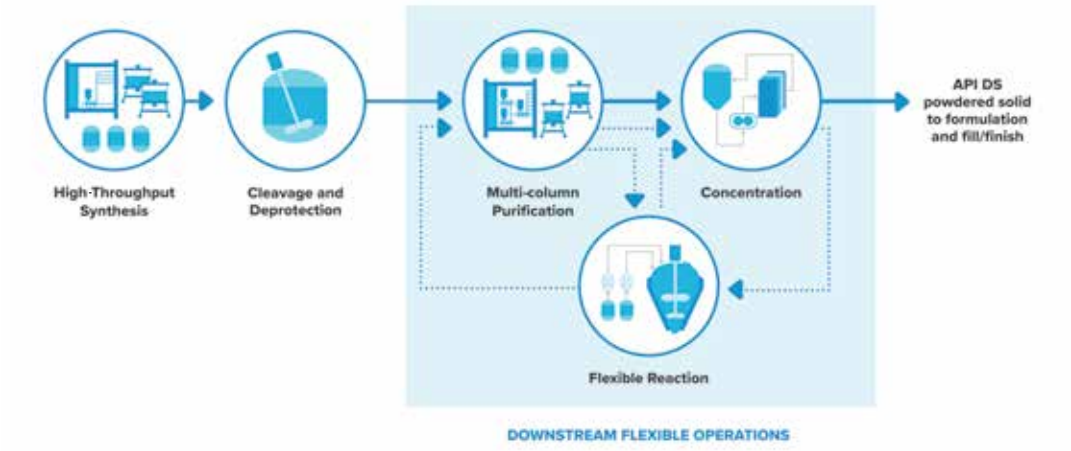
Figure 5: Optimized block flow for oligonucleotide manufacturing.



equipment. Maximizing production of a synthesizer is essential. Figure 4 highlights opportunities to do just that. Synthesis with multiple columns in various stages of processing (packing, synthesis, and cleaning) can maximize equipment occupancy. Synthesis columns have historically been limited in size due to weight and bulk as well as effectiveness of column seals. Synthesis using multiple columns in parallel can allow for larger batch sizes. Rotating multiple columns through various stages of packing, synthesis, cleavage and deprotection, and cleaning can allow for synthesis to be essentially continuous.

The synthesis unit operation routinely takes 8 to 12 hours start to finish, but it can take 3 to 5 days between batch starts using a single synthesis column. Cycling through columns can drastically increase synthesis output.

Combining the incremental process improvements previously mentioned results in an optimized facility, with the adjusted block flow shown in Figure 5. Multiple alternate flowpaths exist between downstream operations, as indicated by the dotted lines. The facility footprint is focused on high throughput and high utilization of expensive process skids. The facility provides a high degree of processing flexibility to account for the variation in molecules and delivery technology, producing liquid phase DS at high purity and yield.

REDEFINING THE STANDARD

Companies have been looking for scalable alternatives to solid phase synthesis in hopes of drastically reducing solvent usage, whether through adaptation of existing biological mechanisms for nucleic acid production or completely novel innovation. Enzymatic synthesis techniques are being explored in the hope that this field's future may look like that of mRNA synthesis, where relatively small batch reactors can produce large quantities of mRNA via assembly of unmodified nucleotides with polymerases and template RNA.

Significant barriers remain to applying this biological approach to oligonucleotides, which are, by their nature, heavily chemically modified for nuclease resistance. At scales approaching tens of kilograms per batch, liquid phase convergent chemical synthesis may prove to be an attractive option. This approach would link fragments 3 to 5 nucleotides long, where the fragments could be manufactured at large scales. This could eliminate the need for highly specialized equipment during synthesis, instead using batch reactors [9]. Ligation of duplex molecules such as siRNA from several starting material fragments is being explored as another approach to convergent synthesis. Any successful enzymatic approaches could augment the efficiency of convergent synthesis.

This article primarily addresses manufacture of therapeutic targets at a length of 1,830 nucleotides per molecule, which encompasses most siRNA and ASOs. These lengths confer good overall reaction yields while utilizing solid support that can be densely loaded. Synthetic guide RNA (sgRNA) molecules are a notable exception to this category of oligos. With lengths often approaching or exceeding 100 nucleotides, sgRNA manufacture by solid phase synthesis exacerbates the problem of high solvent usage; longer synthesis cycles require an increase in reagent and solvent usage proportional to the increase in length.

That solvent usage per gram of usable product is further impacted by reduced overall yields of full sequence length molecules due to accumulated incremental yield loses per coupling. Solid supports for sgRNA have much lower loading relative to shorter molecules due to steric interference at linkage sites, resulting in less moles of product per unit volume of synthesis column. This in turn increases solvent usage per cycle relative to a shorter molecule due to rinse efficiency of the proportionately larger volume beds per gram produced. This increase results in sgRNA manufacturing facilities having a disproportionate solvent and reagent support infrastructure relative to that of an ASO or siRNA manufacturing facility at similar batch sizes.

CONCLUSION

The recent expansion of global oligo manufacturing demand has presented numerous opportunities to design better molecules,

better processes, and better facilities. Better molecules are being designed by taking advantage of chemistry to reduce toxicity, increase bioavailability, and promote interaction with unique cell types. Better processes are being designed to produce more material faster, at lower cost, driving efficiency for these high-value facilities. Better facilities are being designed to increase flexibility to accommodate these process and chemical improvements, to handle variation in chemistries, and to increase throughput. The future for oligonucleotide therapies, and the patients who will receive this combination of best-in-class and first-in-class treatments, is undeniably bright.

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About the author

Brendan Nichols is a Process Engineer at CRB specializing in oligonucleotide facility design. He has an extensive background delivering solutions to oligonucleotide clients on projects of varying scale. Brendan's technical background also includes process engineering of peptide, small molecule API, and cell culture facilities. He has been an ISPE member since 2014.

CHALLENGES AND OPPORTUNITIES in Emerging Digital Health Technologies

By Ryan A. Hoshi, PhD, MBA, and James P. Wabby, MHMS

Digital health is transforming the health care landscape through new technologies and platforms in patient care management, conducting of clinical trials, patient data collection, and the diagnosis and treatment of disease. Emerging digital health technologies (DHTs) may improve the quality of life for patients with chronic and debilitating diseases and provide novel health care solutions for patients with unmet medical needs. As digital health sits at the intersection of technical, scientific, and regulatory disciplines involving medical devices, drugs, and biologics, the successful development of novel DHTs will require significant collaboration with health care stakeholders to overcome regulatory, technical, and life-cycle management challenges.

The COVID-19 pandemic underscores the importance of DHTs through the increased reliance on telemedicine services and remote patient monitoring programs to ensure patient safety and triage scarce hospital resources [1, 2]. Given the public health emergency, health authorities offered greater flexibilities in the use of digital health platforms and technologies such as:

- Enhanced HIPAA (Health Insurance Portability and Accountability Act of 1996) flexibilities in the use of telemedicine services [3]
- Emergency use authorization (EUA) to increase the availability of remote or wearable monitoring devices to treat patients and reduce the risk of exposure of health care providers to SARS-CoV-2 [4, 5]
- Regulatory discretion in the use of virtual patient monitoring and remote clinical outcome assessments for clinical trials during the COVID-19 pandemic [6]

Moving forward, the health care community should adopt important lessons learned from the pandemic by leveraging DHTs to accelerate research and development of new medical therapies, supporting evidenced-based and data-driven health outcomes, and empowering patients in their health care management.

WHAT IS DIGITAL HEALTH?

Digital health is a broadly defined topic that encompasses the application of digital technologies in health care, living, and society to help deliver or provide access to health care products and services [7]. DHTs may include mobile medical applications, health information technology, wearable devices, wireless sensors, telemedicine, electronic health records (EHRs), digital therapeutics, software as a medical device (SaMD), and artificial intelligence and machine learning (AI/ML) technology [8, 9]. More broadly, a DHT may refer to a system that uses computing platforms, connectivity, software, and sensors for health care and related uses [10]. Given the proliferation and confusion of various digital health terms, this article includes a compiled glossary of core DHT terms and definitions (see Table 1). Together, DHTs may be intended as a medical product to improve the prevention, diagnosis, treatment, monitoring, and management of health-related issues; an adjunct to other therapies such as devices, drugs, and biologics; a tool to collect and analyze data as part of a clinical study; or an aid to monitor and manage a patient's lifestyle or habits [6, 11].

DHT TOOLS

In December 2021, the US FDA issued a cross-center draft guidance with recommendations on the use of digital health technology tools (DHTTs) to acquire data remotely from participants in

Table 1: Terms and definitions for DHTs.

DHT	Description
Artificial intelligence (AI)/machine learning (ML)	AI: The use of algorithms or models to mimic human capabilities or behaviors such as learning, making decisions, and making predictions. ML: Subset of AI that contains a model or algorithm that enables a computer to perform a task without being explicitly programmed. An ML-enabled medical device uses ML, in part or in whole, to achieve its intended medical purpose [12].
Digital health technology tools (DHTTs)	The term "DHTTs" is used to differentiate from the broader category of DHTs, but these two terms are often used interchangeably. As clarified in this article, DHTTs are electronic technology tools intended for use in clinical investigations (inclusive of clinical trial and post-market settings) or clinical practice [7].
Digital therapeutics	Digital therapeutics are a subset of SaMD with the primary function of delivering software-generated therapeutic interventions directly to patients to prevent, manage, or treat a medical disorder or disease [7] . An example of a digital therapeutic is EndeavorRx, which is a video-game-based digital therapy for treating patients with attention deficit hyperactivity disorder (ADHD) [13].
Electronic health record (EHR)	An EHR is a subset of health information technology and consists of an individual patient record contained within an EHR system. A typical individual EHR may include a patient's medical history, diagnoses, treatment plans, immunization dates, allergies, radiology images, pharmacy records, and laboratory and test results [14].
General wellness apps	General wellness apps are low-risk products that promote or encourage a healthy lifestyle (general wellness) and are not involved in the diagnosis, cure, mitigation, prevention, or treatment of a disease or condition [15].
Health information technology (IT)	Health IT encompasses the use of computer hardware, software, or infrastructure to record, store, protect, and retrieve clinical, administrative, or financial information. These can include the use of EHRs and electronic prescriptions [16].
Medical device data systems (MDDSs)	MDDSs consist of hardware and software that is meant to transfer, store, convert formats, and display medical device data or medical imaging data. These devices are generally considered low risk if they are not meant to interpret or analyze clinical data [17].
Mobile medical application (MMA)	MMA is a software application that can be run on a mobile platform that incorporates device software functionality that is to be used as an accessory to a regulated medical device or to transform a mobile platform into a regulated medical device [18].
Software as a medical device (SaMD) or software in a medical device (SiMD)	SaMD relates to software that is intended for one or more medical purposes without being part of a hardware medical device. SiMD relates to software that is intended for one or more medical purposes that is used to control a hardware medical device or is necessary for a hardware medical device to achieve its intended use. SaMD and SiMD are also referred to as medical device software under the European Union Medical Device Regulation and In Vitro Diagnostic Regulation [17, 19, 20].
Telemedicine or telehealth	Telemedicine or telehealth is technology that enables patients to connect with their health care providers through live phone or video conferencing, secure messaging, and remote monitoring [21].
Wearables	Wearables are a type of digital technology that users can wear and are designed to collect data or to inform users of their personal health and wellness [7].
Wireless medical devices	Wireless medical devices use wireless radio frequency communication such as wifi, Bluetooth, and cellular/mobile phone technology [22].

clinical investigations for medical products [23]. DHTTs are electronic technology tools intended for use in clinical investigations (inclusive of clinical trial and post-market settings) or clinical practice [7]. The FDA's draft guidance provides additional clarity on the regulatory expectations for selection of DHTTs used in a clinical investigation, for those used in verification and validation activities, use of DHTTs in collection of clinical trial endpoints, and identification and management of associated risks with the use of the DHTT. As the guidance notes, the DHTT requirements may vary depending on whether the DHTT meets the definition of a device and if the DHTT is only meant to be used in the context of a clinical investigation.

Table 2: Risk-based framework for DHTs.

Low-Risk Attribute	Moderate or High-Risk Attribute
Intended to collect, interpret, and/or analyze data solely as part of exploratory scientific research.	Intended to collect, interpret, and/or analyze data to support regulatory decision-making, such as a tool used in a clinical investigation to support a medical product marketing authorization.
Health care provider can independently review the basis of the DHT recommendation or output.	Intended to diagnose, cure, mitigate, treat, or prevent a disease or condition.
Use of the DHT does not pose additional unnecessary risks to the intended user (e.g., invasive monitoring).	Interpret or analyze patient or clinical laboratory test data.
Intended to transfer, store, convert, or display health care data.	Health care provider relies primarily on the DHT recommendation to make a clinical diagnosis or treatment decision.
Intended solely for promoting or supporting a healthy lifestyle (general wellness).	Intended to be used with another medical product that is essential for its safe and effective use.
Uses ML algorithms to make decisions and predictions for a noncritical, nonserious, or nonlife-threatening disease or condition.	Uses ML algorithms to make decisions and predictions for a critical, serious, or life-threatening disease or condition.

The European Medicines Agency (EMA) has also issued regulatory considerations on the use of DHTTs to study or monitor medicinal products [24]. DHTTs subject to EMA regulatory oversight include DHTTs used in the development of a medicinal product or monitoring of a medicinal product before or after authorization, or any DHTT having an impact on the benefit-risk assessment of a medicinal product marketing authorization application (MAA). Important considerations as part of the EMA qualification process include ensuring the technology is fit for purpose, whether the measurement of interest is clinically meaningful, and whether the underlying methodology is reliable and robust. However, beyond qualification of the DHTT as part of a medicinal product development program, EMA guidance is limited on how to apply applicable regulatory requirements for DHTTs classified as medical devices, compliance with EU data protection regulations, and other ethical guidelines.

Expanded adoption and use of DHTTs may accelerate the drug development process by more efficiently collecting and analyzing large amounts of patient-generated data, enhancing pharmacovigilance capabilities, and offering greater participation from diverse groups of patients who may have limited access to clinical investigation sites. However, several challenges and uncertainties remain with the use of DHTTs in clinical investigations because global health authorities have not harmonized on regulatory requirements and standards, nor have they clearly defined regulatory policies on DHTTs based on context of use. There are important considerations if the DHTT is classified as a medical device, which may change the level of regulatory controls and evidentiary requirements to support its appropriate use, such as off-label versus on-label use of a device with prior marketing authorization. As global health authorities develop DHTT regulatory requirements, they need to find the appropriate balance to foster innovation while maintaining product safety, efficacy, and quality.

RISK-BASED FRAMEWORK

To support digital health innovation, a risk-based framework is needed to identify and understand the critical attributes that inform the level of controls to ensure safe and appropriate context for use of the DHT (see Table 2).

For example, a DHT may have a lower risk if it is intended solely for exploratory scientific research and have a higher level of risk if it is intended for collection and analysis of a clinical trial endpoint to support a marketing authorization. Another consideration is if the health care provider uses the output of the DHT as supporting information (lower risk) versus using the DHT output as the sole basis for making a clinical diagnosis or treatment decision (higher risk). Additionally, the use of AI/ML algorithms in a DHT may not necessarily pose higher risks if the output is used to inform a nonserious or nonlife-threatening condition.

The application of risk management principles for DHTs is not clearly defined and depends on whether the technology is classified as a medical product based on its intended use. However, for certain DHTs classified as devices or SaMD, ISO 14971:2019 specifies the terminology, principles, and process for application of risk management [25]. Furthermore, the International Medical Device Regulators Forum (IMDRF) proposed a possible risk categorization framework for SaMD based on a four-tiered system (category I having the lowest level of impact and category IV having the highest level of impact), based on the combination of the significance of information provided by the SaMD to the health care decision as well as the context in which the SaMD will be used [26]. However, this framework is limited because it does not consider DHTs that do not meet the definition of SaMD, nor does it provide recommendations on how category I products should be regulated. Also, this framework does not include considerations for using DHTs in the context of a clinical investigation or as exploratory scientific research.

A DHT should not automatically be classified as a medical device and not all software that is used in the health care setting is considered to be a SaMD. The DHT classification depends on the intended use, potential risks, and specific software functions, where applicable. Understanding DHT regulation and classification under a medical device regulatory framework is complex given the lack of global harmonization and regulatory guidance. For example, although the 21st Century Cures Act (Cures Act) in the United States and the European Union Medical Device Regulations and In Vitro Diagnostic Regulations (EU MDR/IVDR) both include provisions for DHTs classified as medical devices, these two regulatory frameworks are unfortunately not fully aligned.

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Section 3060(a) of the Cures Act amended the Food Drug and Cosmetic Act (FD&C Act) to exclude certain software functions from the statutory definition of a device [27]. This includes certain DHTs that are used for administrative support, maintaining a healthy lifestyle, EHRs, and software that is intended to store or display health care data. The Cures Act also defined clinical decision support (CDS) software that may be excluded from device regulations based on certain lower-risk criteria [28].

Adding to the complexity of the FDA's digital health framework are certain DHTs that meet the definition of the device, but the FDA chooses to apply enforcement discretion given the low risk to patients. The FDA describes these products under enforcement discretion if they are intended to inform clinical management for nonserious situations or conditions, help patients self-manage their disease or conditions without providing specific treatment, or automate simple tasks for health care providers [18, 28]. However, additional clarity is needed for industry in understanding the scope of DHTs under the FDA's enforcement discretion policy, exemptions under the Cures Act, and those DHTs that meet the statutory definition of a device.

In contrast to the US regulatory framework, the EU MDR/IVDR implemented more stringent qualification and classification criteria for software regulated as medical device software (MDSW). Unlike the FDA's risk-based framework for exercising enforcement discretion and exclusion of certain software functions from FDA regulations, under EU MDR/IVDR, the risk of a software product's harm to patients and users is not a criterion for whether the software qualifies as a medical device, nor are there exemptions for certain low-risk medical device software functions [29]. For example, although certain CDS software is excluded from medical device regulations in the US, under EU MDR Rule 11, any software that is intended to provide information to assist in making decisions for diagnosis or therapeutic purposes or that is intended to monitor physiological processes is classified at minimum as a class IIa device requiring a notified body conformity assessment [29].

Additionally, certain MDR/IVDR requirements also apply if the software is meant to process, analyze, create, or modify medical information with a medical intended purpose, or if the software is intended to drive or influence the use of a medical device [29]. Similar to the US regulatory framework, software with a nonmedical intended purpose or software meant for simple search, data storage, archival, or communication is not considered medical device software under EU MDR/IVDR, nor are EHRs, telemedicine, and administrative hospital information systems.

Regulatory divergence with US and EU regulatory requirements makes DHT development and adoption more challenging. To better understand the differences and similarities in how certain DHTs are regulated and classified, Table 3 provides a summary of two hypothetical examples of products that are used to calculate insulin dosing. Table 3 describes the application of three different SaMD frameworks: the IMDRF SaMD Risk Categorization Framework, the US FDA Framework, and EU MDR/IVDR Framework for an insulin dosing calculator and an insulin management system. Table 3 illustrates the regulatory divergence for certain products under the US and EU systems and the limitations of the harmonized IMDRF SaMD Risk Categorization Framework. Also, as shown in Table 3, the product's intended use, technological characteristics, and application of regulatory guidelines can have a significant impact on the product's regulatory burden.

> The health care community should adopt important lessons learned from the pandemic by leveraging DHTs to accelerate research and development of new medical therapies, supporting evidenced-based and data-driven health outcomes, and empowering patients in their health care management.

Life-Cycle Management

Effective DHT life-cycle management requires integrated product development and close collaboration with stakeholders (e.g., users, patients, and health care providers) to ensure effective product design, safety, and quality. Given the rapid and iterative nature of DHTs, organizations need to effectively respond to potential cybersecurity threats, software updates, customer complaints, adverse events, and other potential safety concerns.

To adapt to the rapid and iterative nature of new and updated software, the FDA created the Software Precertification Pilot program [30]. This pilot aims to have a flexible regulatory framework to reduce the time and cost of market entry for software developers that have a demonstrated a culture of quality and organization excellence. The pilot program takes a total product life-cycle (TPLC) approach by ensuring continued monitoring and evaluation of a product's safety from the pre-market development phase through post-market surveillance [31]. However, it remains unclear which types of regulated DHTs may become eligible for FDA precertification and if the excellence appraisal system can adequately safeguard against potential product safety and quality issues.

Beyond a potential precertification DHT regulatory scheme, the current quality management system framework for medical

Table 3: Example classification of DHTs.

	Insulin Dosing Calculator		Insulin Management System	
Description	• Intended for use by a health care professional. • Calculates insulin dose based on accepted clinical practice guidelines and published literature. • Does not control or connect to a medical device.		• Intended for use by a health care professional. • Calculates insulin dose based on a proprietary algorithm that incorporates real-time data and historical patient data from EHR to provide adaptive insulin dosing to support intravenous insulin regimens and optimizes management of a patient's blood glucose in a hospital setting. Insulin delivery is independent of insulin management system.	
IMDRF SaMD Risk Categorization Framework [26]	Category I: SaMD that provides information to inform clinical management for a disease or condition in a nonserious situation or condition is a Category I and is considered to be of low impact.		Category II: SaMD that provides information to drive clinical management of a disease or condition in a serious situation or condition and is considered to be of medium impact.	
US FDA Cures Act Framework [28]	Excluded from the definition of a medical device because it meets all four criteria for CDS described in Section 520(o)(1)(I) of the FD&C Act:		Meets the definition of a medical device and does not satisfy criterion 1 and 4 for CDS described in Section 520(o)(1)(E) of the FD&C Act:	
	1. Not intended to acquire, process, or analyze medical images or signals.	✓	1. Intended to process and analyze a patient's real-time blood glucose measurements.	
	2. Intended for the purpose of displaying, analyzing, or printing medical information about a patient.	✓	2. Intended for the purpose of displaying, analyzing, or printing medical information about a patient.	✓
	3. Intended to provide recommendations to a health care professional about prevention, diagnosis, or treatment of a disease or condition.	✓	3. Intended to provide recommendations to a health care professional about prevention, diagnosis, or treatment of a disease or condition.	✓
	4. Health care professional can independently review the basis for the recommendation.	✓	4. Health care professional cannot independently review the basis for the recommendation.	
EU MDR/IVDR Framework [29]	Example of software qualified as medical device software (MDSW) under EU MDR: MDSW that provides insulin dose recommendations to a patient regardless of the method of delivery of the prescribed dose, whether via an insulin pump, insulin pen, or insulin syringe.			
	Covered by Medical Device Regulations according to decision tree per Medical Device Coordination Group (MDCG) Guidance 2019-11:		Covered by Medical Device Regulations according to decision tree per MDCG document 2019-11:	
	1. Is the product "software" according to the definition of MDCG 2019-11?	YES	1. Is the product "software" according to the definition of MDCG 2019-11?	YES
	2. Is the software an "MDR Annex XVI device," an "accessory" for a medical device according to Art. 2(2) of the MDR or IVDR, or "software driving or influencing the use of a (hardware) medical device?"	NO	2. Is the software an "MDR Annex XVI device," an "accessory" for a medical device according to Art. 2(2) of the MDR or IVDR, or "software driving or influencing the use of a (hardware) medical device?"	NO
	3. Is the software performing an action on data different from storage, archival, communication, or simple search?	YES	3. Is the software performing an action on data different from storage, archival, communication, or simple search?	YES
	4. Is the action for the benefit of individual patients?	YES	4. Is the action for the benefit of individual patients?	YES
	5. Is the software MDSW according to MDCG 2019-11?	YES	5. Is the software MDSW according to MDCG 2019-11?	YES

Note: The FDA also intends to exercise enforcement discretion for software functions that perform simple calculations routinely used in clinical practice [18].

devices needs to be adapted for DHTs to ensure adequate surveillance based on risk. Although the consensus standard, IEC 62304:2006, provides a framework for life-cycle management activities and tasks to ensure safety and performance of medical device software, the framework may not be appropriate for DHTs not classified as medical devices [32]. Also, given the scope and breadth of DHTs using connected systems and platforms, the roles and responsibilities of DHT manufacturers and developers need to be clearly defined to support life-cycle management issues. Additionally, DHT product malfunctions, errors, and adverse events need to be appropriately reported and investigated in a timely manner as part of the continuous improvement process.

Vendor Considerations

To advance digital health innovations, the pharmaceutical industry needs to effectively partner with third-party vendors of novel DHTs. Digital health vendors may have expertise in developing software tools using agile development processes with quick turnaround, but this partnership framework needs to account for patient safety, effectiveness, and product quality.

HealthXL published industry guidance outlining 13 different categories on digital health vendor assessment for clinical trials spanning such issues as quality management principles, data handling, interoperability, and cybersecurity [33]. However, in the context of this article, we propose three key criteria as part of due diligence activities to happen before DHT vendor qualification by a pharmaceutical organization. These due diligence efforts should be commensurate with the "intended use" of the DHT and associated patient harm.

Three key criteria in the vendor evaluation process include technical, quality system, and regulatory expertise:

1. Technical expertise: The vendor should have subject matter expertise and experience in development, launch, and maintenance of the relevant DHT. For example, if considering a DHTT for remote patient temperature monitoring, the vendor should have technical understanding of the temperature sensors, data acquisition, visual display of outputs, and wireless connectivity.
2. Quality system expertise: The vendor should have adequately established processes, procedures, and responsibilities related to the DHT. In the case of a remote temperature monitoring example, processes need to be in place for managing HIPAA and general data protection regulation (GDPR) requirements for the product as required.
3. Regulatory expertise: The vendor should have experience in interacting with health authorities and submitting pre-submissions and marketing authorization applications. The vendor's regulatory experience can enable a better understanding of the appropriate regulatory requirements and pathways for using and commercializing a DHT.

MARKET ACCESS AND REIMBURSEMENT

Beyond marketing authorization, DHTs also need to satisfy payer evidence requirements for reimbursement and pricing, which are essential to gain market access. Policies and guidelines are needed not only for reimbursement of DHTs used as medical products, but also when DHTs are used to generate clinical evidence for medicines. Adding to these challenges, pricing and reimbursement processes remain dependent on regional and country-specific requirements. For example, although a product may be CE marked under EU MDR/IVDR, reimbursement and pricing requirements are not harmonized across EU member states, which makes planning and launching products a major challenge.

DHT developers need to evaluate pricing and reimbursement options as early as possible for cost evaluations and options. In various geographies, the pricing and reimbursement process is less well known or challenging due to political and economic circumstances. Health care delivery depends largely on the technologies available at the point of care. The accessibility of new technologies within health care depends on the availability of the technology to patients. For a technology to be considered in a country, the technology's safety and efficacy need to be evaluated to support the authorization for accessibility. Once the technology has received authorization, it will follow additional assessments to ensure it is a wise use of resources before receiving support for adoption and use within the country. This includes cost-of-illness analysis, cost-benefit analysis, and cost-utility analysis. To understand the challenges with development, coverage, and adoption of DHTs, we outline a three-phase process for their systematic evaluation: marketing authorization, health technology assessment, and utilization decision-making (see Table 4).

Table 4: Process for DHT systematic evaluation.

Phase	Process	Description
One	Marketing Authorization	Evaluation of a technology's safety and efficacy profile to support authorization for use. Marketing authorization does not ensure the technology will be adopted for use in the country's national health care system.
Two	Health Technology Assessment	The bridge between research and decision-making to inform policy makers of their recommendations for use and reimbursement under evaluation.
Three	Utilization Decision-Making	Assessment if the new technology provides any incremental benefit compared to current practice as an economic analysis is executed.

The Centre for Innovation in Regulatory Science (CIRS) published a report on digital technologies for clinical evidence generation, which identified opportunities for reducing barriers for DHTs used in the review and reimbursement of medicines [34]. One of the key recommendations included developing a common digital infrastructure to improve data accessibility, trust, and collaboration between regulators and HTA organizations. Also, the limited knowledge and familiarity of DHTs within the HTA community underscores the need for greater education and harmonization on DHT terms and concepts among stakeholders.

In the US, reimbursement and coverage of breakthrough and innovative medical devices and DHTs remain uncertain with the proposed rule by the Centers for Medicare & Medicaid Services (CMS) to repeal a final rule titled "Medicare Coverage of Innovative Technology (MCIT) and Definition of Reasonable and Necessary" [35]. The MCIT final rule would have established a Medicare coverage pathway for innovative technologies based on the FDA's marketing authorizations of breakthrough medical devices. DHTs would have benefited from the MCIT rule as several notable DHTs classified, as medical devices have obtained FDA breakthrough device designation in recent years [36, 37]. However, with the

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proposed repeal, CMS noted that there is limited clinical evidence of Medicare beneficiaries in the clinical trials as the basis for FDA approval, and the FDA and CMS operate under different statutory and regulatory standards for marketing authorization and coverage. Given the ongoing challenges with DHT reimbursement, the proposed repeal of the MCIT rule may be a significant setback for DHT adoption.

CONCLUSION

The COVID-19 regulatory flexibilities, risk-based framework, medical product development considerations, life-cycle management issues, vendor due diligence, and market access challenges and opportunities discussed in this article provide important reflections on the successful development and adoption of novel DHTs.

However, despite the enormous potential of emerging DHTs, access to essential health care services and great health disparities within and across both developed and emerging economies remain huge challenges. With a growing digital divide, health authorities, health care providers, patient advocacy organizations, and industry stakeholders need to collaborate to develop appropriate guidelines and best practices to foster DHT innovation and ensure access to high-quality medicines.

Recognizing this urgent need, the World Health Organization (WHO) Global Strategy on Digital Health advocates for the development of sustainable digital health ecosystems, robust governance structures, and patient-centered approaches to management of DHTs [38]. As digital health continues to transform the health care landscape, DHTs will significantly improve the quality of life and lifespan of patients with chronic and debilitating diseases as long as the health care community develops and uses DHTs to empower patients with their health care decisions while maintaining privacy, transparency, and integrity.

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2022 ISPE BIOTECHNOLOGY CONFERENCE:

Ongoing Growth and Development

By Susan Sandler

More than 400 attendees learned about the latest developments in biopharmaceuticals, cell and gene therapy, and ATMPs at the 2022 ISPE Biotechnology Conference, held 28–30 June in Boston, Massachusetts.

The conference focused on the ongoing development and growth in these technologies, and featured speakers on a broad range of topics, including advanced manufacturing and how lessons learned from COVID-19 vaccine development can apply to biologics development. Highlights from several plenary sessions and keynotes are provided here; the sidebar addresses a panel discussion about addressing risk management as biopharmaceuticals continue to move forward.

THE ROAD TO ADVANCED MANUFACTURING

The conference opened 28 September with a keynote address by Peter Marks, MD, PhD, Director, Center for Biologics Evaluation and Research (CBER) at the US Food and Drug Administration (FDA). He presented "Advancing the Manufacturing of Complex Biologic Products" and discussed the potential of advanced manufacturing, case studies in COVID-19 and individual gene therapy, and resources from the FDA for product developers.

Marks described some of the successes and challenges of the vaccine production in response to COVID-19. Process development and scale up of manufacturing have been the greatest challenges to COVID-19 vaccine development and deployment,

Figure 1: The FDA's Peter Marks gave the opening keynote address at the conference.

Marks noted. He observed how the development of COVID-19 vaccines was able to compress the traditional de-risked approach to vaccine development to meet the needs of the pandemic. "Condensing phases of development and concomitant manufacturing development can be done, and Operation Warp Speed essentially did this" through Phase 1, 2, and 3 trials, and when data supported good immune response, scale-up occurred. He emphasized that millions of vaccines were produced, found effective and safe, and were rapidly rolled out. "The ability to do so probably saved lives."

The process was not without challenges, Marks noted. Bottlenecks occurred and insufficient raw materials, such as

lipids early on for mRNAs, took some time to resolve. A dearth of disposable supplies and plasticware was another challenge, as were bioreactor capacity and the need for well-trained individuals to make the vaccines. Marks said sterile techniques are a little different for the vaccines than in other areas of manufacturing. "One thing I never thought a lot about until the pandemic was fill-finish capacity, which turned out to be quite limiting early on. Also having enough glass vials to put the vaccines in! That is one reason why there were multiple-dose presentations, since there were not enough glass vials for single doses." He remarked that having a sufficient skilled workforce to complete all that was necessary was a tremendous challenge.

These challenges can help in the industry transition to advanced manufacturing, such as improved agility, flexibility, reliability, and reduced costs of the manufacturing process for biological products by continuous or semicontinuous production, he said. There is potential for vaccines, cell- and gene-based therapies, and other complex biologics.

Vaccine supply could more easily be ramped up on short notice and more rapidly modified for emerging infectious diseases, he suggested, saying that many such diseases come in waves, so a baseline production at 25% to 50% capacity could be in place that could ramp up when an infectious disease surge occurs.

Marks spoke about the promise of advanced biologics manufacturing, giving an example of a bioreactor harvest and feed directly into a purification system, ultimately to be able to formulate into drug product and fill-finish it. Such a concept could help address some of the challenges experienced during the COVID-19 vaccine development, and help essentially decrease the footprint of production. Advanced manufacturing that could work with a prefabricated clean room could allow more distributed manufacturing closer to where the product is going, and could distribute manufacturing more evenly across a country or multiple countries.

The opportunity to produce on a small scale could help with therapies for rare diseases and disorders, Marks said, foreseeing a possible paradigm ahead to move into genome editing to try to correct more common diseases.

Individualized therapies that create the right drug to reach each patient are another challenge in manufacturing because commercial manufacturing has setup costs, such as capital investment to build a site and buy the equipment required to produce the drug. These costs cannot be recouped if production is less than a few hundred doses per year. The technology is there to create small numbers of drugs, but the need is to make these at a cost that is viable to try to treat patients and with capacity to do so on a lot of small-scale dosing regimens. He said leveraging validated processes can potentially facilitate the development of new products.

Devices may be a way to move ahead for upstream production of vectors and for downstream purification. Such devices are being worked on by academics and companies, Marks said. Standard methods for bespoke gene therapy could be a way to make it easier.

Advanced manufacturing offers potential for improved agility, flexibility, reliability, and cost reduction

At the FDA, Marks said the agency is thinking about ways to streamline some regulatory aspects. In appropriate situations, nonclinical data and manufacturing from one product may be able to be leveraged to another (possibly where an original product was already approved). The FDA is working with the National Institutes of Health on a bespoke gene therapy consortium that is a public/private partnership. Other support includes CBER Advanced Technologies Team (CATT) meetings that can benefit those interested in looking at advanced technologies for product manufacturing technologies or platforms. Early and ongoing interaction with CBER before filing a regulatory submission allows for informal interaction that is nonbinding. The FDA's Initial Targeted Engagement for Regulatory Advice on CBER Products (INTERACT) program allows early dialogue to set people up for success.

Advanced manufacturing offers potential for improved agility, flexibility, reliability, and cost reduction for manufacturing biological products, Marks said in summary, and he looks forward to working with science and manufacturing communities in this area.

Narendra B. Bam, PhD, Senior Vice President, Medicine Development and Supply at GlaxoSmithKline, was the next speaker in the opening session, with a presentation on "Biopharmaceutical Manufacturing on the Horizon." He reviewed some work underway at GSK, including innovation in continuous small molecule manufacturing with continuous integrated drug substance and continuous drug product manufacturing; small molecule continuously manufactured product recently launched; and applying the learnings to biopharmaceuticals. GSK is developing an integrated drug substance manufacturing platform with, what Bam said was, a significantly lower capital/footprint and increased flexibility. (He said the bioreactor size could be reduced to under 900 kg per year production rate, which is becoming a "sweet spot.") The company is also working on increased process control with steady-state, highly automated, PAT-enabled production to reduce residence time and help eliminate intermediate holds; supply chain velocity with a scaled-out model for replication; simplified tech transfer; and mitigation of scale-up risk. Bam said, "We hope to make supply chains completely agile!"

Risk Management: Tackling the Unknown to Save Lives

An executive panel on "Risk Management for Future Disruptions" on 30 June addressed the lessons of COVID-19 vaccines and therapies development and how the industry can prepare to respond to future needs. Highlights of the discussion follow.

Collaboration. Scott Billman, VP, Global Engineering, Pharmaceutical Services, ThermoFisher Scientific, noted the tremendous collaboration that contributed to the success of developing vaccines and treatments. He continued that now the industry needs to be able to achieve that level of collaboration in other endeavors.

Inspection adaptations. Seneca Toms, MS, RAC, Drug National Expert, FDA Office of Regulatory Affairs, noted that the US FDA used new and innovative ways to conduct inspections and for data flow and that the pandemic sped up these steps. Both the FDA and the industry are considering the next step: prioritizing innovation and technology, and using alternative methods to conduct evaluations of firms, for the best use of resources.

Materials and supply chain. Several participants noted the importance of being able to access needed supplies. It's key, in the focus of large issues, to ensure even small supplies are not lost sight of, said Marco Cacciuttolo, Senior Vice President, Novovax. Partnering with suppliers that can keep the necessary items coming is critical. International sourcing to be able to work around challenges such as the war in Ukraine is also necessary, as are alternate sources and materials when possible, several speakers said.

Efficiency for responsiveness. Several participants agreed that although supply chain is important, other efficiencies and planning are needed, such as within digital operations, ensuring proper planning, being proactive, and employing other technologies to support efficiency.

Workforce issues. Oliver Hennig, Senior Vice President, Operations, BioNTech, pointed out that it is important to get and keep the skilled workforce necessary to address future challenges, and to ensure the environment is a safe one. His company does a lot of cross training so that there is flexibility in addressing the needs of multiple stations and sites and so that skill sets can be broadened.

—Susan Sandler, ISPE Senior Director, Editorial

Condensing phases of development and concomitant manufacturing development can be done, and Operation Warp Speed essentially did this" through Phase 1, 2, and 3 trials, and when data supported good immune response, scale-up occurred.

TWO JOURNEYS TO VACCINES AND BEYOND

A Foundation for the Future

In the opening session on 28 June, Oliver Hennig, PhD, Senior Vice President, Operations at BioNTech SE, presented on "Manufacturing of High Precision mRNA Medicines Against Cancer." His talk traced achievements of BioNTech in development of the mRNA vaccine for COVID-19 alongside its partners, and looked at the road ahead in applying the science and technology to new areas, including oncology.

He gave an overview of the company's development from its launch in 2008 through Project Lightspeed for the development of the mRNA COVID-19 vaccine. He noted the great importance of risk consideration, having a process to assess and understand it, and discussing it, which enabled and empowered decisions. Partners—including Fosun Pharma, Pfizer, and regulatory agencies—collaborated and participated in the development and rollout of the vaccine in just 11 months.

The new class of medicines possible through mRNA is creating huge opportunities for the entire industry, Hennig said, including

vaccines, protein substitutes, and reprogramming for treatment of cancer, infectious and autoimmune diseases, and regenerative medicine. "mRNA is just getting started," he said.

The mRNA manufacturing process allows for rapid expansion, which may be helpful in responding to the needs in cancer therapy for individualized approaches and fast production. BioNTech has two mRNA platforms for cancer: FixVac, an off-the-shelf indication-specific mRNA cancer vaccine platform targeting a fixed combination of shared antigens, and iNeST, an individualized mRNA cancer vaccine platform, targeting 20 neoantigens unique to each patient. These are the basis of the company's work to expand offerings and make them available broadly around the world through its BioNTainers concept, a modular and scalable vaccine production approach for which models are being developed. Smaller-footprint standard manufacturing with ready-built modules that can be shipped to different locations is the goal, he explained, although it will not be suitable for all manufacturing needs.

The mRNA manufacturing process allows for rapid expansion, which may be helpful in responding to the needs in cancer therapy for individualized approaches and fast production.

Building a New Platform

Juan Andres, Chief Technical Operations and Quality Officer, Moderna, gave the closing keynote on 30 September, "Ideas to Performance: The Impossible Journey." He traced the journey of Moderna through its achievement of producing a vaccine for COVID-19 (which turned out to not be an impossible goal!). He spoke about the first decade of Moderna and its work with mRNA, and the path to preparing the vaccine and then ramping up distribution, as well as current realities and the path forward.

The journey began with the idea that making mRNA work for one solution could provide opportunities to apply it to many other solutions. This was not without risk; as Andres noted, risk management is essential to the work of building a new class of medicine. Moderna approached its development with the idea of building a manufacturing site that could scale up quickly, choosing from the start to work with an MES system, in a paperfree environment, and by monitoring movement of people to determine placement of equipment. All of these early decisions helped the company tremendously in its approach to creating a fully integrated and digital facility to produce mRNA and applying it as a platform to address rare diseases.

In 2015, Moderna introduced its first development candidate in its prophylactic disease modality, an H10N8 flu vaccine candidate; the next year, it began to build its Norwood, Massachusetts, facility, which opened in 2018. The ongoing development required every decision to consider both funding and technology focuses, he said. By 2019, among other achievements, the company announced dosing of its first monoclonal antibody encoded in mRNA in a clinical trial.

By January 2020, discussions were underway about whether the company was going to become involved in developing a vaccine to combat the "new virus," COVID-19. Although there were concerns that the company was not ready to produce product at the needed level, it decided to proceed. Within days, it had several mRNA candidates to consider. Its mRNA platform and technology helped the company be able to move swiftly to a first GMP batch on 7 February 2020, with clinical trials started in early March 2020. The science, previous work on mRNA, and prior collaboration with the government were all helpful, Andres noted, despite the lack of scale, infrastructure (including people), and funds.

Through March and April 2020, Moderna employees worked seven days a week for up to 14-hour days. The company had experience with preclinical and clinical batches, and CMC variability was top of mind. The kit concept was established—a standard drug substance production train linking mRNA and lipid nanoparticles (LNP) manufacturing—to allow for reproducible production to permit broader-scale production. After success at small-scale production, Moderna joined forces with partners, including Catalent and Lonza, as the vaccine progressed through Phase III and then emergency use authorization (EUA) status. Having experienced partners was necessary to success, he noted, and included Operation Warp Speed officials as well as suppliers. Shortages of materials (including plastic and glass), funds to purchase equipment, and the wait for equipment were also challenges.

The launch of the vaccine was a collaborative effort, he noted, with great commitment from Moderna employees and those working with its partners. The lessons learned during those months have potential to be applied elsewhere. Moderna has grown from 300 people to 3,000 and has over 40 programs underway in vaccines as well as immunology, oncology, and rare diseases. "This is just the beginning," he said.

ABOUT THE AUTHOR

Susan Sandler is ISPE Senior Director, Editorial.

COMMUNITIES OF PRACTICE PROFILES: Shaping the Future of the Combination Products Industry

By Marcy Sanford

Combination Products is one of ISPE's newest Communities of Practice (CoPs). It started as a Special Interest Group to help people in the industry collaborate and learn from each other.

According to ISPE Combination Products CoP Chair Susan Neadle, "a combination product is composed of two or more differently regulated medical products, i.e., constituent parts, that are to be used together, or are being studied for use together, to achieve an intended use, indication, or effect. Given terminology differences across jurisdictions, these products are sometimes more broadly referred to as 'combined use systems.'

"Such combined use inherently raises questions that need to be considered and that may lead to a range of risk management approaches during product development and postmarket life cycle. There are a plethora of examples spanning a wide gamut of therapeutic areas: for example, drug-prefilled syringes and auto-injectors, metered-dose inhalers, medicinal patches, drug-eluting discs, drug-eluting stents, and, increasingly, connected health applications. The regulatory frameworks for these products vary from country to country. In the US, each constituent part retains its regulatory identity in a combination product. The cGMPs that apply to each constituent part of a combination product also apply to the combination product, and necessitate assessment of, and controls for, any potential interactions of the constituent parts."

The Combination Products CoP is "focused on the evolution of combination products technology and combined use systems, as well as the shifting global landscape of regulatory expectations for these products," Neadle said.

CoP DEVELOPMENT

"I became active in the combination products space during my 26-year career with Johnson & Johnson," Neadle said. "While there, I provided end-to-end global functional and program leadership for drug-device combination products, establishing an integrated cross-functional business model to meet combination products' health authority regulations while still ensuring the business sustained growth momentum.

"I saw an opportunity to collaborate with and support colleagues across the industry in this space and got approval to start a special interest group in ISPE. We started with about eight people five years ago, and now are a full-fledged CoP, with more than 55 active members from US, Europe, Canada, and India."

In addition to serving as Chair of the CoP, Neadle is Principal Consultant, Combination Products Consulting Services, LLC; she also serves as lead author on both the ASTM International Combination Products Standard and AAMI Combination Products Committees, teaches a master's curriculum on combination products at University of Maryland Baltimore as part of ISPE Workforce of the Future initiative, serves on AAMI faculty, and is active on a number of other impactful industry committees.

Pharmaceutical Engineering® recently spoke with Neadle about the CoP and issues related to the importance of combination products in the industry.

Why is your CoP's work critical to ISPE and the industry?

Combination products are designed to offer greater benefits than the drugs or devices acting alone, and increasingly, drugs are dependent on medical devices for their administration. This is particularly the case in the rapidly growing biologics space. Couple this with connected health and the promise of improved healthcare through digital technologies, and the possibilities seem endless. Health authorities recognize that bringing together these drug and device systems brings more risk and complexity, and they are shifting their regulatory frameworks to ensure safety, efficacy, and functionality of the combined use systems.

Our charter includes four main priorities. We want to (1) raise awareness regarding the evolving global combination product regulatory landscape; (2) help shape evolving regulations through commenting, industry publications, and advocacy—we have already submitted comments this year on evolving regulations to the European Medicines Agency, Health Canada, US FDA, and the World Health Organization; (3) educate our members by sharing best practices, supporting successful combination product development through postmarket life cycle management; and (4) be a space for combination products networking and collaboration.

What is most important for ISPE members to know about the CoP?

We have industry representatives spanning international pharmaceutical, biotech, and device companies, as well as consultants. We have monthly presentations on a range of interest areas by CoP members and guest speakers covering current state-of-the-art technology, quality, and regulatory hot topics.

Our CoP also has subteams. For example, we have a subteam on regulatory intelligence and another that is supporting the ISPE effort to develop a streamlined Module 2 QoS to incorporate combination product considerations.

The CoP meets monthly. Our agenda always includes at least one hot topic presentation by industry leaders. For example, Edwin Bills, Principal Consultant, ELB Consulting, presented on risk management and ISO 14971:2019 at a recent meeting. I presented on the US FDA's proposed rule for 21 CFR 820 and global combination products harmonization efforts. Jennifer Riter, Senior Director, West Pharmaceutical Services, presented on extractables and leachables in primary containment systems and medical devices. We have also had presentations on combination product essential performance requirements, human factors, post marketing safety reporting, digital health, reliability, and validation. The presentations are recorded and minutes issued so that CoP members have access to the great presentations and discussions after the meetings.

Another way that we have shared information about combination products is through blogs on iSpeak. For example, one of our CoP members, Ryan Hoshi, Director, Regulatory Policy and Intelligence, AbbVie, recently published a blog on digital health. We are also planning to submit articles to *Pharmaceutical Engineering* on combination product EPRs, human factors, and digital health.

At the 2022 ISPE Annual Meeting & Expo in Orlando, Florida, representatives from the US FDA commented on evolving regulations and enforcement, and Boaz Eitan, CTO, Eitan Medical, presented on evolutions in technical solutions for medicinal therapies.

How can ISPE members become involved in the CoP?

Just reach out! You can email me directly at sneadle@combinationprod.com.

> Combination products are designed to offer greater benefits than the drugs or devices acting alone, and increasingly, drugs are dependent on medical devices for their administration.

The connections I've made through this CoP have meant a lot to me. The group has developed friendships and a wonderful network of people with like interests. There are so many opportunities for knowledge networking and helping one another. It is very fulfilling to see what we are accomplishing and knowing we are making a collaborative positive impact on the industry and the patients we all serve.

About the author

Marcy Sanford is ISPE Publications Coordinator.

Enabling More Efficient and Effective C&Q Through GEP

By Chip Bennett and Jörg Block

When the ISPE *Baseline Guide Vol. 5: Commissioning & Qualification,* 2nd ed. was published in 2019, most of the attention was focused on the incorporation of quality risk management (QRM) into the integrated commissioning and qualification (C&Q) approach. That attention was merited, as the guide established the industry-standard approach, strategy, and rationale for science- and risk-based design and delivery of engineered systems. However, equally important from both a business and regulatory perspective, the guide established good engineering practice (GEP) as a key enabler for the integrated C&Q process. Just as QRM drives effectiveness of the integrated C&Q process, GEP drives the efficiency of that process.

The 2021 publication of the ISPE *Good Practice Guide: Good Engineering Practice,* 2nd ed., (GEP GPG) updated the definition and understanding of GEP within a regulated industry, establishing GEP as a life-cycle approach supporting the effective, efficient design and delivery of engineered systems and enabling the QRM-based integrated C&Q process.

An effective C&Q process results in systems that are installed and operating in a manner fit for intended use and meeting all user requirements and stakeholder expectations. For critical systems, fitness for intended use is defined by system critical design elements (CDEs) being installed and operating in a manner to deliver system critical aspects, which ensures system performance to control critical process parameters (CPPs) and process performance to produce product meeting its critical quality attributes (CQAs).

Aligning with the ISPE *Baseline Guide Vol. 5, Commissioning & Qualification, 2 ed.,* the GEP GPG recognized GEP as a life-cycle approach, encompassing "all aspects of engineering related to the design, delivery, and operation of facilities and engineered systems, from conceptual design to retirement." Maintaining the qualified state of critical systems with focus on CDEs throughout their operational lifetime is in the scope of qualification per good manufacturing practices (GMP), whereas maintaining engineered systems installed and operating in a manner fit for their intended use falls under the scope of GEP core concepts and practices. This article discusses the application of GEP to enable more efficient and effective C&Q primarily within the scope of the design and delivery of engineered systems (i.e., through system acceptance and release).

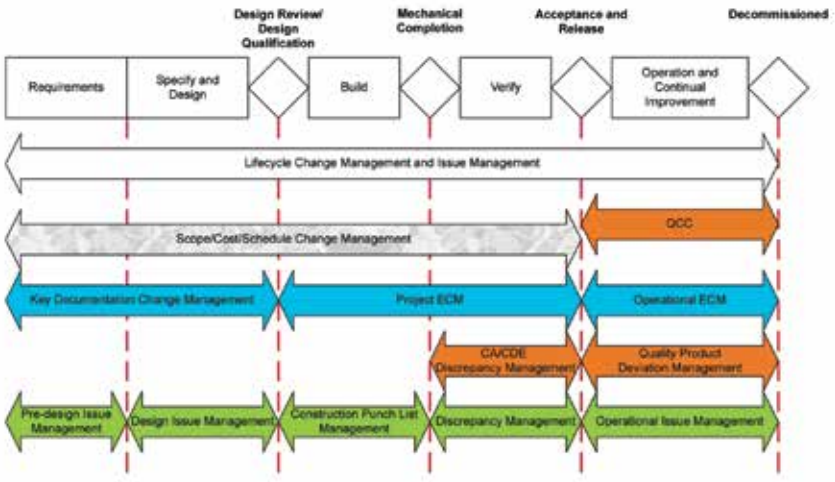
SYSTEM LIFE-CYCLE PROCESSES

Application of engineering change management (ECM), engineering document management, and engineering issue management throughout the C&Q process can significantly reduce time, cost, effort, and risk. These systems ensure that management efforts are properly scaled to risk, complexity, and system life-cycle stage and that management decisions are risk-based and are led by appropriate SMEs. Appropriate ECM and document management ensures that proposed changes are identified, assessed for impact, implemented, and verified. Appropriate engineering issue management, including issues, punch lists, and discrepancies, ensures that observed issues are properly identified, managed, investigated, resolved, and verified (see Figure 1).

During the requirements definition and specification and design stages, ECM ensures that changes to key documentation, including user requirements specifications (URS) and the design development, are managed appropriately. Engineering issue management ensures that design issues identified through design review are tracked and managed to resolution.

During the build/construction, installation, and verification stages, project ECM ensures that changes to design and implementation are managed appropriately, with quality oversight

Figure 1: Overview of life-cycle change management and issue management processes.



focusing on CDE-related changes only. Punch list management ensures that issues observed during build, construction, and installation are managed appropriately. Discrepancy management during verification ensures that verification testing and documentation discrepancies are documented and resolved appropriately.

Documentation of these changes and issues provides traceability of the system state throughout the design and delivery process and as such is critical to eventual acceptance and release of systems. The acceptability of documented engineering management of system and documentation changes and design/build/verification issues represents a key driver of system acceptance and release to manufacturing by the quality unit, which ultimately defines the effectiveness and efficiency of the C&Q process.

PROJECT ENGINEERING-RELATED PRACTICES

Robust application of risk management through the project execution plan, including use of a project risk register, can help identify, prioritize, and control project risks to scope, schedule, and budget, as well as risks to the quality of the delivered system. Risks identified early in a project are generally easier and mostly less costly to control. Rigorous control, monitoring, and reporting of project costs drives cost-effective delivery of engineered systems.

SYSTEM DESIGN-RELATED PRACTICES

Since rigor of system design and delivery must be commensurate with risk (particularly risk to product quality and patient safety), correct identification of systems and process functionality that potentially impact product quality and patient safety play a significant role in ensuring that overall effort and documentation of the C&Q process is right sized in terms of scope, schedule, and cost. Accordingly, determination of system boundaries and appropriate definition of system user requirements directly impacts the strategy, effectiveness, and efficiency of the C&Q process. System boundary definitions should consider inclusion/exclusion of CDEs, system intended use, anticipated future system modifications, physical interfaces to other systems, and linkages to automation, control systems, and data handling and storage.

A typical industry example is design of cleanrooms and the HVAC systems that supply them, where the cleanroom is the quality impacting system and the HVAC system is a separate system with a terminal HEPA filter at the system boundary. Where the system boundary can be defined such that the HEPA filter is included in either the cleanroom or the HVAC system, the boundary decision will have significant impact on the scope, schedule, and cost incurred in design and delivery of the two systems. This typically is decided in an early stage of the project. Including the HEPA filter with the cleanroom ensures that all CDEs for the two systems are contained within the boundary of a single, direct-impact system (the cleanroom), resulting in the HVAC system not being direct-impact and significantly minimizing the rigor and documentation required to design and deliver the HVAC system. Alternately, including the HEPA filter with the HVAC system results in CDEs being included within the boundaries of both systems, which are then both direct-impact systems, significantly increasing the rigor and documentation required to design, deliver, and maintain the HVAC system.

System requirements definition through the URS should align with system boundary definitions. The URS then becomes the driver for demonstrating that a system is fit for intended use through verification activities that document system installation and operation conform to the URS. Well-defined user requirements thus drive the effectiveness and efficiency of the C&Q process.

What is specified in the URS must generally be demonstrated and documented through the C&Q process; therefore, the efficiency of the C&Q process can be significantly impacted by the scope and quality of the URS. The URS should include system/

equipment CPPs traceable to product CQAs delivered or impacted by the system. Requirements should focus on key stakeholder requirements—what is required of the system—and should generally not include engineering standards/specifications, design definitions/assumptions (how the system will be implemented) or vendor contractual obligations. Requirements should be differentiated between those that potentially impact product quality and patient safety and those that do not, such as business- or safety-related requirements. Requirement specifications should be SMART: specific, measurable, achievable, realistic, and traceable. SMART requirement specifications lead to SMART design specifications and SMART verification acceptance criteria, and therefore directly impact the scope, time, and cost associated with system design and delivery.

Design review plays one of the most critical roles in driving effectiveness and efficiency of the C&Q process. A robust design review process ensures that the design definition satisfies both the quality impacting and non-quality impacting user requirements, identifies and manages design discrepancies to resolution through application of engineering issue management, and therefore minimizes the time and cost associated with resolution of design issues, particularly when compared to the cost of issue resolution during verification of systems following build/construction and installation.

SYSTEM DELIVERY PRACTICES

Applying risk management to vendor selection and management can have significant impact on delivery of systems meeting user requirements and on the suitability of vendor documentation to demonstrate system fitness for intended use. Appropriate vendor management can significantly impact overall time and cost for system design and delivery. Ensuring vendors follow GEP for system design and build, including vendor document, change, and issue management, will reduce design/build time and cost, will minimize issues that must be resolved later in the project (such as during factory acceptance testing or post-delivery/site acceptance testing), and will increase the likelihood of suitability of vendor documentation to contribute to the overall verification effort and documentation. Where vendor documentation is suitable for verification, non-value-added redundant verification testing and its associated costs, schedule, and resources can be significantly reduced or eliminated.

Established GEP procedures for construction, handover, and startup similarly ensure that documentation produced during these activities can contribute to the overall verification effort while minimizing rework and testing redundancy.

ENGINEERING QUALITY PROCESS: THE ENABLER

Finally, development of an engineering quality process (EQP) ensures that the quality unit is aligned with application of GEP to design and deliver critical systems and that engineering documentation produced through the C&Q process is suitable to accept and release systems for use in manufacturing. The EQP provides a means for the quality unit, through auditing and other appropriate oversight, to develop trust in the established and maturing GEP processes used to design and deliver engineered systems through the C&Q process.

Unlike in the legacy C&Q process, where direct quality oversight (review, pre- and postapproval, and use of "quality" protocols) was required to "leverage" engineering verification testing and documentation into qualification, the QRM-based integrated C&Q process applies the principle that engineering testing and documentation produced by appropriate subject matter experts and following appropriate, established GEP procedures stands on its own. The EQP provides the critical linkage between established GEPs that yield engineering verification testing and documentation and the requirements of the quality unit to accept it. As stated in the GEP GPG, "The purpose of establishing an EQP is not to introduce quality oversight and control of engineering activities performed under established GEP, but rather to provide a mechanism for quality to provide appropriate oversight of engineering management and control of GEP processes, so that those GEP processes can be applied by engineering in the delivery of critical (quality impacting) systems through the C&Q process." (ISPE GEP GPG, 2nd Edition, Chapter 13, Enablers–Engineering Quality Process [EQP], Section 13.1.1, Purpose).

CONCLUSION

The effectiveness and efficiency of design and delivery of engineered systems and facilities play a crucial role in speed to patient. Applying GEP ensures that design and delivery efforts are commensurate with risk; engineered systems and facilities are delivered in a state of installation and operation fit for intended purpose; and unnecessary overhead, oversight, testing and documentation redundancy and overall scope, schedule, and cost are minimized.

About the authors

William "Chip" Bennett is a PMI Certified Project Management Professional (PMP) and a recognized industry expert, speaker, and published author. He is a consultant with more than 20 years of experience in the pharmaceutical and regulated nonpharmaceutical industries and with expertise in risk-based C&Q, aseptic manufacturing, cleaning validation, quality systems, and owner project management. Chip is responsible for developing and implementing quality risk management (QRM)-based commissioning and qualification programs and projects, with a particular focus on assessing and training clients regarding development, implementation, and transition to risk-based approaches. As a quality consultant, Chip has experience with quality systems, QRM, risk assessment, root cause analysis, change control, CAPA, and failure investigation. Chip has managed facility qualification and cleaning validation projects for clients in the medical device and regulated non-pharmaceutical industries. Chip holds a BS in chemical engineering and certifications in Crucial Conversations, Crucial Accountability, and The Power of Habit Training. He has been an ISPE member since 2003.

Jörg Block is a Chemical Engineer with a PhD in biochemical engineering at Bayer AG Pharmaceuticals. Jörg has more than 30 years of experience in the pharmaceutical industry and is now taking care of GMP compliance in pharmaceutical engineering. He has held positions in engineering, project management, production, development, and QA engineering. He is a member of the ISPE Commissioning and Qualification Community of Practice Steering Team, and an author of several ISPE guidance documents including the ISPE *Baseline Guide, Vol. 5, Commissioning and Qualification,* 2nd ed., and the *Good Practice Guide: Good Engineering Practice*, 2d edition. He has been an ISPE member since 2003.

New GPG Explores Membrane-Based WFI Systems

For nearly a century, production of water for injection (WFI) was universally accepted to be distillation-based. As emphasis on costs and environmental concerns has grown, pharmacopeias around the world have focused on the quality attributes of WFI to allow for consideration of other production technologies.

In 2017, the European Pharmacopoeia joined the US, Japan, and many other regulatory bodies (with the exception of China) in accepting membrane-based technologies for WFI production. The ISPE *Good Practice Guide: Membrane-Based Water for Injection Systems* provides expert guidance on the design, operation, maintenance, and quality aspects of membrane-based WFI systems, including generation, storage, and distribution.

"Membrane-based water for injection is a state-of-the-art method that should be used whenever possible," said Good Practice Guide (GPG) Co-lead Fritz Roeder, Global Engineering Manager, Merck Healthcare KGaA. "This GPG will be useful to engineers, production, quality assurance, and quality control professionals and regulators who have some water expertise."

This is a first-of-its-kind guide that presents a global view of membrane-based WFI generation technologies and their impact on the storage and distribution system. It "provides an objective discussion of current best practices as well as critical technical information pertaining to membrane-based WFI systems," said Guide Co-lead Brian Pochini, Principal Engineer, Sanofi. "The guide reflects an industrywide collaborative effort by a diverse range of experts that includes equipment providers, engineering firms, consultants, and pharmaceutical manufacturers to present a holistic view of the pros and cons of membrane-based WFI systems."

For more information about the guide, visit ISPE.org/publications/guidance-documents

—Marcy Sanford, ISPE Publications Coordinator

Meet the ISPE STAFF

Tim Postlethwaite

In each issue of *Pharmaceutical Engineering®*, we introduce a member of the ISPE staff who provides ISPE members with key information and services. Meet Tim Postlethwaite, Director of Technical Communities.

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

My primary role is to work with more than 20 ISPE Communities of Practice (CoPs) and Special Interest Groups (SIGs) that generate much of the key ISPE output: Guidance Documents, webinars, PE magazine articles, iSpeak Blog posts, training materials, and conference content. I meet through standing meetings with the CoP Steering Committees and SIG leadership teams, comprised of nearly 350 ISPE member volunteers, to support and guide their efforts, including generating and executing annual content plans. I serve as a liaison between the technical community members and other ISPE staff members who facilitate content delivery. I work with the ISPE Knowledge Network Council, ISPE senior leadership, and the ISPE Board of Directors to monitor the health of each community, to sunset communities, and to establish new communities as the needs of the pharmaceutical industry evolve.

What do you love about your job?

Having spent time working in the pharmaceutical industry prior to joining ISPE, I really enjoy maintaining contact with pharmaceutical professionals across the globe daily. I am constantly astonished by the commitment and knowledge our volunteers bring to bear to create outstanding content to forward the entire industry. ISPE provides a place where technical communities comprised of subject matter experts, many from competing companies, come together to share best practices and contribute to the betterment of the industry. My role also provides the opportunity to collaborate with most ISPE staff, which is a fantastically supportive group of colleagues.

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

Having recently relocated to Lake County in central Florida, I enjoy boating, bass fishing, dodging alligators, and DIY home projects. My wife and I enjoy spending time with family and friends, traveling, and keeping up with our daughter who is pursuing a graduate degree at Florida State University.

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AI RETROFIT:

Tackling Challenges with Cutting-Edge Technologies

By Christian Stirnimann and Julien Janda

This artificial intelligence (AI) retrofit project was a unique approach to implementing AI technology in a pharmaceutical environment within three months. This project tackles a commonly known industry challenge by integrating AI into an existing automatic visual inspection (AVI) machine. The proof of value allowed us to benchmark added value through AI compared with state-of-the-art automated visual inspection. We also gained process and business insights that contribute to AI implementation and strategy. Outcomes derived in this project were transformed into implementation guidelines and requirement specifications to support AI in other initiatives. Key success factors describe how to leverage the powerful AI potential to create value for patients.

Visual inspection is an essential step in parenteral drug production, as it ensures the safety of the drug product in its container. Manual inspection and automated systems can achieve a similar level of sensitivity, but there are specific strengths and weaknesses for both methods. Pharmaceutical companies rely on AVI to overcome challenges associated with manual inspection, such as low inspection throughput and performance variations. However, AVI machines have a trade-off between the configuration of the AVI sensitivity and the false rejection rate (FRR). The more variations and details that an inspection task considers, the higher the number of falsely identified defects in safe products. This article discusses a project that explored AI capabilities to leverage the inspection performance on an existing application and gain additional business insights by tackling a real-world challenge.

PROJECT SCOPE

Glass ampoules, as illustrated in Figure 1, offer protection against air and contaminations and are widely used as the primary packaging for pharmaceutical drugs. They are hermetically sealed by melting the thin top with an open flame, and once closed, provide superior imperviousness to gases and liquids.

One specific defect in the inspection of ampoules are black spots in the tip area (Figure 2), which occur during the fill and finish process. Today's available machine vision technology is capable of catching these tiny black spots. The technology combines high-resolution cameras with a backlight setup, which highlights the tiny black spots as dark pixels on a white background in the image. The challenge of such systems occurs when additional bubbles of the liquid product stick in the tip area of the ampoule. Based on their size, geometric form, and location, these bubbles can look similar to black spots, which ultimately challenges

Figure 1: Glass ampoules for pharmaceutical products.

classic machine vision algorithms to distinguish between bubbles and real defects. This common industry issue often results in an increase in the FRR.

The optical setup provided the resolution to visualize defects and therefore fulfilled the basic requirement of using advanced AI algorithms to tackle a real-world challenge in an existing production environment. Enhancing the inspection tasks with AI algorithms covered the central part of the project scope. An agile approach combined with specific requirements for a minimum viable product (MVP) enabled the team to integrate the AI box, collect images and store them in a classified image database, and deploy the first AI model within 24 hours. Following this approach not only established a realistic benchmark using AI algorithms in a qualified process, but also provided valuable business insights regarding the inspection process in a GxP environment.

Figure 2: Black spots (red) and bubbles (green) in machine vision technology.

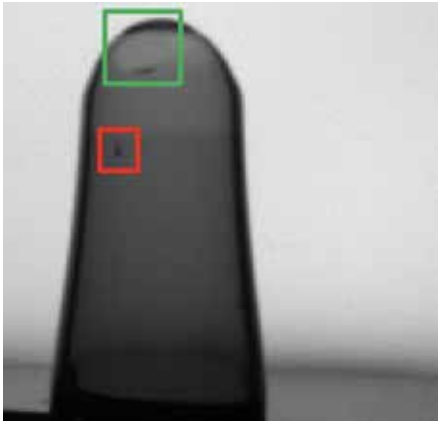
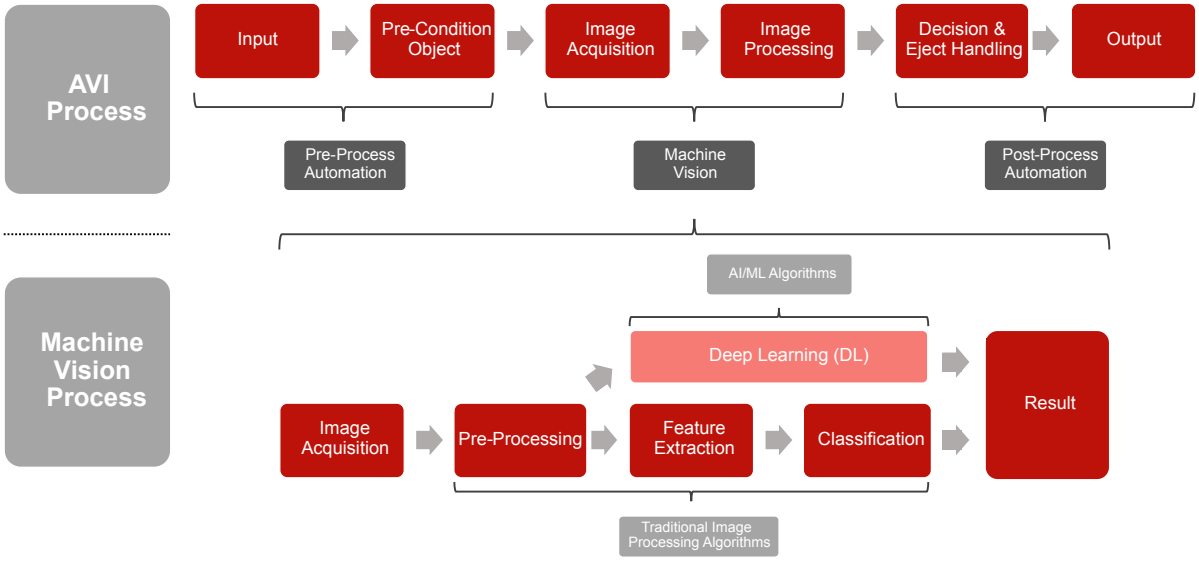


Figure 3: AVI and the machine vision process.



INTEGRATING AI INTO AN EXISTING AVI MACHINE

A successful AVI process, illustrated in Figure 3, ensures ideal interaction between mechanical engineering, optical imaging, image processing, and automation. In this project, the ampoules are smoothly rotated and presented to the tip inspection stations, which encompasses the pre-process automation step. Two cameras capture the tip area from different angles, with five images per camera, to establish a 360-degree view during rotation. After processing these images and inspecting for defects, the AVI machine rejects defective products according to the result of the visual inspection process.

The main challenge in integrating the AI retrofit was determining how to enable access to the images in the vision system and then process them through a neural network and return a result within the given timeframe of the AVI process. Different solutions are available to solve this problem. The evaluation process for this use case resulted in the integration of the deevio AI-Box. The deevio AI-Box is a proprietary vendor solution that provided a powerful AI platform equipped with all the necessary interfaces to ensure a smooth integration into an automated process that was parallel to the traditional image processing algorithms, emphasized in the visual inspection process flow shown in Figure 3. Additional pre-processing steps, such as cropping images, further increased the AI processing time by a factor of two and optimized the bandwidth by focusing on the essential parts in the images.

Figure 4: Integration of the deevio AI-Box into the existing system architecture.

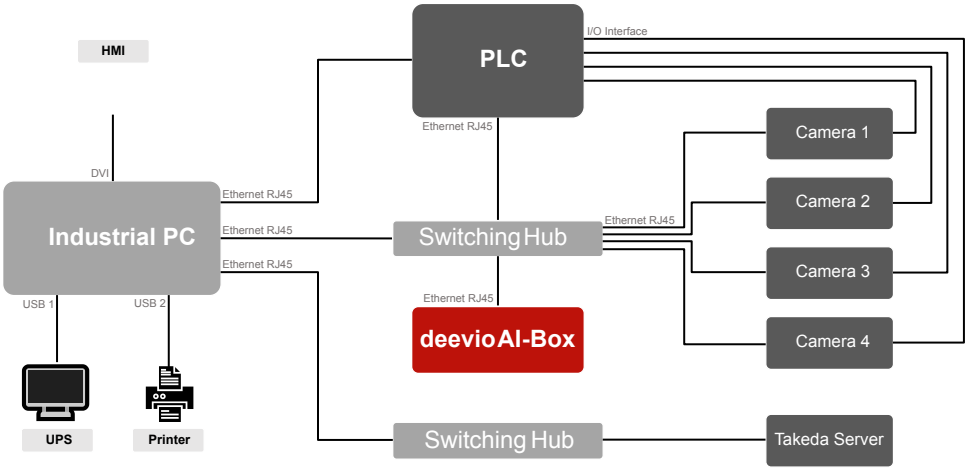


Figure 5: AI/ML approach in the continuous improvement process.

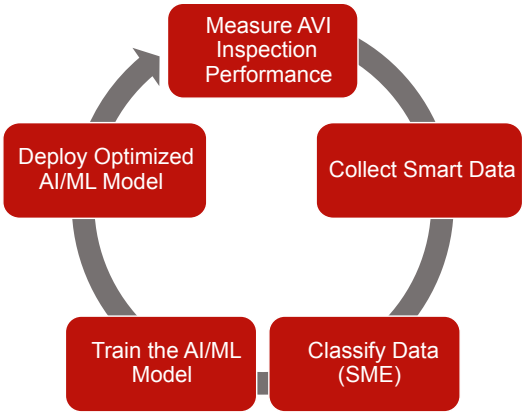


Figure 4 illustrates the straightforward integration of the deevio AI-Box into the existing system architecture by connecting the AI box to the switching hub. A simple file transfer protocol and additional settings in the inspection stations relayed the images to the deevio AI-Box, which processed these images through neural networks within milliseconds to comply with the given time constraints of the machine. Finally, an inspection performance of 420 ampoules per minute, or seven ampoules per second, was achieved.

KEY SUCCESS FACTORS IN USING AI

The foundation for every successful AI project is to build a database that consists of high-quality images and high-quality data labels. Because the team used the existing vision system already in production, the high quality of the images itself was given, which made it easy for a human to distinguish between images without any defects, classified as OK, and images containing defects , which were classified as not OK (NOK). The starting point to train the first AI model was the image collection of a test set of ampoules, including defective samples and good samples, that were processed through the machine. Having the AI box running in parallel to production continuously increased the image database with real production experience and consequently enabled continuous but controlled learning of the algorithm. Figure 5 illustrates the AI learning approach within the continuous improvement process.

Two factors improved significantly: the accuracy of the AI model and the labeling process. First, it is imperative in the development of the AI model to have the images labeled by subject matter experts (SMEs) who are familiar with the visual inspection process, specifically with the defects. Second, determining how to handle the sheer amount of data produced by an AVI machine during the labeling process is also integral. During the MVP phase, over 3,000 images were collected and classified into a sustainable database. In addition to the user-friendly interface provided by deevio's user interface tool, the confidence score of each image was also archived, which enabled a pre-sort of the latest images. This function made the labeling experience quite convenient and allowed the team to efficiently maintain the database and create a smooth labeling process.

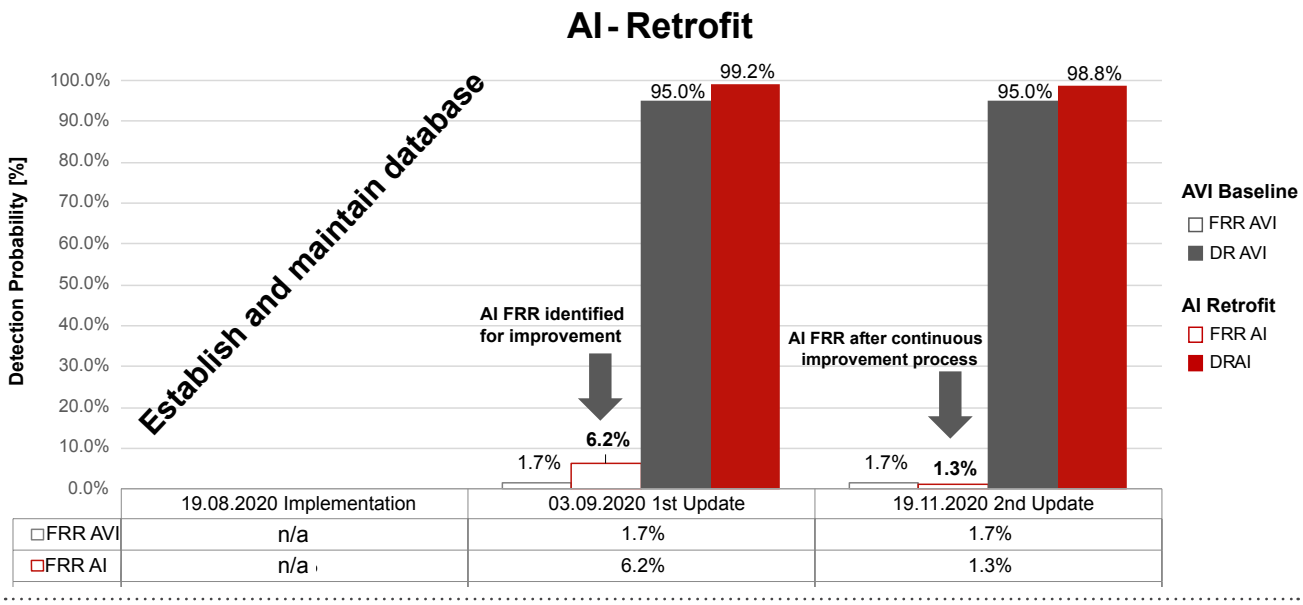
PROOF OF VALUE

After the successful integration of the MVP, we had an AI system running that enabled us to gain further understanding of AVI in combination with AI. As a result, the project team started to explore the proof of value by focusing on three specific use cases.

Use Case 1: Benchmark of an Existing System Equipped with AI Algorithms

While the AVI machine ran in production, the AI system continuously collected images in parallel. This setup allowed us to

Figure 6: Benchmark AI performance.



compare the detection rate (DR) and the FRR with an existing and qualified system that was in production for over 6 years. Figure 6 shows the evolution of the inspection performance throughout the project timeline. The goal was to outperform the average baseline of 95% DR and 1.7% FRR generated on the AVI machine specifically for black spots. The first 3 weeks after the implementation were used to collect images and establish a database.

Optimizations on the first AI model achieved a DR of 99.2%, which outperformed the baseline by 4.2%. However, the FRR of 6.2% needed to be improved during the following weeks. Adding images, improving data label quality, and the recall optimization approach of the AI model—which is the performance metric targeted to decrease the FRR—were the primary goals in the improvement process. Finally, 3 months after implementing the deevio AI-Box, a second AI model was deployed that outperformed the baseline with a DR of 98.0% and a significant drop of the FRR from 4.9% to 1.3%, which is 0.4% better than the target FRR.

The performance of the AI model can still be further improved by optimizing the recall of the AI model and providing more well-labeled data in the future to decrease the FRR value close to 0%. The consequence might be that the DR value gets slightly worse. However, the addition of further data can solve this problem. All decisions taken in the optimization cycle are risk based and consider quality and business aspects. Creating a benchmark of the two systems not only confirmed the positive impact of AI, but also transformed the added value into tangible and comparable data that can be useful for business case considerations.

Use Case 2: Develop the Process Behind the Technology

In addition to the performance of new technology, its integration into an existing pharmaceutical environment is important, including its challenges. Therefore, processes were developed to integrate AI into a GxP environment. An important consideration was the evaluation of the most suitable algorithms to solve the specific problem statement. The deep learning (DL) method seemed to be a promising approach for our use case. DL is based on neural network architectures with multiple layers and has been successfully used to solve multiple problems in image recognition. The visual inspection process illustrated in Figure 3 identified AI algorithms as an algorithm set complementary to the traditional machine vision algorithms. Therefore, the process to deploy AI models according to Figure 5 was developed and adjusted to the AVI standard continuous improvement process to enable a smooth integration into the existing AVI process.

Previous experiences have taught us to use a supervised learning approach because of the possibility of freezing a model before the deployment on an AVI system. This enabled controlled learning and was an essential outcome for the qualification concept of an AI algorithm in a GxP environment. Furthermore, in the pharmaceutical validation processes, it is crucial to understand how and why AI models work. Therefore, integrated gradients were introduced to answer these questions and increase the understanding of AI models. This function aims to explain the relationship between a model's predictions and its features by creating a

colored mask that is overlaid on the original image. Based on the model's decision, all important areas and pixels are then highlighted according to a color scheme that is instantly and intuitively visible to the user, which ultimately provides a better understanding of the model's predictions.

Use Case 3: Business Insights from Implementing AI Algorithms into Existing Equipment

This specific use case explored the business perspective derived from the MVP. The development of an AI solution that was relatively easy and fast to implement and test as well as being cost efficient solved a real-world challenge. Further, it ultimately increased the awareness and understanding of AI technology, specifically the importance of image acquisition, capabilities of the hardware components, integration in current system architecture, and handling of large data sets. All these outcomes were consolidated and summarized as user requirements or implementation guidelines to support future AI projects. Finally, important lessons were learned to support a data-driven and AI-enabled organization, such as exploring required infrastructure, capabilities, interfaces, and processes; defining an AI governance; and establishing other valuable inputs to the AI strategy.

KEY TAKEAWAYS

The impressive performance achieved by the AI MVP outperformed the existing system in only 3 months and highlighted the powerful potential of AI solutions. The AI retrofit project not only confirmed an improvement in the inspection performance but also enabled valuable insights into implementing AI technology in the manufacturing environment. On a technical level, user requirements—such as the importance of high-quality image acquisition, powerful hardware, and software components—were identified. One key success factor was establishing and maintaining a sustainable database, which set the foundation for other AI solutions.

The implementation of AI into an existing AVI machine also allowed us to develop guidelines and concepts to cope with existing processes and pharmaceutical regulations. Another significant outcome was using critical thinking and a risk-based approach when relying on AI algorithms. It is never a one-size-fits-all solution. Finally, the AI retrofit approach started with a clear value proposition, but it also leveraged additional business insights to generalize further AI implementations and enabled the organization to explore and improve AI capabilities for future projects.

NEXT STEPS

An essential next step for the project team is to tackle the technology challenges identified during this project, such as the feasibility of updating the hardware components in the existing machine, equipping the vision system with the needed computing power, and integrating the AI solution in the AVI system, including different communication layers and user interactions (e.g., visualization or recipe and user management). The project's successful outcome was also directly linked to the ability of the project team to develop new out-of-the-box ideas beyond the AI retrofit project, which consequently triggered new AI initiatives within the network and identified opportunities to improve AI capabilities. Finally, the project team is interested in fostering discussions around AI topics with other pharmaceutical companies, AI suppliers, and communities to exchange best practices and lessons learned to drive AI solutions in the pharmaceutical industry.

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REMOTE ACCEPTANCE TESTING of Automation Projects

By John O'Sullivan, Tom O'Kane, and Brian O'Flaherty, MSc, PhD

Before the COVID-19 pandemic, it was unthinkable for a system integrator to suggest remotely conducting an acceptance test for an automation project. This article shows how automation engineers and client validation personnel were successful in navigating COVID-19 restrictions and overcoming previously held preconceptions about remote testing to meet end-user and regulatory requirements. Although there were some advantages, both testers and reviewers found the experience inefficient and unsatisfactory in terms of rapport and visibility.

Before the COVID-19 pandemic, acceptance testing of automation projects was conducted in person, with multiple subject matter experts attending. Factory acceptance tests (FATs) were conducted on the system integrator's (SI) premises, executed by a representative of the SI and witnessed by a representative of the client. FATs could be a simulated operation of the automation system on a bench or the full operation of a machine, skid (prefabricated modular process), or system. Site acceptance tests (SATs) were conducted on client sites in situ, after initial commissioning and before operations. During SATs, all field equipment is connected and operational.

Acceptance test protocols are executed during FATs and SATs. They are approved before execution and during execution; the tester and reviewer/witness initial and date each test and sign that the tests were conducted correctly. The aim of the tests is to verify that the system is compliant with the requirements and the design specification. The granularity of the requirements can vary between industries. In the pharmaceutical sector, the ISPE Good Automated Manufacturing Practice (GAMP) [1] is used as a guide.

Measures had been put in place to reduce the close contact of engineers during COVID-19 restrictions, including working from home, and this presented a unique set of challenges for those working in the sector. The writing of requirements, design documentation, and test scripts, and the configuration of hardware and software, can be conducted from home. However, conducting remote factory acceptance testing requires a methodology to allow projects to proceed to the site for site acceptance testing for validation before handover. The objective of our research: What techniques and procedures are required to enable reliable remote acceptance testing of automation projects?

This was a qualitative field study conducted on five automation projects across three SIs and four clients. One client is a medical device manufacturer in Ireland. Another two clients are pharmaceutical manufacturers, also in Ireland. The fourth client is a waste recycling company in Australia. Seven interviews with automation testers and client reviewers were conducted. Qualitative data analysis using the thematic analysis methodology was performed. As reported by Pazhayattil and colleagues, remote testing of biopharmaceutical manufacturing facilities has been successfully executed [2].

Due to the COVID-19 pandemic and associated restrictions, remote acceptance testing was the only way these tests could be conducted. In these scenarios, the tester is present with the equipment and the reviewer is remote, either at work or at home. Computer screens are shared via remote viewing software; equipment is viewed using webcams, smartphones, or wearable cameras; and participants communicate using telephone, voice over internet protocol (VOIP), or text message. Despite the prevalence of remote acceptance testing in the COVID-19 pandemic, a search for literature on remote acceptance testing yielded no appropriate results.

RESEARCH OBJECTIVE

The research objective is to determine the techniques and procedures that are required to enable reliable remote acceptance testing of automation projects while maintaining compliance with regulatory requirements and industry norms. During the COVID-19 pandemic, the US FDA issued guidelines for remote evaluations of drug manufacturing and bioresearch facilities [3]. This is preliminary research based on a limited number of participants with a view to prompt publication.

Research Questions

The following research questions serve to achieve the research objective:

- What techniques and technologies are employed to facilitate remote testing?
- What are the advantages and disadvantages of remote testing compared to in-person testing?
- How are projects affected from commercial, quality, and schedule points of view?

RESEARCH DESIGN

As a sociotechnical system, research in the field of information systems needs to be defined in a number of ways in order to establish the best approach, methodology, data collection, and analysis choices.

Philosophical Overview

The philosophy chosen, and hence the methodology, depends primarily on where the research sits on the objectivism–subjectivism continuum. Without going into the detail of how it was established, the author chose a value-free axiology, a conventional ontology, and an opinion-based epistemology [4]. The combination of regulation and subjectivism leads to an interpretivist philosophy of research [5]. In this article, the phenomenologist paradigm approach is taken, i.e., using the lived experience of the participants to understand the phenomena. Trustworthiness and authenticity are measures of quality in interpretivism [6].

Theory Development and Methodology

In this research, themes emerge from the data collected, which in this case were interviews with practitioners. This is the definition of the inductive approach to theory development. The methodology, strategy, and time horizon were chosen with the development of a timely report in mind. Forgoing the luxury of triangulation, due to limited access because of COVID-19, a monomethod was chosen. As the research lent itself to a qualitative study, the quantitative strategies of experimentation and survey were discounted. It was decided that a case study [7] of recently executed acceptance tests would be the most practical approach. As the scope and depth of the investigation is narrow, it has been considered an exploratory field study. In order to produce a timely report, it was decided to take a cross-sectional approach. Future research could be conducted after the COVID-19 pandemic for comparative results.

Data Overview

Access was limited to existing contacts including work colleagues and clients of the researcher. This enabled short lead times to conduct interviews and had the further advantage of a familiarity with the context. The personal credibility of the researcher and the goodwill between the researcher and the participants aided the access to participants and data collection.

The sampling was of a nonprobability nature, purposive and typical case, selecting engineers who had performed remote acceptance testing since the start of the pandemic. Participants were asked to recommend other participants and one extra contact was found using this snowball method.

Seven remote video conference interviews were conducted with participants of remote acceptance tests using Microsoft Teams. Four were testers, three were reviewers. All were male. The range of experience varied, with two having over 20 years of industry experience, three having approximately 10 years of experience, and two having less than 5 years in the industry. Seven companies were represented: two automation and control SIs, four clients, and a project management company. The client companies were two pharmaceutical manufacturers, a medical device manufacturer, and a waste recycling company. One reviewer worked for a project management company on behalf of the pharmaceutical client. The remote testing discussions were conducted on five projects. Three were in Ireland, one was in Australia, and one was in Germany. For the German project, the reviewers were based in Ireland and for the Australian project, the tester was based in Ireland.

Table 1: Interview data.

Interviewee	Project	Duration of Interview	Word Count
Tester 1	Project 1	16 m 28 s	1,823 words
Tester 2	Project 3	12 m 19 s	1,386 words
Tester 3	Project 2	9 m 7 s	1,268 words
Tester 4	Project 4	21 m 22 s	2,044 words
Reviewer 1	Project 2	14 m 57 s	1,370 words
Reviewer 2	Project 2	12 m 10 s	1,581 words
Reviewer 3	Project 5	21 m 36 s	2,678 words

Table 2: Phases of thematic analysis.

Phase	Description
1: Familiarizing yourself with the data	Transcribing data (if necessary), reading and rereading the data, and noting down initial ideas.
2: Generating initial codes	Coding interesting features of the data in a systematic fashion across the entire data set, and collating data relevant to each code.
3: Searching for themes	Collating codes into potential themes, and gathering all data relevant to each potential theme.
4: Reviewing themes	Checking if the themes work in relation to the coded extracts (Level 1) and the entire data set (Level 2), and generating a thematic "map" of the analysis.
5: Defining and naming themes	Ongoing analysis to refine the specifics of each theme, and the overall story the analysis tells, and generating clear definitions and names for each theme.
6: Producing the report	The final opportunity for analysis. Selection of vivid, compelling extract examples, final analysis of selected extracts, relating back of the analysis to the research question and literature, producing a scholarly report of the analysis.

The interviews ranged from just under 10 minutes to just over 20 minutes, resulting in transcripts with word counts from approximately 1,200 words to over 2,500 words. In total, approximately 2 hours of recorded interviews resulted in 12,150 words, transcribed (Table 1).

Qualitative Data Analysis

There are a number of qualitative data analysis techniques available: grounded theory [8, 9], thematic analysis [10], narrative analysis [11], discourse analysis [12], content analysis [13], and interpretative phenomenological analysis (IPA) [14]. The chosen one should suit the research design. Thematic analysis was chosen because of its flexibility and adaptability, being independent of any research philosophy [5]. Thematic analysis as outlined by Braun and Clarke [10] uses six phases, as shown in Table 2.

Table 3: Codes.

Codes	
Advantages	Paperwork writing and signing
Agreement	Personal property
Audio-visual communication	Physical human interaction
Change of mind	Planning preparation
Commercial	Positive sentiment
Delays	Previous experience
Disadvantages	Professionalism
Feeling curious	Quality
Feeling strange	Remote test after COVID - No
First remote test	Remote test after COVID - Yes
Guessing and assumptions	Roles
Hiding	Schedule impact - longer
Improvement suggestions	Schedule impact - shorter
International	Stress
Internet connection	Success
Language	Surprise
Location	Text communication
Mistakes	Time saved on travel
Mixed sentiment	Trust honesty
Multitasking	Using camera or smartphone camera
Negative sentiment	Using remote desktop viewing
New company	View only
New country	Visibility

Table 4: Themes and subthemes.

Subthemes	Further Analysis	Themes
Technology and communications requirements Procedural requirements Human factors	→	Requirements/ enablers
Negative sentiment Positive sentiment Ambiguous sentiment	→	Sentiment
Future Time Miscellaneous	→	Miscellaneous

All six phases were used in this field study. The interviews were transcribed and read to gain familiarity with the data. The transcriptions were imported into the computer-assisted qualitative data analysis software (CAQDAS) NVivo [15] to generate initial codes from the transcripts. Once generated, the codes were collated into themes and the themes were again categorized and a thematic map was created.

CAQDAS is a tool for transparent display of codified data but the researcher still uses the data analysis method of choice and sets up the CAQDAS to accommodate that method [16]. The CAQDAS provides a transparent and portable audit trail of the researcher's efforts.

Ethics

The research was submitted to the University College Cork (UCC) Social Research Ethics Committee (SREC) for approval. The participants are either work colleagues or clients of the researcher/interviewer, which could be perceived as a conflict of interest in that the results could be manipulated to benefit the company. A perception of coercion to participate could also arise. These considerations were mitigated by giving full transparency of the nature of the research to all participants and receiving signed informed consent forms.

Confidentiality concerns were addressed by the anonymization of all persons and organizations in the transcripts, the deletion of interview recordings after transcription, and the plan to destroy the interview transcripts after publication. All emails scheduling the interviews were deleted. Interview recordings and anonymized written transcripts are stored on the university's secure server before destruction. There should be no General Data Protection Regulation (GDPR) concerns, as anonymized data do not fall under GDPR regulations.

RESULTS

Codes

After the initial search, 46 codes emerged. These are shown in Table 3.

The codes were then distributed across nine subthemes, and the subthemes were further analyzed and organized under three main themes, as shown in Table 4.

Three Pillars of Remote Acceptance Testing

The requirements to enable remote acceptance testing were collected into the subthemes of technology and communication requirements, procedural requirements, and human factors. These were collected into the theme "requirements/enablers."

Technology and communication requirements

Essential to the operation of remote testing, the technology and communication requirements include the ability of the participants to see and hear each other, to see graphical screens, to see equipment installed and operational, and to view documents being completed and signed. This is achieved by off-the-shelf technology. Zoom, MS Teams, and Webex are some of the video conferencing systems used successfully. Webcams, smartphone cameras, and sports action cameras were also used to allow equipment to be inspected remotely. This was used to confirm that the correct hardware was installed, that it was constructed correctly, and that it used the specified techniques.

The objective of our research: What techniques and procedures are required to enable reliable remote acceptance testing of automation projects?

Procedural requirements

During in-person testing, test protocols are completed (pass/fail, initial and date) by the tester, and the reviewer signed that they are satisfied that all testing is complete and successful. For remote testing, several procedural changes have been made to accommodate the capturing of document approval. For some, the protocols were signed on camera. In other cases, the tester signed the protocol and the document was scanned and emailed to the reviewer daily, weekly, or on completion. In some cases, the tester was granted the authority to sign on the reviewers' behalf once the reviewer was satisfied.

Human factors

The participants described various ways in which the lack of personal interaction hindered the testing. The rapport established during in-person testing is missing.

- Reviewer 3: "In a real FAT, you go have dinner, you have a few beers, and the next day, you'd be on first name terms. When you're doing a remote, that doesn't happen."

The lack of the firsthand experience meant that more explicit explanation was required.

- Tester 2: "In some ways, you needed longer to explain things. If a client had been there, sitting there, doing it, interacting with it themselves, they would have seen it more clearly and you might not have had to spend more time explaining it then."

With the lack of rapport, more effort had to be made to establish trust between the participants. This was made all the more difficult by the perceived ease with which mistakes could be overlooked in the remote scenario.

- Tester 2: "You do need understanding from customers that will have that level of trust and give you credit for being honest. When you build relationships with people, it's easy for them to do that."
- Tester 2: "It was the customer who mentioned it in this case, that there has to be a degree of trust. And they trusted that I was being honest in what I was saying."
- Reviewer 1: "I've been surprised about the professionality and honesty of the people involved."

Sentiment

Codes were organized into the subthemes of positive, negative, and ambiguous sentiment. These subthemes were collected into the theme "sentiment."

Figure 1: Tester and reviewer sentiment toward remote acceptance testing.

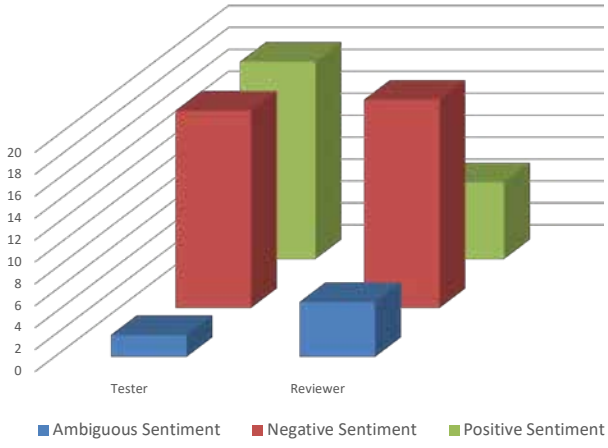


Figure 2: Tester and reviewer estimates of time taken to conduct remote acceptance testing relative to in-person testing.

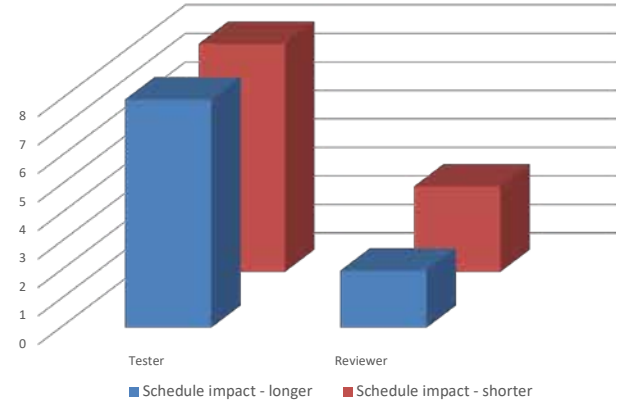
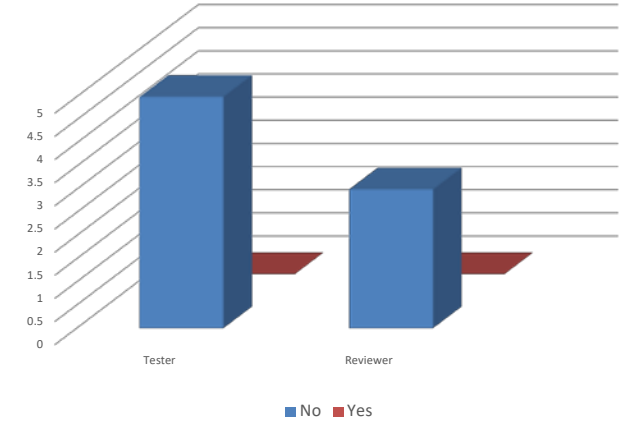


Figure 3: Tester and reviewer preference to conduct remote acceptance testing after COVID-19 restrictions have lifted.



Some examples of negative sentiment include the lack of visibility.

- Tester 1: "Maybe from the point of view of seeing what he wanted to see or experiencing what he would have wanted to experience, it probably wasn't ideal. Certainly not as effective as in-person testing."

Another disadvantage was the lack of the personal connection.

- Reviewer 2: "It's a disadvantage that I couldn't actually meet the clients in person or the people I've been working with. The personal communication, the personal touch."

Positive sentiment included the ability to multitask and the ability to have subject matter experts attend for short productive spells:

- Reviewer 2: "Yes, so maybe with the likes of online, we didn't have to waste time. While he was doing that, I was able to do other work."
- Reviewer 2: "Like my supervisor could have dialed in. All I had to do was IM him, 'could you dial in for a minute?' and he came in for 10 minutes to figure out the problem and he could go away then again with his day's work and he's not tied up all day at a FAT."

The remaining codes were collected into subthemes of future, time, and miscellaneous. These subthemes were collected under "miscellaneous."

Time saved traveling to and from the test site was seen as an advantage.

- Reviewer 3: "That would normally be a full-day exercise, a flight over the night before. And we got it done in 2.5 hours."
- Tester 3: "Not so much for us, but long term if there was another FAT and it had to be at the client side or abroad, you're looking at time saved traveling, hotels, money, all that."

Some ambiguity was expressed.

- Reviewer 1: "I would say that pros and cons were really 50/50."
- Tester 2: "Plusses and minuses in that way, really for me."

Tensions

Once coding was complete, the data were queried using a matrix coding query to establish agreements and tensions between the testers and the reviewers. A matrix coding query creates a table to find intersections of codes, to discover patterns [15]. Tester sentiment was split evenly between positive and negative sentiment, but reviewers had an overwhelmingly negative sentiment about the experience (Figure 1).

When asked if remote testing took more or less time than in-person testing (not including time saved on travel), both reviewers and testers were divided in their opinions on an almost equal basis (Figure 2).

Testers and reviewers overwhelmingly agree that they would prefer not to continue using remote testing when the COVID-19 restrictions are lifted. Both groups would prefer to return in-person testing (Figure 3).

CONCLUSION

The ability to perform remote acceptance testing has been implemented as a work-around in the period of travel and meeting restrictions imposed by the COVID-19 pandemic. It has allowed automation projects to progress to site. Methods, procedures, and techniques that would have been rejected as unacceptable before the COVID-19 pandemic are now de rigueur.

However, after analyzing the data collected in the seven interviews, it is clear that the engineers involved would prefer to conduct the testing in person. They felt that the rapport between colleagues working together builds trust which, along with the unrestricted visibility available in situ, allows for a more efficient and effective test. The major advantage identified was saving time and cost associated with travel to test sites. When one or more parties is required to travel internationally, the savings can be considerable. The savings may outweigh other considerations after COVID-19 restrictions are lifted.

Avenues for future research include investigating the savings to be made by reducing international travel and accommodation costs, studying the dichotomy between the commercial savings and the inconvenience of the testers, and researching the impact of reduced communication and relationship building resulting from remote testing.

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