PHARMACEUTICAL ENGINEERING®

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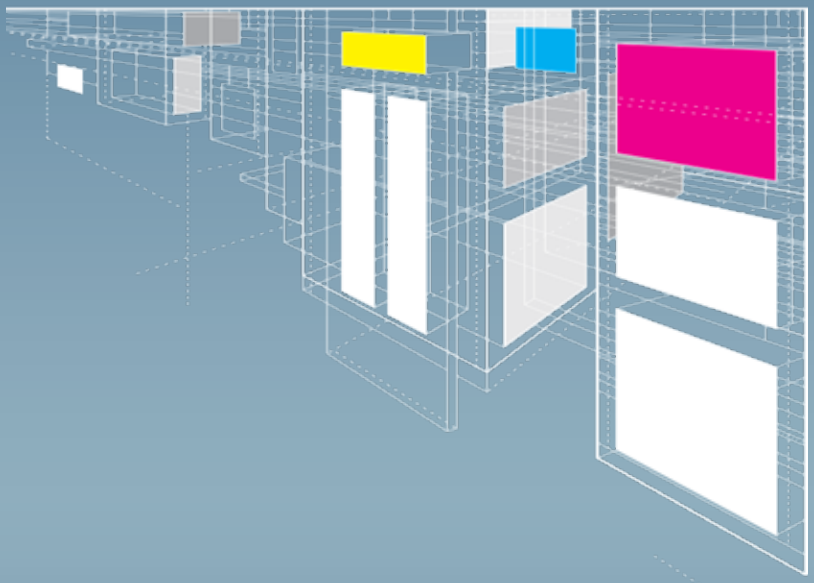

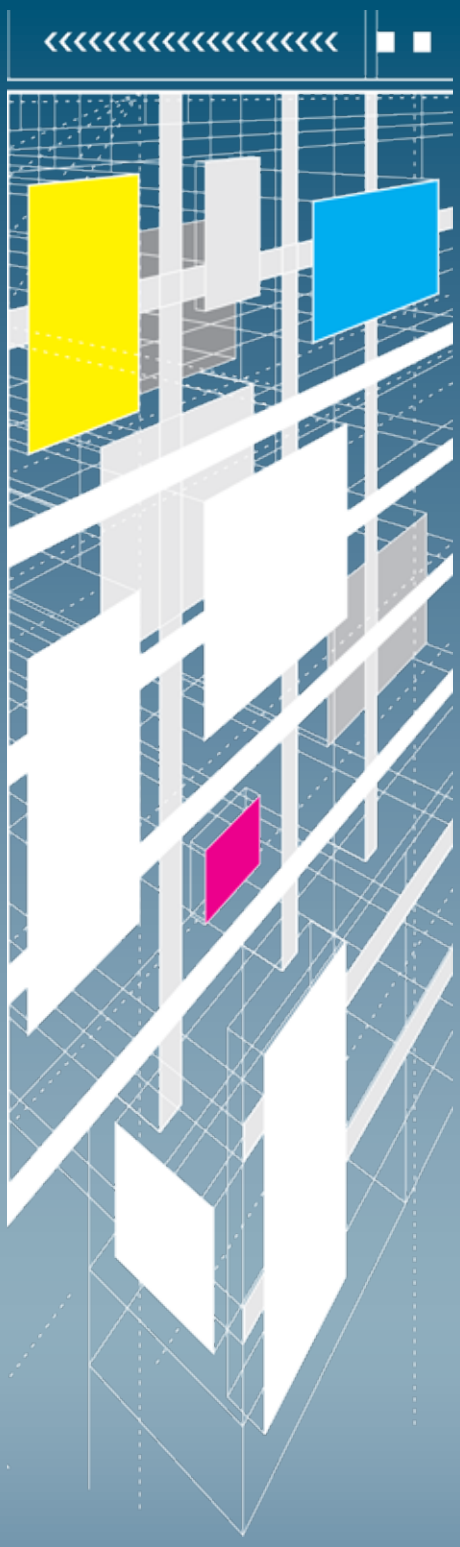

Viral Vector Platforms: Intersection of Facility and Program

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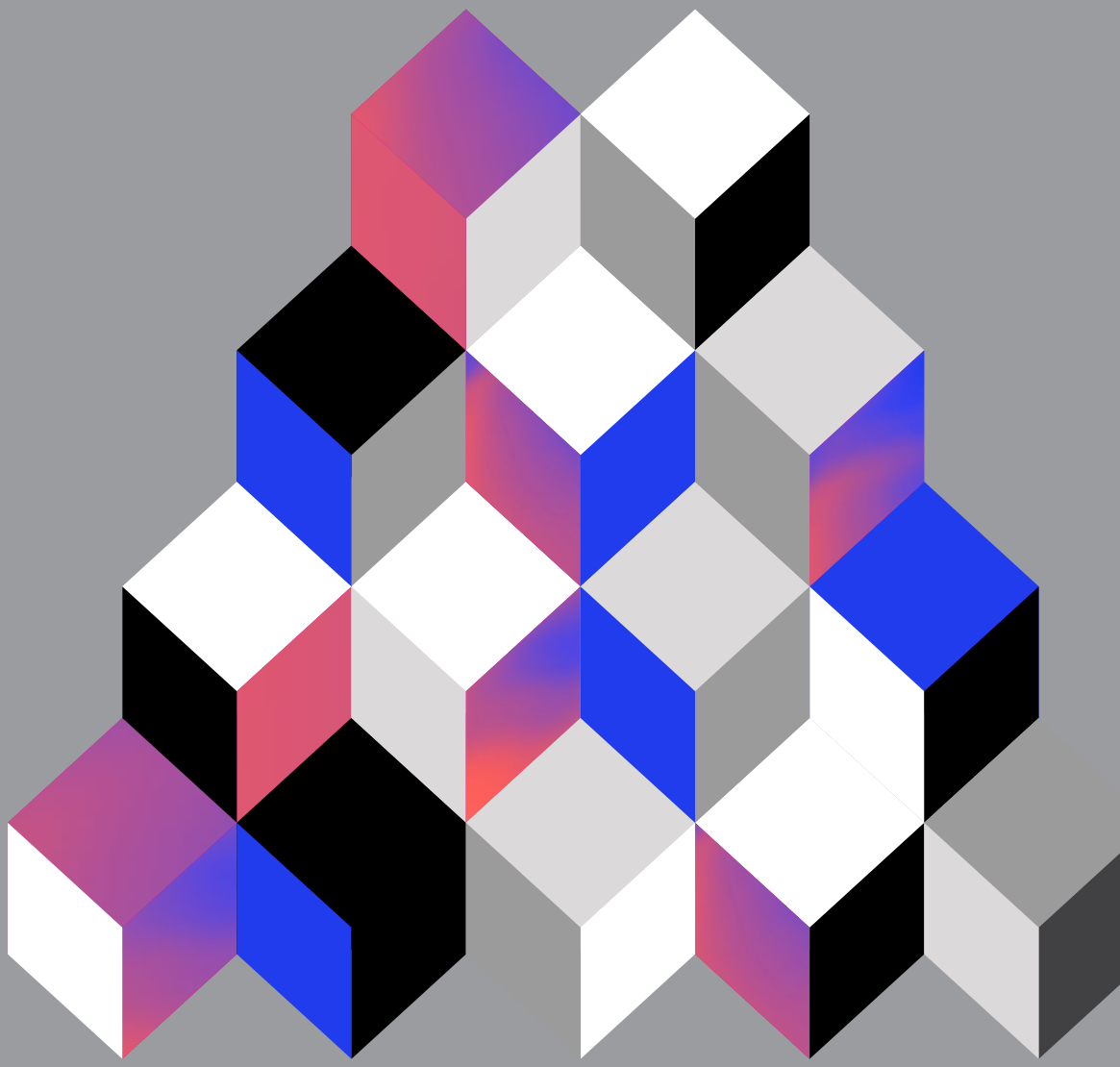

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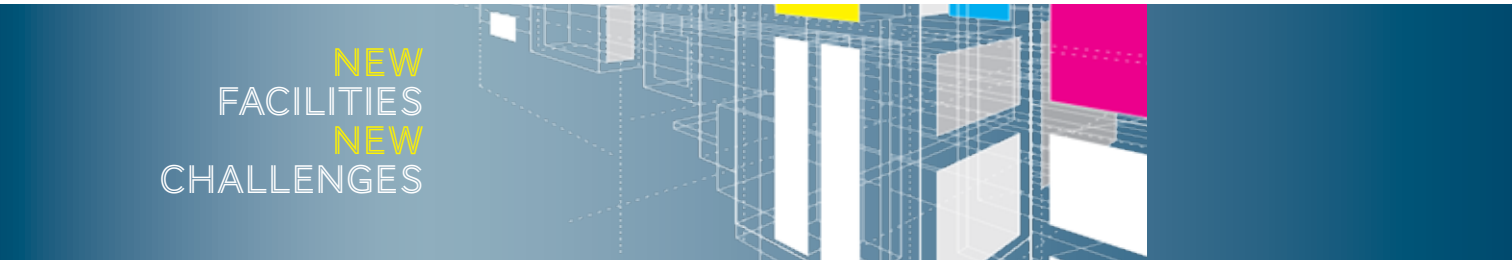

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By Jörg Zimmermann


Jörg Zimmermann

The Return to Live Conferences

The unprecedented speed in the development and global rollout of vaccines and treatments for COVID-19 over the last two years has made it possible to get back to a new normal. The 2022 ISPE Facilities of the Future Conference in February brought us together in person again and included a virtual option.

More than 300 people gathered for cutting-edge presentations and lively discussions at the conference, including featured projects from ISPE's Facility of the Year (FOYA) program. Presentations also focused on successful projects in advanced therapy medicinal products (ATMPs) and cell and gene therapy (C&GT). It is fantastic to see how these new therapies are getting traction, and while some products are marketed now, there is no one way of doing it due to the variety of processes needed for production.

For me, highlights of the conference were the presentations by Matthew Hepburn, MD, Senior Advisor to the Director, Pandemic Prevention, US Office of Science and Technology Policy, Executive Office of the President; Arlene Joyner, Branch Chief PCI Division, BARDA; and Tom Warf, Director, Manufacturing, Facilities and Engineering, DHHS/OS/ASPR/BARDA. Having lived through the pandemic and helping shape the industry response, it was fascinating to see the activities undertaken by the US government and their determination to protect the people. Early on, the right decisions were made to combat the virus, such as using multidose vials for the vaccines and securing the supply of polymer syringes and needles for the vaccination.

It is fantastic to see how new therapies are getting traction, and there is no one way of doing it due to the variety of processes needed for production.

Viral vectors are one way to deliver the product (a gene) to cells. Produced in cell culture similar to large-scale biotech production, the virus is the product rather than the contaminant. In this issue of *Pharmaceutical Engineering*®, an article explores design basics for viral vector production facilities. Also in this issue, past FOYA category winners and honorable mentions share insights about what

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made their successful facilities projects that supported development of treatments and cures for patients.

ASEPTIC CONFERENCE

The 2022 ISPE Aseptic Conference was held in March, which was very well attended with over 250 people on site (and 80 more attending virtually). Speakers included Andrew Spasoff, Senior Director Quality, AstraZeneca, who discussed the final stages of their COVID-19 vaccine in a presentation called "Pre-PPQ Vaccine Lots—They Weren't So Crazy After All," sharing details on how commercial-scale production was made possible in such a short timeframe.

ATMPs and C&GT were also featured, with an industry panel of experts from operating companies, engineering companies, and equipment suppliers discussing challenges and solutions for these new modalities.

As always, the regulatory panel with representatives from US FDA and this time, Health Canada, was a very popular session at the Aseptic Conference. Brooke Higgins, Alonza Cruse, Rick Friedman, Bob Sausville, and Paul Gustafson responded in a live setting to previously submitted questions, including a discussion about regulatory expectations and challenges in interpreting guidelines. Everybody is eagerly waiting for the publication of the final updated version of Annex 1, and speculations about what is in it and what is not are heated. As Annex 1 with its adaptation by PIC/S and WHO is a truly global document, the differences in culture and quality maturity become apparent. We will provide coverage of the regulatory panel session soon in PE magazine's Online Exclusives.

BUILDING THE WORKFORCE OF THE FUTURE

The future of the pharmaceutical industry is largely dependent on attracting talent to our companies. For me as a pharmacist, it has always been my intrinsic interest to participate in making the lives of patients better, but with the predicted growth in the industry and the war for talent, we need to be extra careful.

Student Chapters and the ISPE Emerging Leaders program play vital roles, but there is another aspect to building the future workforce. One area where the pharmaceutical industry is lagging is in terms of diversity. Observing the ongoing efforts in this space, we can see that progress is slow because many wrongly believe that diversity and inclusion efforts are nice to have and "look good" in marketing materials. In reality, a diverse workforce provides us with so many more viewpoints and cultural aspects, and that is what we can put to work to our advantage as a global industry. In reality, diversity is a business must-have, will drive the bottom line, and should be adopted as a key element to prepare our industry for the future.

Gilead Sciences has been a major sponsor of the ISPE Foundation's Diversity Internship Program (IFDIP). You will find an article in this issue by Joydeep Ganguly on Gilead's engagement with the program, which is also supported by Nephron and WuXi, and other diversity initiatives. Every year, students can apply for the IFDIP summer internship programs, and we can proudly announce that some have found their first permanent placements in industry there, right out of university!

On ISPE major projects in 2022, I can report a lot of progress: The One ISPE Charter, which regulates the relationship between ISPE International and the Chapters and Affiliates, has been signed by the vast majority of Chapters and Affiliates. They now benefit from the many incentives that were introduced, including a managed growth fund to attract new members, incentives for student members, training materials that they can use at the local level, no restrictions on content for local events, and many more. A big thank you to all the leadership in all the regions!

The refresh project on the ISPE Strategic Plan is also making good progress, and we are on track to unveil this at the 2022 ISPE Annual Meeting & Expo in Orlando, Florida, 30 October–2 November.

Before then, we hope you were able to join us at the ISPE Europe Annual Conference in Madrid, Spain, 25–27 April. Featured themes were Sustainability, Annex 1, Digital Quality, Trends in Pharmaceutical Engineering, and Project Management.

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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METTLER TOLEDO

By Jennifer Lauria Clark

Jennifer Lauria Clark

RISKS AND REWARDS

As a part of taking care of yourself, one must risk something. For me, taking a risk can be scary. I get nervous, anxious, and, at times, begin to doubt myself. Then I remember why I'm taking a risk and what the potential rewards will be, and confidently move forward with my decision.

In our new working world after two years of the pandemic, we feel we are risking something every time we leave our homes. We are not sure if we have our mask sand sanitizer, and we often wonder, "will they require me to wear a mask or sit six feet apart from someone?" We also probably feel like we are taking a risk with the new app we downloaded to help us be more productive. Who wants to agree to those terms and conditions when it could backfire on us?

However, taking risks can be healthy if approached with the right mindset. In risk analysis, risk is defined as the probability of an event occurring combined with the potential impact of the event. Taking a risk makes us better people, leaders, and employees (and volunteers). I was once separated into a group of three by our former CEO. I was quite nervous as my colleagues were all huddled together at other tables. Then, our CEO announced to the team, "These three are the risk takers. We need more risk takers to move our company forward."

PHARMA RISK-TAKING

I am in awe of those taking risks in technology, particularly in the pharmaceutical industry. The advancements that have been made over the past decade to bring patient treatments and cures for a better life are astounding. Who would have thought we would have gone from dreaming of a cure for hypotonia (floppy baby syndrome) to being able to treat patients with Zolgensma, the gene therapy medication, to prolong and save babies' lives?

Thank you to those risk takers in our industry who are fighting for more research-based programs to advance emerging technologies and challenge the status quo. The people and organizations who take a chance on someone's new idea, invention, cure, or new process are the bedrock of innovation in our industry. Regardless of the outcome, we cannot succeed unless we try. In today's technological society and mindset, we have a wealth of information

Thank you to those risk takers in our industry who are fighting for more research-based programs to advance emerging technologies and challenge the status quo.

literally at our fingertips. However, taking a risk to break new ground comes from within our own ideology, our thought, and our creativity. These attributes are what truly set people apart from one another!

PARTICIPATE IN ISPE

As humans, the biggest risk we can take is to do nothing, sitting idly by and watching the world move forward. Be an agent of change. ISPE gives us the tools we need to take risks and creates an environment where we can collaborate in Communities of Practice and build relationships with people through volunteer opportunities to advance our curious minds. Please be curious, and please take a moment to take a risk: What is the worst that can happen?

I challenge you as you read this editorial to think about how you can take that extra step in your professional or personal lives to not only make yourself better, but to also advance our industry in some way that makes a difference. If you have an idea, go for it. Life is short, times are tough, and success feels good every time you achieve it.

Take a risk and join our ISPE WIP community to learn more about yourself, the industry , and how to improve the working world.

Jennifer Lauria Clark is Vice President, Sales and Account Relationship Management, at CAI, and the ISPE Women in Pharma® 2021–2022 Steering Committee Chair. She has been an ISPE member since 2003.

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By Heather Bennett-Kelley


Heather Bennett-Kelley

RESILIENCE IN THE PHARMA INDUSTRY

What do innovating new therapies, surviving the start-up phase of a company, and entering an industry workforce have in common? All three of these, if successful, demonstrate resilience.

Reaching the point of "success" can take a long time: years, a lifetime, or even multiple generations. Of course, success also comes in many forms, and holds a different definition depending on the context. Regardless of the meaning of success, getting there takes perseverance to overcome challenges especially in the face of adversity.

According to National Business Capital, 90% of startups fail [1]. Thousands of pharmaceutical products fail in the process of getting to market, a process that can take more than 10 years. All students had to adapt their learning styles during the pandemic to the virtual classroom format. The difference in a student moving towards graduating or not was the student's ability to adapt and move forward when they were hit with unforeseen difficulty. How much resilience did the student have? This is not generally a skill that is taught, but picked up by practice and from your environment. Resilience is gained just like in weight training, tearing the muscle fibers to get stronger, or going through difficulty to increase the ability to deal with stress.

Resilience is the ability to recover from stress [2].

BUILDING RESILIENCE

How do we actively build resilience? How can we provide the tools or opportunities for our employees (especially our young people) to build resilience? The Cornell Health Center gives the following suggestions to build resilience [3]:

- Social engagement: Positive relationships provide connection and life strings to pull on to spring back.
- Self-awareness and self-care: Paying attention to these will provide the space to respond to stressors, and realize when we are being impacted by stress.
- Attention and focus: These allow you to focus on the task at hand and not allow distractions that are not relevant at the time.
- Meaning: Having a purpose can improve our mental health.
- "Growth mindset:" Being open to other ways of thinking.

These points can be practiced on a daily basis, or when we remember, to help build these muscles. Mentors and managers can help their teams practice these by leading by example, changing the structure of meetings, and encouraging people to consider an alternate view.

"GRIT" OR PASSION

Something that often is confused with resilience, but actually goes hand in hand with it, is grit. Angela Duckworth, the author of *Grit: The Power of Passion and Perseverance*, wrote, "We define grit as perseverance and passion for long-term goals. Grit entails working strenuously toward challenges, maintaining effort and interest over years despite failure, adversity, and plateaus in progress"[4]. So, basically the difference between grit and resilience is the ability to push through versus the ability to bounce back. Some of the COVID-19 vaccines were originally developed for something else that didn't end up working. Those scientists and organizations had resilience to come back from failure, but they also had grit to keep pushing forward for the larger goal of improving patient's lives with this product or the 500th iteration of it.

We have all been faced with adversity, especially over the last couple of years. Let's help each other come back from it and push through to the next sunrise.

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VIRAL VECTOR PLATFORMS:

Intersection of Facility and Program

By Michael J. Gorman and Emily Heffernan, PE

Realizing the promise of any novel viral vector therapeutic depends on the innovator's ability to constantly meet evolving program requirements set in the product's preclinical; clinical; chemistry, manufacturing, and controls (CMC); and market strategies. A key enabler to success is establishing a robust yet nimble viral vector manufacturing platform that delivers high-quality product on time and in full while managing costs.

Many paths are available in designing, delivering, and operating a viral vector manufacturing facility. This article explores a foundational design decision process that developers face: choosing an adherent versus suspension cell culture platform. Design considerations shift with each progressive stage in the product life cycle. Navigating the tradeoffs well amid high complexity and uncertainty is vital to success.

VIRAL VECTORS IN GENE THERAPY

Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use [1]. There are multiple approaches for gene therapy delivery, but the use of viral vectors is the most common [2]. Viral vectors are viruses that have been modified to deliver a genetic payload to a cell while controlling the immunogenic and pathogenic risks associated with wild-type viruses (Figure 1).

Several types of viral vectors are commonly used in the pharmaceutical industry, each with their own tropisms, attributes, and features. Although an adenovirus vector has been predominant in the manufacture of COVID-19 vaccines, the most prevalent viral vectors used in gene therapy today are adeno-associated viruses (AAVs) and lentiviruses.

Though there are a number of notable differences between AAVs and lentiviruses—including genome type, size, and packaging capacity—the most notable distinction is that lentiviruses integrate into the host genome, whereas AAVs remain episomal. Integration into the host genome is associated with a higher risk of oncogenesis due to the risk of off-target integration [3]. This in turn dictates the use of each viral vector type.

Figure 1: Viral vector structure.

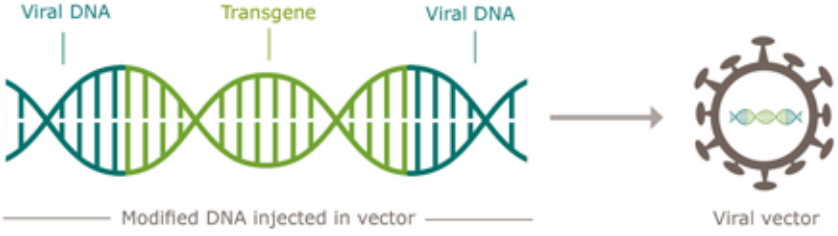
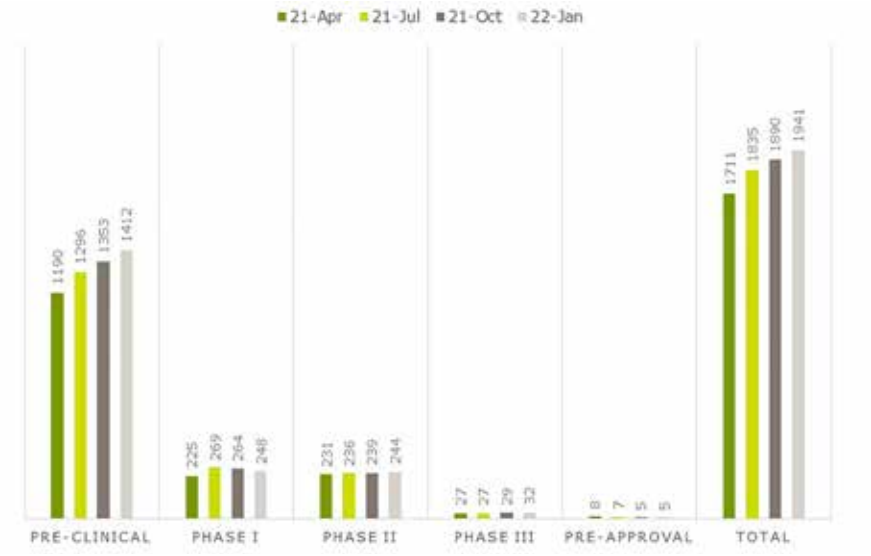


Figure 2: Gene therapy market for US clinical trial data through Q1 2022 [5].



Because of their low immunogenicity, broad tropism, and nonintegrating properties, AAVs are typically used in therapies that are administered directly to the patient (in vivo therapies). Lentiviral vectors are predominant in therapies that are ex vivo, with the viral vector delivery occurring in cells that have been collected from the patient [4]. With ex vivo therapies, lentiviral vectors can be safely used because the cells can be analyzed to confirm integration at the correct site prior to reintroduction into the patient.

GENE THERAPY MARKET

The gene therapy pipeline is primarily focused on the oncological therapy area, with almost half the products in clinical trials focused on anti-cancer therapeutics, mainly lentivirus applications. Other product indications include rare diseases, neurology, and sensory therapy, which mainly utilize AAVs (Figure 2).

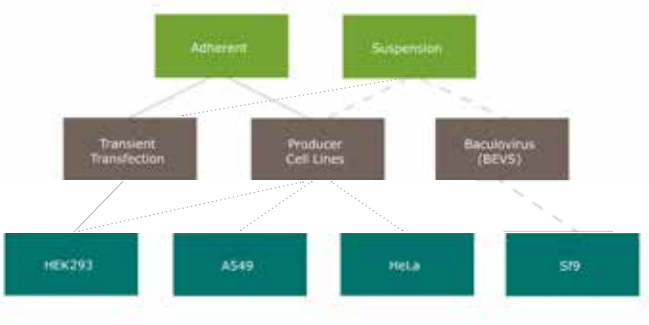
The gene therapy market continues to grow, with 2021 setting record numbers for funding. According to the American Society of Gene & Cell Therapy, the total number of gene therapies (including genetically modified cell therapies) in US clinical trials was 1,941 as of Q1 2022 [5]. The gene therapy market was expected to reach USD 3.42 billion by end of 2021 with a projected compound annual growth rate of 20.4% from 2021 to 2028 [6].

This sustained increase in demand for viral vectors presents a rising challenge across the pharmaceutical industry to develop laboratory and manufacturing facilities to supply the clinics and commercial markets with much-needed product.

ADHERENT VS. SUSPENSION: DESIGN CONSIDERATIONS

Figure 3 depicts the relationships between viral vector cell culture platform, viral vector production method, and host cell type.

Figure 3: Relationship of cell culture platform to viral vector production methods to host cell type.



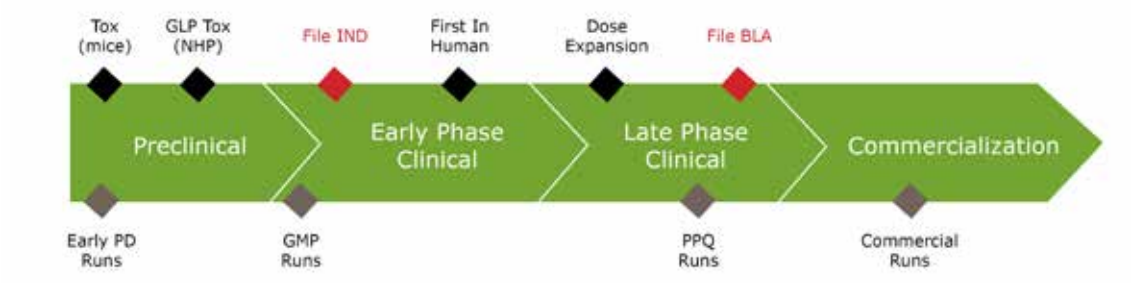
Adapted Cell Lines

Gene therapy manufacturing employs a host cell line to produce viral vectors. Most host cell lines used for gene therapy manufacturing are human cell lines, although insect cell lines may also be used with specific technology platforms.

Human cell lines, which are developed from tissues, are inherently adherent in nature, requiring attachment to a solid surface in order to grow. In practice, this can be accomplished by using 2D platforms such as roller bottles or cell factories, and for 3D platforms with the use of microcarriers.

Suspension cell lines are cells that are grown floating in a culture medium with no anchorage dependence. Suspension cell lines are typically adherent cell lines that have been adapted to grow without dependence on a solid substrate. Elimination of serum-containing media is a step in the adaptation process from adherent to suspension. This step is beneficial because serum is a potential process contaminant.

Figure 4: Example of a viral vector product life cycle.



VIRAL VECTOR MANUFACTURING PLATFORMS

With both adherent and suspension cell lines, several different technology platforms are available for viral vector production. The most common methods include transient transfection, use of producer cell lines, and infection of insect cells with baculovirus expression vector systems (BEVS). Other platforms are also available, but less prevalent in the pharmaceutical industry. The benefits and shortcomings of each platform are discussed next.

Transient Transfection

Currently, transient transfection is the most popular method [7] of viral vector production because of its ability to introduce genetic material into the host cell line without the need to reengineer the host cell line for each distinct product.

Genetic material is introduced into the host cell line (typically a human cell line such as HEK293 cells) using multiple plasmids, each of which delivers critical material for the formation of a complete viral vector capsid. The genes are divided among multiple plasmids to prevent the formation of replication-competent viral particles through recombination. Typically, three-plasmid systems are used, although two- and four-plasmid systems are also options.

Higher volumes present challenges. Although transient transfection is effective at smaller volumes, when production is scaled up, transfection efficiency tends to decrease. This effect is a function of multiple factors: volume of transfection mixture (ratio with culture volume in bioreactor), mix time (overmixing can be detrimental), mixture incubation time prior to addition to the bioreactor, addition rate into the bioreactor, and various bioreactor conditions.

Producer Cell Lines

With the use of producer cell lines, the genetic material required to produce the viral vector is engineered into the host cell. Similar to transient transfection, a human cell line is typically used, although in this case it could be a HeLa or A549 cell line as well as HEK293 cells. Co-infection with a helper virus may be required to engineer a complete viral vector capsid.

Although producer cell lines are expected to deliver higher titers than transient transfection, there are downsides. A stable cell line that is engineered for the appropriate transgene must be engineered for each therapeutic treatment. Engineering and characterizing these stable cell lines require additional time and expense.

Baculovirus Expression Vector System

A third platform for viral vector production is the use of BEVS in *Spodoptera frugiperda* insect cells. Studies show that BEVS can result in up to a 10× increase in yield compared with production using transient transfection [8]. This is largely attributed to BEVS being far less susceptible to fluctuations in environmental conditions in the bioreactor and the resultant inefficiencies.

With use of BEVS, baculovirus vectors must be engineered to deliver the therapeutic transgene as well as the viral vector structural components. A concern with using BEVS is that post-translational modifications may differ from human cell lines due to the use of insect cell lines.

PRODUCT LIFE CYCLE IN PROGRAM DEVELOPMENT

Innovators must heed the dynamic requirements of the product over its life cycle (Figure 4) to successfully execute viral vector programs. Decisions at every stage will critically impact subsequent stages and the success of the program.

Per an approved business case, the product must meet the sponsor's regulatory, preclinical, clinical, and commercial program milestones. An integrated project plan draws a critical path across workstreams of process development, analytical development, stability, manufacturing, supply chain, quality, regulatory, and commercialization.

Amid high complexity, uncertainty, and changing conditions, the project team must act with agility and speed in making constant tradeoff decisions. It is imperative that they keep the patient's needs central in satisfying the quality, safety, and efficacy guidelines in the quality target product profile [9].

From early in the program, operational design criteria such as clinical and commercial process scale, supply chain capacity, process control strategy, manufacturability, and life cycle product cost should be factored in.

Viewing the entire product life cycle, we have observed several factors to consider for each phase when choosing an adherent or suspension viral vector platform.

Preclinical Phase

In the preclinical phase, a viral vector candidate is selected from a screen of dozens if not hundreds of permutations. Process understanding is limited, and associated challenges include high variation, low productivity, poor product characterization, immature analytical methods, and high process and product impurities.

Very small volumes of vector are commonly made from adherent cell lines in roller bottles or multilayer cell culture trays to support preclinical studies. At this scale, high-efficiency transient transfection is relatively fast and easy to develop, and is fit for purpose to keep pace with ongoing screening work and candidate selection.

In preparation for toxicology studies (tox), process developers must plot the course to either scale out 2D adherent technology (e.g., cell factories, fixed-bed bioreactors) or scale up and change to a suspension process. In any case, there are multiple benefits of having a tox process generating data early in the life cycle that is representative of the future commercial process.

For an ultra-rare gene therapy indication with relatively small anticipated commercial demand, adherent scale-out may be the best approach. However, for programs calling for high annual vector output, the use of adherent cells has volume constraints [10]. A fixed-bed bioreactor can be used, though these do not exceed 600 m^2 per unit. Another option is 2D cell factories. These are highly manual unit operations that can quickly scale to a tipping point where operational complexity and the related labor costs make this approach unfeasible for a commercial manufacturing facility.

Here, a switch to suspension culture may be viewed favorably due to its scalability. As noted previously, this change adds the burden and risk of having to adapt the cell line to a serum-free medium. This is a complex and lengthy process, and success is not guaranteed. It is common to find that cells adapted to suspension have a slower growth rate and may be genetically unstable [11]. Once cells are adapted to growth in suspension, conventional single-use bioreactors can be used, ranging in size from 50 L to 5000 L, which is beneficial to operations. Stainless steel options are available at even larger volumes. This tradeoff decision is a pivotal one in the viral vector program.

Early and Late Phase Clinical

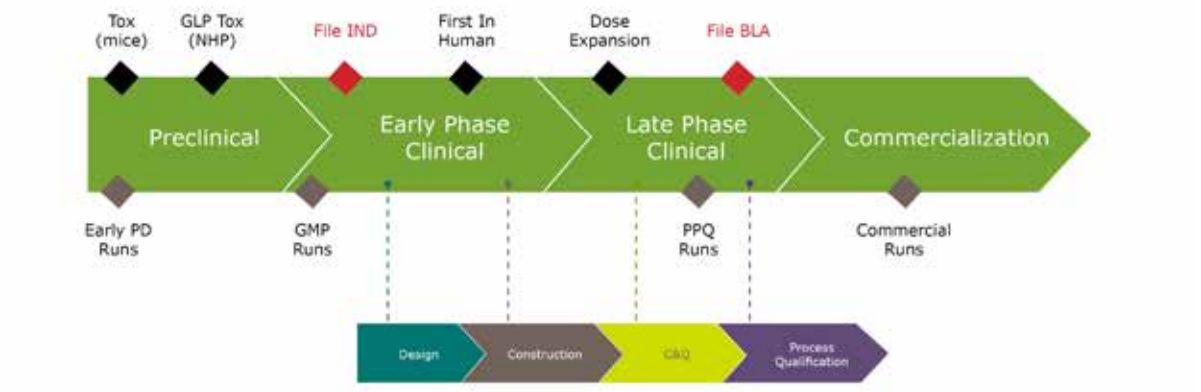
Informed by tox batch data, small-scale studies, and the developing clinical and market strategies, the GMP manufacturing process for human clinical trials can be locked down. The manufacturing and supply chain strategy defines a make versus buy approach, driving technology transfer of the process to either a contract and development manufacturing organization or an in-house GMP production facility. Analytical methods follow a similar track.

In the US, GMP manufacturing data generated will be included in the investigational new drug (IND) application. If the IND is cleared by the US Food and Drug Administration, this GMP viral vector will be used to dose patients in the first-in-human clinical trials and subsequent clinical trials. The manufacturing process supporting the late phase clinical trials must demonstrate consistency in the process performance qualification (PPQ) series where batches are run at commercial scale.

Through the clinical phases, it is ideal to stay the course with the chosen viral vector platform. However, major changes in viral vector demand may be discovered in the clinical phase. There may be multiple causes, ranging from clinical (e.g., high-end patient dose selected from the pivotal studies readout) to market (higher than expected patient adoption; accelerated plans to commercialize to new regions) to process (low cell culture titers and/or low downstream yield means fewer patient doses/batch at current scale). In this case, commercial supply cannot meet up-shifted demand, impairing the economic calculus of the baseline manufacturing strategy.

It is not unthinkable when heading into commercialization with the version 1 process that a parallel-path postmarketing process change might be prudent. This may mean a very late change from an adherent to a suspension platform, or from 500 L suspension to 1,000 L or even 2,000 L suspension. This decision is not taken lightly due to the heavy regulatory burden related to comparability requirements, technical risk, quality risk, potential delay, and the massive capital expense.

Figure 5: Facility life cycle as a function of product life cycle.



The project team must act with agility and speed in making constant tradeoff decisions.

Commercial Phase

With a successful PPQ series and related characterization work completed, the program prepares for a biological license application (BLA), product launch, and commercialization. With BLA approval and demand clearly in view, the process design and operational plans can be finalized with a manufacturability mindset.

In considering the growth path to commercialization, sponsors may elect to construct a new GMP viral vector facility. Finding the right timing requires a delicate balance. Figure 5 depicts a scenario of an aggressive fast-to-market strategy, initiating a capital project facility build beginning in the early phase (phase 1/2).

While this can be a big win in removing lead time, it exposes the business to scope change risk. Finding the right investment trigger criteria means avoiding the risk of initiating too soon (with limited information) or too late (delaying time to market). Aligning capital project state gate decisions with product life cycle milestones (e.g., favorable clinical data readout) allows major capital investment projects to proceed with a more managed investment risk profile.

Investing in a feasibility study in the early design stage can be a beneficial mitigation tactic. A lot will change from the time of the original product business case. Stemming from the adherent or suspension platform approach, factors of scale and technology will help establish a specification for facility user requirements including an estimated required footprint, which is a good parametric predictor of overall facility capital cost.

Running a high-level comparative project financial evaluation of a commercial-scale adherent versus suspension solution sheds new light on estimated capital expense and operational/life cycle expense. Even if it is only an order of magnitude of precision, it can be a pragmatic time-saving approach.

MANUFACTURING FACILITY CONSIDERATIONS

In the manufacture of viral vectors, especially at larger scales, the application of suspension bioreactors may look similar to traditional biologics manufacturing. However, there are some unique facility design considerations for viral vector facilities.

Unlike monoclonal antibody facilities, which are typically classified as good large-scale practices or BSL-1, viral vector facilities are most often classified as BSL-2. With increasing biosafety levels, greater protective measures are required to protect both operators and the environment from potential exposure to infectious agents. This difference is driven by the use of human host cell lines (HEK-293, HeLa), helper virus (adenovirus), and the viral vector in production (lentivirus).

Additionally, containment is a critical aspect of viral vector manufacturing that drives the design of the facility layout, including unidirectional flow of personnel, materials, and waste as well as HVAC strategy. Viral particles are difficult to detect and eliminate if a breach occurs. Primary containment is achieved through the use of closed-unit operations, with secondary containment provided through air locking and HVAC design.

Unidirectional flow mitigates the risk of cross-contamination, especially in multiproduct facilities. However, it increases upfront capital expenditure costs, with features such as dedicated supply and return corridors, segregated incoming and exiting personnel, and material airlocks added to the overall facility footprint.

The HVAC strategy can include the dedication of air handlers to viral positive production areas, once-through air for critical processes, and pressurization schemes that provide for both containment and adherence to GMP manufacturing guidelines.

Downstream Design Considerations

Each approach in the production of viral vectors has a characteristic set of tradeoffs to consider for the design and operation when effectively pairing a GMP purification process train to the upstream process.

An important consideration that impacts facility design is upstream production bioreactor scale in relation to downstream technology. Because these factors are dependent on the maximum size bioreactor in use (either adherent or suspension) and the yield of that bioreactor, multiple upstream bioreactor runs or batches may need to be pooled to have an efficient and GMP-capable downstream process.

Due to the longer duration and passaging time associated with cell culture as well as the current limited size of production bioreactors, it is not uncommon to have multiple upstream suites feeding a single downstream suite in viral vector manufacturing facilities. This may change in the future as technology improves and efficient vector production in larger single-use bioreactors becomes a reality.

For adherent cell lines in a fixed-bed bioreactor system, there is the benefit of retaining the cells within the single-use consumable. This leads to a reduction in the depth filtration required compared with a suspension-based platform, since less cell mass must be removed from the product.

A major purification challenge of note in viral vector manufacturing is the generation of empty capsids; that is, viral vector capsids that do not contain the gene of interest (GOI). Partial capsids can also form that contain truncated GOI vector or encapsidated genetic impurities. At very small scale, removing empty capsids and partially full capsids from the process stream is effectively performed via gradient density separation using ultracentrifuges. However, ultracentrifugation is a highly manual process that must be performed in small batches, and it is not a scalable technology. Moving forward, most manufacturers are adopting anion exchange chromatography as a scalable solution for the removal of empty or partially full capsids from the product.

Producer cell lines in AAV manufacturing require the use of a live helper virus such as adenovirus to co-infect the cells, thus necessitating an additional purification step to inactivate the live virus. Producer cell lines by design intend to improve vector production efficiency compared with transient transfection while removing the safety risk of residual plasmids as an impurity in the process stream.

CONCLUSION

Viral vector therapies are becoming increasingly popular for virtually every metric, from clinical trial applications to investment dollars spent on new facilities. As this industry grows and evolves, innovators must choose one of many paths to supply patients and markets with a safe and efficacious product to meet the rising demand.

Choosing the best manufacturing platform is far from straightforward. Central to this decision is understanding the advantages and disadvantages of applying either an adherent or suspension platform to your product and program. This compels product sponsors to create and execute a viral vector manufacturing strategy synchronizing technical, quality, and operational considerations based on the current product life cycle phase while anticipating future program and regulatory requirements. To make good decisions, one must constantly keep the end goal in mind: ensuring product safety, efficacy, and quality at every stage.

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ATMP FACILITIES:
Adapting to a Multimodal Future

By Peter Walters and Matthew M. Hewitt, PhD

In a recent advanced therapy medicinal products (ATMPs) innovator survey, two-thirds of respondents reported that they are developing multiple drug platforms [1]. Without a guarantee of commercial success for any single product, many companies are making smart choices by creating new therapies to tackle different diseases and mitigate risk.

The complex raw materials, such as viral vectors, that ATMP manufacturers require further drive the need for multimodal facility development. Some manufacturers may opt to commission these materials from a contract development and manufacturing organization, though many will choose to incorporate different process modalities into their facility to produce these materials in house. Although this approach adds complexity to the design, it mitigates development control and supply chain risk.

Regardless of the drivers for multimodal design, practicality and budget constraints are propelling most manufacturers toward single-facility operations, leaving engineers and architects to solve the complex challenge of maintaining a segregated multimodal environment while scaling to meet the fast-growing and evolving cellular therapy market. Currently, two critical issues need to be addressed: First, how to adapt manual and/or semiautomated processes that cannot be scaled efficiently and second, how to adapt traditional facility design when it does not meet segregation requirements.

GROWTH OF MULTIMODAL FACILITIES

The growth of multimodal facilities and personalized cell therapies is driving the migration to automated closed processing. In early R&D and discovery, there is little motivation to move away from open manual processes in cell therapy. As cell therapies move into early clinical activities, it is possible for teams to manage complex open manual manufacturing processes for a small number of patients. However, difficulties tend to arise when programs are successful and must be scaled to meet commercial demand.

Demand for ATMPs is on the rise. Recently, Abecma (manufactured by Bristol Myers Squibb and bluebird bio) was commercially approved to treat patients with multiple myeloma [2]. Other multiple myeloma cell therapies will likely receive commercial approval soon; Cilta-cel from Janssen and Legend Biotech has recently been approved. These approvals will open the largest patient population to date for cell therapy, and it's likely that manufacturing will be a pain point reflected in increased vein-to-vein turnaround times.

In a traditional facility, where closed and automated process technologies are designed to manufacture high-volume batches of identical products, it is relatively straightforward to build reliability into the process, and a spoiled batch, though not ideal, can be replaced by the next one coming down the line. This is not the case for cell and gene therapy, where in some cases, the product is completely personalized to a single patient.

Consider the process: a sample, a solid tumor, is removed from a patient in a clinic in Denver. It is shipped to a facility in Philadelphia. Intake and chain of custody procedures help manage the sample as it goes through a multi-day manipulation and growth process. The resulting dose is formulated and introduced into a product solution profile, filled into a container, and shipped back to the clinic to be administered to a patient.

It is not difficult to see that a manual open process increases the risk of error or contamination, and the impact on the patient is direct—and potentially catastrophic. In addition, as patient numbers increase, the impracticalities of open process manufacturing approaches become obvious. Processes using manual or semiautomated manufacturing are unlikely to be sustainable or to reduce therapeutic costs.

In a recent case study [3], we examined how to manufacture 10,000 personalized (autologous) cell therapies per year with a manual or semiautomated manufacturing process. We found that it would require the manufacturing site to initiate 30 new patient processes per day and end 30 new patient processes per day. Assuming a process length of 10 days, this would necessitate 330 patient lots running in parallel.

Continuing with this scenario, the staffing requirements for manufacturing would approach 1,700 full-time employees for a single facility. Hiring and training the required skilled staff would be exceedingly difficult, likely requiring operations spread across different sites in multiple cities and the use of a stratified workforce involving less skilled operators. This would leave the site's productivity heavily dependent on staffing and could lead to a potentially significant bottleneck. Our case study strengthens the argument for automated processing.

Human resources aside, there is also the challenge of segregation within the facility itself. Even excellent HVAC design and pressurization to control air movement through the facility has limits when you add the flow of people and materials into the equation.

However, if you can achieve segregation at the equipment level, it not only relieves the facility and the staff from the pressure of managing segregation and contamination but also promotes product quality. With fully closed equipment, you can reduce the risks of running multiple product lines within a shared facility—even for highly personalized therapies. The environment has far less impact on the process stream itself, which offers a means of containing the process and providing quality.

> The growth of multimodal facilities and personalized cell therapies is driving the migration to automated closed processing.

AN EQUIPMENT EVOLUTION

An automated closed system segregates the process and saves space. With fewer human interactions, it can be scaled vertically to

The industry is heading into a new precision medicine era that requires flexible solutions.

increase manufacturing density, driving down the total facility cost while increasing facility capacity. An additional advantage is the introduction of improved process quality and consistency. Automation offers the opportunity to deliver a more consistent product while capturing critical process analytics.

Consider a manual process with a lab technician working with a pipette. Each step must be measured and recorded by an individual, leaving the process open to variation and error. An automated system is tailored to take measurements and create a data stream, which is logged, stored, and assigned to a batch. This real-time process monitoring ensures a robust, secure, and repeatable process, and sets the stage for embracing a more future-facing Pharma 4.0™ mindset.

Although automation offers the clear benefits of robust tracking and quality assurance, it does require an auditable, verifiable data infrastructure with operational and compliance procedures to support it. Companies marketing to the US will need to comply with FDA 21 CFR Part 11 [4], whereas companies manufacturing for the EU will need to comply with EudraLex Volume 4 Annex 11 [5]; both of these outline regulatory GMP requirements for computerized systems.

MODERN MANUFACTURING FACILITIES

With personalized cell therapy, there is no utility in scaling up an established process: It must be scaled out. Although this might be seen as a disadvantage at first, scaling out offers the opportunity to optimize and future-proof a facility.

A templated approach to design allows team members to find efficiencies in real time, and these improvements are replicated as the facility scales. Perhaps even more important, inadequacies and risks are propagated out. The more that the design and engineering team can leverage industry innovations and best practices into a standard template, the better.

Quality is preengineered into the process, adding confidence with scale. As the facility grows, staff can walk into identical suites at multiple production sites and begin working quickly with little orientation. Teams are flexible and training is simplified.

There is also an advantage to building only what is needed *when* it is needed. Guesswork is minimized because there is no reliance on drawn-out market projections, and there is no need to pay for a facility that is larger than needed in anticipation of future developments: Simply expand at the right time for business needs. It is straightforward to increase capacity by building templated spaces leveraging modular components offsite, and careful upfront planning can ensure that the installation has minimal implications for existing or ongoing operations.

CONCLUSION

Allogeneic therapies will continue to be a market presence, but there is no denying the potential and inevitable growth in personalized therapies. The industry is heading into a new precision medicine era that requires flexible solutions.

As personalized cell therapies expand to include solid tumors, an efficient scaling method is via automated closed processing coupled with templated facilities constructed using prefabricated, offsite construction and modular design. Taking advantage of iterative design means the facilities of tomorrow don't have to suffer the problems of the facilities of yesterday. This is an exciting and critical juncture for the ATMP industry, and these elegant solutions are the future of pharmaceutical health care.

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FOYA WINNERS SHARE LESSONS LEARNED in Facilities Development

By Marcy Sanford

What do recipients of ISPE's prestigious Facilities of the Year Award (FOYA) know that has helped their projects succeed? What are the lessons learned from achievements in facilities development, including forward-looking projects that encompass and inspire changes in the industry? *Pharmaceutical Engineering*® spoke with nine FOYA winners from recent years about the lessons they learned and their advice for those challenged with building a new facility or renovating an existing one.

Patience is key when embarking on a new project and the approach to facilities planning is a long one, according to project leads for FOYA-winning projects. "Overseeing any project is a journey and each day is a little, or sometimes, a lot different from the one before," said Eric Schnake, Global Engineering Capital Projects and Portfolio Lead for Takeda Pharmaceutical Company's Plasma Operating Unit. "A project is a little life all in itself. It can take two to three years to complete, or longer. It is not a sprint, it is a long-term commitment, it has a life of its own and goes through cycles."

The first of those cycles starts with planning, and good planning starts with determining the "why" for your project. "The business case for doing the work is likely the most important and common early consideration on all projects. I can't remember a time in my decades in the pharmaceutical industry when a customer simply said, 'I want it and I don't care what it costs or how long it takes,'" said Thomas Piombino, Vice President, Americas, IPS-Integrated Project Services, LLC. "However, I've learned that the cost is not always measured in dollars. In the case of the United Therapeutics project, the cost and schedule of the facility construction was a factor, but the real cost was not meeting the therapeutic needs of their pediatric patient community." (See the Sidebar that presents an overview of the projects discussed in this article; complete profiles of the projects are at ISPE.org/facility-year-awards)

PROPER PLANNING FIRST

Proper planning at the beginning of a project can save major headaches and setbacks later on. Even if the design stage takes longer than originally imagined, it is important to take the time you need to make sure all the details are in place. "Make sure business requirements are aligned with business scope and objectives," said Schnake. "You may have people pushing you to get started right away but you have to be able to absorb some of the push back on schedule to make sure that when you start, it is going to work. Balancing the cost and schedule impact with future performance is key. The performance of the plant always has to win. At the end of the day, nobody will remember if the project is a little late or a little over budget, but if you can't meet capacity, they will remember that."

Bob Myers, Global Engineering Director, Pfizer, agreed. "Define a clear scope and stick to the scope. Focus on safety and make it integral to the project success, and understand and plan for any country-specific project requirements, permits, inspections, and approvals." As part of the planning for Pfizer's Biotechnology Campus in Hangzhou, China, local codes and standards were incorporated early in the design to avoid redesign and schedule delays. They also worked with the Hangzhou Economic Development Area to make sure all documents were in order for imports and road-tested various ground transportation routes.

The COVID-19 pandemic has highlighted worldwide supply chain and labor issues. David Mallonee, Associate Director, Project Management Design Division, IPS-Integrated Project Services, offered advice on how to incorporate lessons learned from the pandemic into project planning going forward. "Modularization and off-site fabrication have become commonplace in our industry. The benefits are well known but one that has risen to the top recently is the result of the supply chain and labor

FOYA Projects Featured in this Article

Bristol Myers Squibb Cruiserath Biologics Campus

FOYA AWARD: Project Execution 2020
Location: Tyrellstown, Dublin, Ireland
Total Facility Size: 500,000 square feet

Mission: To transform an existing Bristol Myers Squibb Active Pharmaceutical Ingredient site into a state-of-the-art Biologics Drug Substance Manufacturing Campus that includes consideration for future commercial projects.

FOYA Judges said: "The project demonstrated an exemplary, positive collaboration between all project stakeholders and team members. The project was extremely fast-tracked, with mechanical completion achieved for the manufacturing building within 26 months of start of detailed design, which coincided with the start of construction on site. The project was completed safely, on time, on budget, delivered a successful Process Performance Qualification campaign, achieved LEED Silver rating, and is well on the way to delivering product to patients. The facility now serves as a much sought-after employer in the area and provides a comfortable, aesthetic work environment for employees."

The Government Pharmaceutical Organization Biological Product (Vaccine) Production Plant

FOYA AWARD: Social Impact 2021
Location: Saraburi Province, Thailand
Total Facility Size: 119,469 square feet

Mission: Providing equal access to vaccines for all Thai citizens in a zero-waste facility.

FOYA Judges said: "Increased patient access, such as the kind GPO offers, prevents drug shortages by manufacturing critical medications for patients at home and helps mitigate the consequences of rapidly developing public health crises through rapidly deployed vaccines. GPO's sustainability in its facility design has reduced the environmental impact of GPO on Thailand and, ultimately, the world."

Grand River Aseptic Manufacturing Large-Scale Fill-Finish Facility

FOYA AWARD: Operational Agility: COVID-19 Impact 2021
Location: Grand Rapids, Michigan, US
Total Facility Size: 61,500 square feet

Mission: To develop a state-of-the-art, customer-centric facility with plenty of manufacturing flexibility.

FOYA Judges said: "This project was selected for creating a facility that was able to support a pressing need of the day, response to the COVID-19 pandemic. GRAM's sense of urgency, commitment to creative project execution and collaboration are commendable and the facility design reflects flexibility, speed, and operational agility."

Janssen Sciences Ireland Bio Cork2

FOYA AWARD: Project Execution 2021
Location: Ringaskiddy, County Cork, Ireland
Total Facility Size: 200,000 square feet

Mission: To expand the existing biologics manufacturing facility to ensure a sustainable supply.

FOYA Judges said: "Janssen and their partners worked as an integrated team throughout the project to ensure the workers were focused on safety, compliance, and schedule always. The team overcame many issues during the more than three years of execution, including proceeding forward during the COVID-19 pandemic, which happened as they completed construction and started in full commissioning."

Janssen Raritan CAR-T Clinical Manufacturing

FOYA AWARD: Honorable Mention 2020
Facility Location: Raritan, New Jersey, US

Mission: To construct a facility in rapid fashion where a cell therapy (JNJ-4528) for patients with multiple myeloma can be manufactured for clinical studies and commercial launch, in conjunction with partner Legend Biotech.

FOYA Judges said: "Janssen used an innovative Commissioning, Qualification, and Validation and hybrid parallel construction approach on the project. The project team expertly executed the innovative Johnson & Johnson Specification, Design, and Verification (SD&V) program for manufacturing systems and equipment and designed utility systems with a focus on sustainability."

Locus Biosciences Commercial Phage Production Facility Upfit

FOYA AWARD: Honorable Mention 2021
Project: Commercial Phage Production Facility Upfit
Location: Morrisville, North Carolina, US
Total Facility Size: 12,000 square feet

Mission: To provide a cGMP commercial phage production environment with maximum flexibility to generate, purify, and aseptically fill therapeutic doses of antibacterial phage to fight critical unmet medical needs and diseases.

FOYA Judges said: "The design attributes and operational procedures Locus Biosciences incorporated into their new facility go beyond the Regulatory requirements."

continued next page

Pfizer, Inc. Global Technology Center

FOYA AWARD: Facility Integration & Project Execution 2019
Location: Hangzhou, China
Total Facility Size: 341,000 square feet

Mission: To design, construct, qualify, and deliver a $195 million Biotechnology Campus on time and on budget with a blemish-free safety record.

Pfizer won two awards for the same project.

FOYA Judges said: "Overall, Pfizer's Global Biotechnology Center had a very high degree of integration from the selection and development of the large molecule network manufacturing platform to the design of the Hangzhou facility and to the program that enabled construction completion within 25 months."

"The Hangzhou Global Biotechnology Center was completed with a perfect safety record; zero lost time injuries, with 2.7 million hours of site activity. The project team trained 3,700 workers on Pfizer's safety program. Additionally, the project was completed on time and on budget."

Takeda Georgia Manufacturing Facility

FOYA AWARD: Honorable Mention 2019
Location: Social Circle, Georgia, US
Total Facility Size: 1,100,000 square feet

Mission: To build a manufacturing facility that could meet the current demand for Takeda's plasma-derived therapies, expand to adapt to increased demands, and support the emotional, physical, and financial well-being of employees while adhering to strict safety standards.

FOYA Judges said: "The project brought together an unprecedented collaborative effort of subject matter experts from around the world to successfully design, develop and construct a state-of-the-art facility that not only meets Takeda's production goals but positively impacts the wellness of employees and was built with a stellar safety record."

United Therapeutics Dinutuximab Dedicated Oncology Medical & Analytical Laboratory

FOYA AWARD: Social Impact 2020
Location: Silver Spring, Maryland, US
Total Facility Size: 31,486 square feet

Mission: To build a facility that would integrate into the existing United Therapeutics campus and the Silver Spring community, where United Therapeutics could increase the production of Unituxin to provide it to patients with a rare pediatric cancer and to conduct research for numerous other life-threatening illnesses.

FOYA Judges said: "This project faced unique challenges and obstacles to build the facility but never lost focus on why they were doing this work—to provide medicine for an unmet medical need. The project also took the time to consider the impacts to the community both during and after construction, even including external artwork for the facility."

shortages we are experiencing right now. Most projects that started just prior to the pandemic did not understand how much impact this would have on their project costs and timelines. We are all learning from these challenges and adapting to them. Integrating supply chain knowledge and logistics management into project execution has become paramount. The right mix of modularization and off-site fabrication is a great way to mitigate these issues."

Thailand's Government Pharmaceutical Organization (GPO) learned how changes to design can become a major setback to a project. "There was a significant design review to follow evaluated requirements for BSL-2 plus production facilities. Consequently, an additional budget had to be approved by the Thai government, which took a long time to get due to political instability in Thailand at the time," said Withoon Danwiboon, Managing Director of GPO.

"The delayed budget approval also affected the contract management. We learned that having the right design from the very beginning was crucial. In addition, it is advisable to work with the FDA early for facility designing steps."

LOCATION CONSIDERATIONS

Once a plan is in place, determine where to locate the facility. Often, a project's location is predetermined due to existing facilities, which can be added on to or renovated. When embarking on a greenfield project, a new development on an undeveloped lot, there are many factors to consider. Both Grand River Aseptic Manufacturing (GRAM) and United Therapeutics chose their sites because of proximity to existing facilities.

GPO's facility was a new build and Danwiboon said access to supplies and infrastructure were key criteria when they were looking at sites. "To produce an egg-based vaccine, vaccine quality egg supply is crucial. There are several local egg suppliers around Saraburi province. Transportation to the nearest airport or seaport and product distribution were also taken into account. One of the main reasons we decided to locate our vaccine plant in Saraburi province was that there are several industrial estates located in the area. In other words, supporting systems, such as electrical power, city water, transportation, communication, and healthcare, were available and accessible. Moreover, because many industrial facilities had been constructed in the

neighborhood, Saraburi province had many skilled workers and a large construction workforce, which minimized skilled labor shortages."

Having existing space that can be renovated may make the location decision easier, but renovation projects have the challenge of trying to make something new fit into an already existing infrastructure. "It is important to have a clear understanding of the capabilities of existing infrastructure—including critical utilities, electrical, chilled water, HVAC, and compressed gases—to ensure there is adequate capacity and identify redundancy gaps in light of business continuity," said Jeffrey Reinhardt, Director, Advanced Therapies Supply Chain, Janssen.

"Renovating a facility, as we did at Locus Biosciences, requires a careful design and a well thought-out plan to minimize production interruption," said Paul Garofolo, CEO, Locus Biosciences. "But this melding of old and new also presents an opportunity to address current problems and to extend the longevity of existing infrastructure as well as facilitate the upgrading and change-out of obsolete systems."

TEAM BUILDING

After determining the why and where, the next step to a successful project is to identify who will be on the facility team.

"Build the best team you can get and then retain them for the duration," said Alan Bateman, Make Asset Management Site Lead, Janssen. The project team for Janssen's BioCork2 project was comprised of people from 40 different countries. Janssen relied on interactive workshops and visits with global partners, and integrated the teams, management techniques, and values throughout project execution to ensure that the transition from concept to fully operational plant was smooth and seamless.

Bristol Myers Squibb's (BMS) Multi-Product Cell Culture (MPCC) Project was a major success due to their "One Team" project philosophy. "A 'One Team' project approach was promoted by BMS from the outset and ensured the project team focused on the end result, and the collective success of the project," said Noel Heaney, General Manager Cruiserath Site, BMS.

"All team members partnered with a focus on open communication, transparency, collaboration, flexibility, fairness, rapid and local decision making, and safety. The 'One Team' approach was a key reason why the project was successfully completed on time, on budget, and to the highest safety standards," said Anthony Carter, Director, Project Realization, BMS. "A key driver behind the 'One Team' philosophy was the assertion that 'bad news does not get better with age.' This promoted open communication and transparency and resulted in a collaborative team of individuals from multiple companies working together for a common goal, with the intent of resolving issues as 'One Team' together for patients."

Myers added that once the team is in place, it is important to empower them to make decisions, partner with world-class companies and top local contractors, treat all partners as peers, develop shared goals, and encourage a philosophy of mutual respect for all people.

After determining the why and where, the next step to a successful project is to identify who will be on the facility team.

Challenges are bound to arise with any project. Some, like Pfizer's need to transport 77 production modules from Europe to Shanghai to Hangzhou safely and on schedule, can be foreseen and planned for ahead of time. Others, like political unrest and global pandemics, are not as easily predictable, but with the right design and the right team, it is easier to determine next steps to overcome challenges and get the project back on track, or sometimes switch tracks.

"Every project, especially one at this scale, comes with challenges," said John Wichelt, Vice President, Client Pharmaceutical Services, GRAM. "The most unexpected and unpredictable challenge we met was having a pandemic start while we were in the middle of qualifying GRAM's new equipment. We had contractors from out of the country on site for equipment startup and qualifications, and when the news arrived about COVID-19, they had to leave immediately. Our team stepped up right away, went to virtual sessions with the contractors, and performed all the startup and qualification activities themselves. This was a huge success and allowed the project to stay on schedule, which ultimately resulted in GRAM becoming one of the companies to manufacture a vaccine for COVID-19."

"The most challenging aspects of this project were timing and safety, in that we were midstream when the pandemic hit," said Garofolo. "Despite COVID-19 presenting significant challenges across the industry, we were able to successfully complete a world-class modular cGMP viral vector manufacturing facility through continued innovations and dedicated partners. Construction began on 4 November 2019, and was complete 12 August 2020, and there were no COVID-19 cases or impacts on any worker and zero recordables or lost time."

About FOYA

Each year ISPE's Facility of the Year Awards (FOYA) provides a platform for the pharmaceutical science and manufacturing industry to showcase its accomplishments in facility design, construction, and operation while sharing the development of new applications of technology and cutting-edge approaches. FOYA seeks to recognize the shared commitment and dedication of individuals working for different companies worldwide to innovate and advance pharmaceutical manufacturing technology for the benefit of all global consumers. For more information and to read complete profiles of winning projects, visit ISPE.org/facility-year-awards

About the author

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2022 ISPE FACILITIES OF THE FUTURE CONFERENCE:

Emerging Technologies

By Susan Sandler

Two sessions at the 2022 ISPE Facilities of the Future Conference in early February captured varied views of emerging technologies in the pharmaceutical industry, and the industry's work to embrace these technologies.

Sau (Larry) Lee, PhD, Deputy Director of Science Chair, Emerging Technology Program, Office of Pharmaceutical Quality/CDER/FDA, provided an update on the FDA's Emerging Technology Program (ETP) during the morning session, "Benefiting From Emerging Technologies" on 2 February.

In a presentation titled, "Experience in Pharmaceutical Innovation: US FDA Perspective," Lee provided some background and the current status of the ETP. The program was established in 2014 to promote and facilitate adoption of innovative approaches to pharmaceutical product design and manufacture, including work to date in small molecules, therapeutic proteins, and multiple products. In 2021, the program received 13 proposals and approved 10, held a total of 35 sponsor meetings, and conducted six site visits.

The program faces several challenges as it continues to grow, Lee said: an increased workload limits the program's ability to support all new technologies, industry members want more dedicated time from the program, and team members left FDA. In response, a process has been implemented to move forward, including the ETP 2.0 model and road map for implementation, which are currently being applied.

Framework for Regulatory Advanced Manufacturing Evaluation (FRAME) has been launched as a multiyear initiative to take a systematic and phased approach to develop a regulatory framework in support of new technologies. Now in its third phase, FRAME seeks inputs on gaps and pain points to help inform FDA thinking before implementation begins. Lee said that the program will sync input, eliminate hurdles, clarify expectations, and harmonize internationally. A draft white paper will be released for public comment.

MRNA FUTURE AND PRESENT

In the presentation titled "mRNA Technology: Beyond COVID-19 Vaccine," David Estapé, PhD, Technology Manager, Biotechnology at CRB Group, discussed mRNA's potential. Huge impact is expected, he noted. Two types of facilities can use mRNA: large facilities such as those that have produced COVID-19 vaccines and can serve other needs for large amounts of material, and facilities for personalized medicine where small quantities are needed multiple times per year.

Questions to consider: Will the industry use current facilities to provide mRNA products? Or will the industry need to consider different approaches in facilities? Estapé noted that mRNA facilities need to be high-throughput facilities, requiring high integration of all areas, with automation/digitalization playing a key role.

Facilities of the future will need to be flexible and adapt to the needs of producers, Estapé predicted. The greater efficiency of mRNA compared to typical monoclonal antibodies (mAb) means that about 1,000 times less material is needed, he said. And mRNA production speed can be two to four days, compared to two weeks for mAb. As a result, mRNA facilities should be small, capable of high throughput.

When it comes to GMPs for mRNAs in the EU and from the PIC/S perspective, there is ambiguity so far, he said. For instance, the European Commission's EudraLex Volume 4–Good

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Manufacturing Practice (GMP) guidelines does not see mRNA as a typical ATMP, whereas the new Pharmaceutical Inspection Co-operation Scheme (PIC/S) Annex 2A for ATMPs addressed mRNA for the first time.

Estapé reviewed the risk profile for mRNA, noting that the cell-free, enzymatic processes mean a low risk of microbial contamination or bioburden, and aseptic or sterile processing is not required. There are no viral vectors and thus no associated risks to patients, unlike with adeno-associated virus or lentiviral vectors.

It is up to the industry to discuss and find prescriptive GMPs, understand the risk profile, and make a decision based on the risk. The speed of the move from R&D to commercial manufacturing for COVID-19 vaccines raises some questions and areas for improvement:

- Process/product optimization: storage temperatures, formats, etc.
- Scale-up versus scale-out
- Single-use versus stainless steel and reuse of equipment
- Level of automation versus manual intervention

Oliver Hennig, Senior Vice President, Operations, BioNTech SE, shared insights into the company's COVID-19 vaccine development during the session. After providing background about the company's development and emphasizing the importance of working with collaborators, he discussed why mRNA is a beneficial approach for vaccines.

The arrival of COVID-19 brought change: before then, there was no mRNA commercial product on the market, but several companies—including BioNTech—had significant experience with mRNA. He noted that mRNA is a logical choice for vaccines because it does not require the addition of adjutants or the use of a viral vector for administration; it is non-integrating into DNA and non-infectious, unlike attenuated live virus and DNA-based vaccines; it is high purity and animal-free; and it has highly scalable production, which is the most important factor. Hennig described some differences in the use of mRNA for oncology treatments, which can be highly individualized.

He traced some of the steps that were followed to produce the vaccine quicky and in the necessary volume, including distribution challenges during the early months of the pandemic. Shortages of materials such as gloves affected sourcing; volume was needed in proprietary raw materials for mRNA production; CMOs and suppliers from around the world worked on purification, concentration, formulation, and fill-finish; and warehouses had to be at -80°C for hundreds of millions of doses. The severe supply chain issues impacted the work as well; for mRNA production, detailed and long-term capacity planning was required prior to regulatory approval; reporting, production, and transportation had to be harmonized across regions; capacities and materials for formulation and filling were restricted; and distribution planning and fulfilment of local requirements had to be achieved. All of this was undertaken with commitment to the highest safety and quality standards to produce more than 3 billion doses, with ongoing work in continuously improving the supply chain.

> Facilities of the future will need to be flexible and adapt to the needs of producers.

Despite the challenges, the need to produce so many batches consecutively with so many partners gave the company the ability to achieve highly accelerated readiness and significantly faster learning than in a "normal" setting, Hennig noted. As for variants: the technologies and experiences are there and available to address these. The ability to employ technologies where they could work on the shop floor brought very fast learnings and will inform how they make mRNA in the future.

NEW TECHNOLOGIES

An afternoon session on 2 February continued to explore emerging technologies, focusing on concepts promoting rapidly advancing manufacturing technologies that are enabling improvement in quality and process robustness, supply chain agility, and reduced costs.

The first presentation in the session was "Domestic Infrastructure and Capacity: The Pandemic Impact," and had provided input from Thomas Warf, Director, Manufacturing, Facilities and Engineering, with the Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response (ASPR)/Biomedical Advanced Research and Development Authority (BARDA), and Arlene Joyner, MS, PMP, CSSGB, Branch Chief CDMO Network, PCI/BARDA/ASPR/HHS.

BARDA was part of the US government's Operation Warp Speed within HHS and with a mission of working on both COVID-19 and future pandemics, Joyner said. Tasks included working on the ultra-cold storage needs early in the COVID-19 vaccine development process and distribution to support an entire country, which required significant coordination and support, as well as capacity issues for fill, label, and distribution with CMOs in early 2020.

Warf discussed collaborations in vaccine manufacturing consumables, noting that it was understood from the start, and from previous pandemic experience, that obtaining the needles and syringes—in addition to other materials—to administer the vaccines in development was going to be a key issue. So it established partnerships with various companies to provide these materials and others, including vials, and addressing issues with facilities including fill-finish impact on other medicines when operations were changed over to vaccine production, and supply chain surveillance of bottlenecks in raw materials, consumables, and vials.

Joyner said that they also arranged for reservation contracts to obtain space in production facilities for risk mitigation to provide capacity in case of a disaster at a filling facility.

BARDA has also been preparing for future pandemics with the Industrial Based Expansion program, which is planning for essential vaccine inputs, including raw materials such as nucleotides, lipid nanoparticles and synthetic cholesterol, chromatography resins, and cell culture media; program management; and partnering with the US Department of Defense. For vials and consumables, it is working on specific materials including single-use assemblies, filtration equipment, and sterilization capacity. For end-to-end capability, it is working on biosafety level 1 and 2 lines; drug substance/drug product storage; and labeling, inspection, and packaging capacity.

Another issue for the future is onshoring. Many products were not available domestically and when borders are closed or other countries decide to keep resources within their borders, it can present problems.

DIGITALIZATION

A second presentation in the session, "Elements of Effective Digital Technologies," looked at the importance of digitalization and Pharma 4.0™ to facilities. Yvonne Duckworth, PE, Senior Automation Engineering and Digitalization Lead at CRB, gave an overview of digitalization and Pharma 4.0™, noting that digital technologies require a robust control system and network infrastructure for support. She gave some history of digitalization and explained about the technologies in Pharma 4.0™.

Recommended starting steps for building a digital strategy include assessing the current digitalization level, determining the desired level, and creating a road map for implementation. As part of this process, an interview for "pain points" will help with input from manufacturing, filling, packaging, warehouse, quality, maintenance, and automation/IT. She suggested being practical, seeing where there is value, and considering what you are trying to fix.

To build the road map, consider what technologies are available, current industry trends, costs for initial investment and recurring costs, return on investment, which vendors can provide services, and which integrators can implement.

Also consider the risks (security and operational), what changes to the workforce may be needed (more/fewer workers, training), opportunities to test and learn at an existing site, a phased approach, and impact on design (layouts, network infrastructure, and equipment skid specifications).

Sumit Verma, Senior Vice President, Commercial Manufacturing at Iovance Biotherapeutics, Inc., provided some case study details from Iovance about its road map for implementing Pharma 4.0™ at its the cell therapy center. The facility is positioned for more scale-up and to execute a digital technologies road map, including flex and core workstations, quality control, supply chain, and scalable workforce in areas including manufacturing; quality assurance and quality control; supply chain; manufacturing, science, and technology; and IT.

The next steps for systems integration, digitalization, Pharma 4.0™, and automation strategy will be determining the approach for the facility, identifying systems to be included in integration, and defining the integration strategy. The company is taking a phased approach and building a robust network infrastructure, including a business corporate network, industrial controls network, and other elements. The manufacturing execution system will include electronic batch records, review and release by exception, SOPs, equipment and warehouse management, and order management.

Disclaimer: This is an abridged, unofficial summary of presentations by regulators and government agency representatives during sessions at the 2022 ISPE Facilities of the Future Conference that has not been vetted by any regulatory or government agency. The content is an informal and brief synopsis of the presentations and does not represent official guidance or policy of any regulatory agency or government.

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REIMAGINING CPV for a Pharma 4.0™ World

By Mark O'Connor, Pablo Sáez, and Alicia Tébar

The life cycle approach to process validation stresses the need for continued monitoring of process performance to ensure that the manufacturing process remains stable and predictable, i.e., in a state of control. This life cycle stage is known as continued process verification (CPV) or ongoing process verification (OPV) [1–3]. In the last decade, regulators have issued revised process validation guidance that puts more emphasis on demonstrating that pharmaceutical manufacturing processes remain in a state of control throughout the product life cycle by applying recurring data analysis [1, 2].

The process validation life cycle is defined as the collection and evaluation of data from the process design stage throughout production that establishes scientific evidence that a process is capable of consistently delivering quality products [1]. It is a regulatory expectation that manufacturers understand their products and processes, regardless of whether products are manufactured internally or at contract manufacturers. This includes periodic review and monitoring to ensure a state of control—see guidance from the US FDA, WHO, and European GMPs, as well as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q8 R2, ICH Q10, and Pharmaceutical Inspection Co-operation Scheme (PIC/S) Annex 15 [1, 2, 4–7].

The application of CPV/OPV has become a core regulatory requirement and goes beyond traditional annual process reviews (APRs) and product quality reviews (PQRs): CPV programs also monitor critical in-process parameters and material attributes throughout the product life cycle and are typically performed on a more frequent basis. The concepts described in this article should be considered distinct from *continuous* process verification, which is an alternative approach to traditional process validation in which manufacturing process performance is continuously monitored and evaluated [4]. This science- and risk-based real-time approach typically involves inline, online, or at-line controls and monitoring of process performance and product quality on each batch.

However, the combination of Pharma 4.0™ concepts—which enable organizations involved in the product life cycle to leverage the full potential of digitalization to provide faster innovations for patient benefit—and the application of performance-based control strategies may mean these concepts will be one and the same.

SURVEY OF CURRENT INDUSTRY CPV PRACTICES

Even though a CPV process has been required by EU GMP regulation since 2015 [5], full implementation is still far from a reality. Completing data gathering, analysis, and reporting at higher frequency than the annual APR/PQR demands resources, which is just one of the many possible reasons for industry's lagging adoption of CPV. To further analyze the factors affecting CPV adoption, we designed and distributed a survey for pharmaceutical companies from countries in the ISPE Iberia Affiliate (Spain and Portugal) to evaluate the level of CPV implementation in those countries.

The survey was completed anonymously by 28 companies. Among them, 75% had 250 or more employees. Although it is not a large overall number, the variety of profiles including innovator, generic, biologics, CMO, medical device, and API, is significant and therefore the results can be considered representative.

The frequency of reviewing data and issuing CPV reports can be controversial. Some companies still do this annually, integrating this review into the PQR. This is increasingly being questioned in inspections and audits, however, because a retrospective study is not the objective of the CPV; rather, the CPV's goal is to complete a prospective study with the aim of detecting trends and early signs of loss of process control to take preventive actions for these risks. The study found that 46% of companies may not have yet implemented real (non-annual reporting) CPV when considering frequency.

Data acquisition, from both the process and the controls carried out over the process, often consumes many resources, especially when the information is recorded in a paper or hard-copy format and comes from different sources. The time and staff

necessary to gather the data decreases with digitalization (electronic records) and with the integration of the various sources of information into repositories. This allows the export of data to the corresponding analysis and reporting tools—a much more agile way that still preserves data integrity.

Digital data management facilitates obtaining information from the process in real time, which is the spirit and ultimate goal of the CPV. The survey revealed that 46% of responding companies have a medium to advanced level of digital data management with integrated electronic data solutions. A follow-up question about the time necessary to gather the data for CPV per product found that 18% would require less than an hour for this task. This is one of the indicators presented by the most advanced companies in digitization. Other respondents would require four hours or more to gather data for CPV. It is also noteworthy that 82% of companies include critical quality attributes (CQAs), critical process parameters (CPPs), and critical material attributes (CMAs) as variables for CPV monitoring and only 18% measure CQAs alone.

Statistical analysis follows data collection. This can be approached with a classic statistical process control with control charts and capability analysis to verify that the process is stable and capable. In some cases, control chart alerts may indicate a risk to product quality that should be addressed. Other data analysis tools can help identify a problem's root cause. In pharma, multivariate statistics and other advanced analytical tools are beginning to be used due to their effectiveness in analyzing increasingly large and complex data packages. Most companies use spreadsheets or standard statistical packages, but a significant 11% use advanced analytics.

In relation to the personnel who complete these tasks, 71% of responding companies claim to have personnel trained in statistics or data scientists. Regarding the use of the CPV outcomes, companies were asked: Does your company use the CPV information in any way other than GMP compliance? In response, 32% said no and 68% responded yes. Of that 68%, answers on how CPV information was used fell into the following categories:

- Control of variability and process improvement
- Early detection of trends and changes
- Correlations and troubleshooting
- Use as key performance indicators
- Comparisons between different sites and business decision-making

Finally, we asked if the companies had cost estimates for digitizing or automating the ongoing verification process. Twenty-five percent of the companies had performed this exercise and predicted a period of two to five years for implementation and a cost between €300,000 and €1 million.

CPV MATURITY SCORE

By assigning scores to each survey response, we obtained a classification based on the degree of maturity in CPV practice, meaning in the degree of process monitoring and maintenance of the control state. Approximately 20% of responding companies likely are not complying with current GMP requirements; 50% are complying but do not use the full outcomes of the information provided; and nearly 30% have the appropriate systems to use the full potential of the information to improve both the quality and efficiency of their manufacturing plants.

These findings demonstrate how the technological factor (digitization and systems integration) makes a difference by drastically reducing the need to allocate resources (staff and time) to data collection and the subsequent analysis and reporting. These tasks can be automated, which would allow time and staff to be shifted to more valuable activities, such as improvement and decision-making tasks, based on the available information.

VALUE BEYOND GMP COMPLIANCE

The benefits of implementing an automated CPV (or CPV 4.0) extend well beyond compliance. Adequate and timely process monitoring ensures robust processes through early detection of drifts in performance before they result in deviations. In our experience, these deviations not only require time and resources to investigate, but can also sometimes lead to batch failures, supply chain problems, and increased production costs.

Robust processes enable pharmaceutical manufacturers to meet supply chain requirements, including introducing new sources of active pharmaceutical ingredients (APIs) or raw materials and transfers to new sites. Further, CPV monitoring enables and enhances cross-site and cross-product learning. To achieve these advantages, a gradual implementation is recommended.

CPV PERSONNEL

Two groups of personnel are involved in completing CPV. The names of these groups may vary across organizations, so here they are referred to as CPV data analysts and manufacturing staff. Data analysts create the CPV report and implement changes from the improvement actions. Technical service, engineering, and quality assurance staff are some examples of CPV data analysts.

Manufacturing staff are the personnel directly involved in the goods treatment process: operators and their supervisors, operations quality, and maintenance. The manufacturing staff benefit from the knowledge acquired from the CPV report for improvement opportunities that is used to create corrective and preventive actions (CAPAs). The knowledge acquired during the product commercial life is considered valuable for the development staff, both as feedback for continuous improvement and as knowledge to be applied to new products.

COMPLETING CPV

Data Collection

The first step is for CPV data analysts to gather the data. Before a full CPV program is deployed, data may come in different formats: from centralized systems with powerful spreadsheet reports, .txt/.csv/.pdf reports with numerical data that each system creates, manual data taken from batch reports, or even text data

from investigations, reports, and other written documentation that must be manually read to extract relevant data.

When a fully automated CPV process is implemented, all data will be gathered automatically in real time. The system will read from all data sources. It could even be a real-time reading of data sources, and the CPV could also take information from human-written reports such as investigations, although these features may be implemented in later stages of the CPV. Even though the technology to gather data automatically is well established in the market, its implementation may still be one of the biggest challenges because it may require a lot of resources (i.e., money, time, and work). This high resource consumption also means that being too ambitious may drive the project to fail. Implementation phases will be covered later in this article.

Data Formatting and Contextualization

The second step is for CPV data analysts to format and contextualize the data so only relevant data is used in the report and it has the correct format for the software that analysts use to be able to process the data (this is usually referred to as data cleansing). As mentioned, data will come from disparate sources, in different formats, and with different contextualization. Data may be structured in well-formatted tables, but also in plain text with missing metadata (data that gives meaning to the numbers), in pictures, or written by people. When the automated CPV is fully installed, the data-gathering process will also automatically perform the data cleansing process previously mentioned. As a result, the CPV data analysts will have a single and well-structured data repository.

Data Analysis

Once all data are clean, CPV data analysts will use statistical and advanced analytical tools to pull information from the data. This information will, at first, be used for compliance needs such as verifying the process capability and the state of control. In later stages of automated CPV, the data will give deeper insights and increase understanding of the process. And, of course, a fully implemented CPV will generate the report automatically.

AUTOMATED VS. MANUAL CPV

So far, the biggest value yet achieved is changing from a manual to an automatic process. The most obvious benefits of automated CPV are gaining resources such as time and staffing and lowering the risk of manual entry error. These also drive higher data integrity levels. But the real benefit is found beyond automating these tasks. If CPV data analysts do not have to spend time gathering data, cleaning data, and writing reports, they can focus on creating better and more comprehensive insights in a continuous manner. Through statistical analysis (either classical or through machine learning and artificial intelligence), it will be possible to determine the influence of each process parameter (either critical, CPP, or not) over each CQA. Reports could also be configured so that the CPV would indicate the future behavior of the process (predictive information).

CPV would provide a better process understanding. Further, it would allow earlier detection of critical-to-quality events, leading to a more efficient root-cause investigation and issue resolution. Root causes can be derived from complex multivariable models, which are able to define the most influential input variables for the event. In one of the last stages of the CPV, the system would even be able to indicate what actions should be taken (prescriptive information). It would be possible for CPV data analysts to create a new set of CPPs based on what is actually influencing quality, or to update the already existing set.

Future models to be included in fully automated CPV will be able to predict a deviation on a CQA based on how each process indicator affects the process. This is possible because statistical algorithms may discover hidden influences, from process events to the process outcome. This way, the process knowledge that the CPV data analysts obtain from the predictive models will enhance the knowledge from classic process engineering sources based on deterministic models (physical, chemical, and/or thermodynamic laws based). There is even more to come. Once advanced CPVs are implemented together with process analytical technologies, then continuous process verification (validation on real-time basis) and even real-time release testing can be considered.

BENEFITS OF AUTOMATED CPV

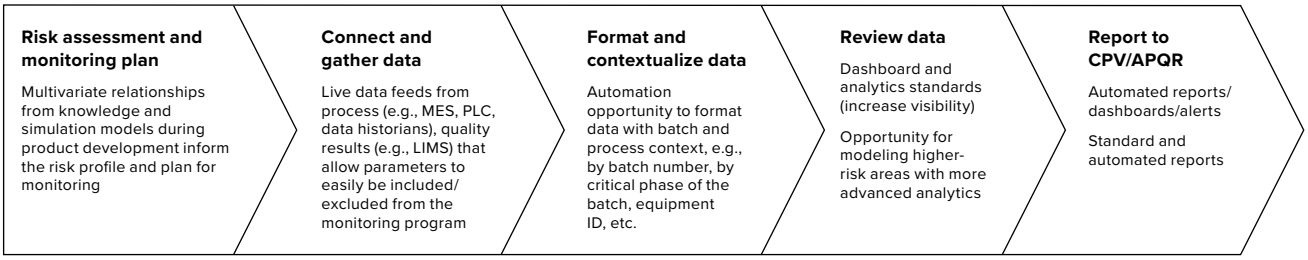
The first benefit is having quality information about the process performance. Using this information, it is possible to create new indicators in the process, as well as discover the importance of others that may already exist but are unrecognized. These process indicators will not only tell if a variable or CQA has moved out of limits (simple information), but also how big the risk is to product quality during a whole process (complex information). It will also be possible to have all the information on a real-time basis due to automation.

An automated CPV will inform earlier about critical events using predictive algorithms. For manufacturing staff, this means that both expected and unexpected events can be handled in advance. Moving from preventive maintenance to predictive maintenance has many benefits. First, changing from a schedule-based machine stop to an accurate prefailure machine schedule means fewer stop times throughout the year, which allows more machine availability and, in turn, higher production capability. Next, knowing if a machine or a process is about to fail reduces the number of unexpected stops that could drive to a quality issue and, thus, to a product loss.

Predicting events is not the only advantage. As information may become available faster, quality decisions can also be made faster. Some alarms may be created to prompt because of complex indicators that measure changes over many variables, which will allow more processes to move to approval by exception, lowering the workload of quality departments, reducing human error, and reducing production lead time. This will allow the process to be continuously validated on a real-time basis.

Having complete information about the process and equipment will help process engineers modify the plant to create more

Figure 1: Examples of automation and lean process improvements to lower the barrier to CPV reporting today.



efficient and robust processes. This, in turn, will lead to using fewer resources such as fewer intake materials, less energy, and less time. CPV not only increases production capabilities, speed, and quality, but it also reduces the cost of the finished goods.

CPV AUTOMATION OPPORTUNITIES

It is evident from the survey results that implementing CPV has not been a straightforward task for many. Digital trends within and outside the industry, specifically advances in data infrastructure and analytics approaches, offer more opportunities to achieve value in process monitoring than a decade ago. Before embarking on any digitalization effort, we recommend identifying opportunities to implement a lean process for CPV (see Figure 1).

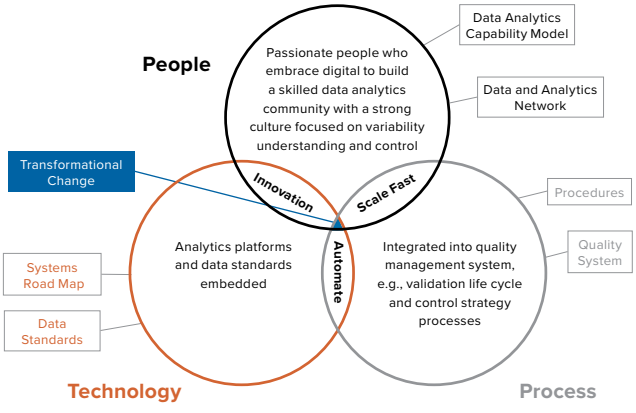
RISK-BASED MONITORING

Quality risk management is a key enabler for CPV [8]. The CPV risk assessment, typically initiated in the development of the product and process, should initially focus on identifying which inputs (typically material attributes, process parameters, analytical methods, manufacturing efficiency, and yield data) could have an impact on the variability of the process output (in process controls [IPCs] or the output CQAs) to determine a monitoring approach that is commensurate with risk.

Consideration must be given to the level of control already in place for a particular input, and whether variability within that level of control is likely to have a significant impact on the CQAs. The experience and knowledge of the cross-functional team should focus on the inputs that are likely to have an actual effect on the variability. Once the inputs and outputs have been collated, the effect of each input must be assessed on the outputs/CQAs. The impact score will be based on the experience and knowledge of the team and, where possible, this will be supported with evidence or prior data. For example, if an input has a specified range (e.g., purchase specification or process control range), but it is known that variation within that range has a significant impact on one or more CQAs or the full range of variation has not been previously observed, then this would score "high" for those CQAs.

Although it is important to trend CPPs from a reporting perspective, they tend to be well controlled with tight acceptance criteria or batch alarms. This means that when modeling these against an output, they do not usually exhibit sufficient variability

Figure 2: Considerations of moving CPV from a compliance mindset to a performance mindset.

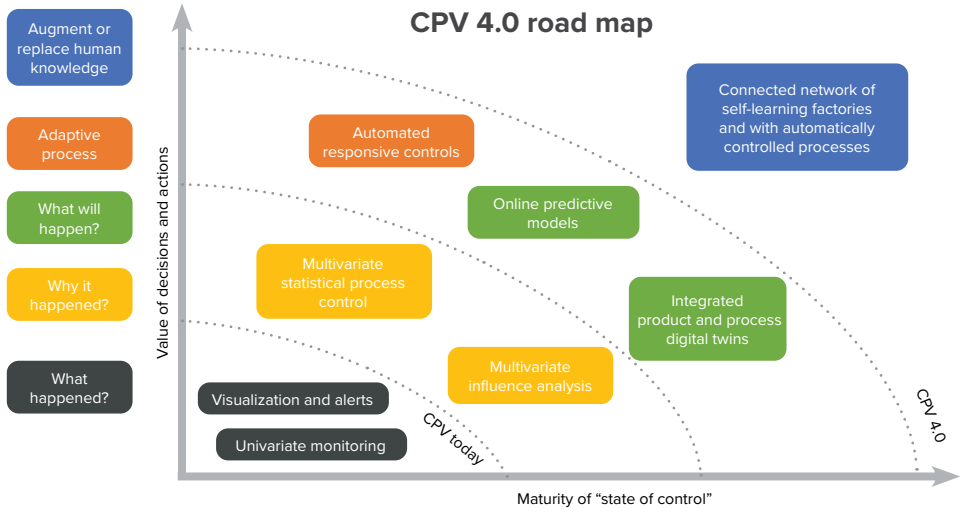


alone to be strong predictors of an output quality attribute. To truly benefit from multivariate techniques, we need to understand related noncritical parameters, intermediate quality attributes, and other process indicators (e.g., force, power consumption) to determine how difficult it is to control that input process parameter. For example, variations in process indicators can give a clue as to changes within the material being processed. These process indicators, in combination with process parameters and material attributes, can be useful in forming a better picture of what is driving the output variability. It is important that these process indicators are based on robust science from development to factor them into the risk assessment process.

ORGANIZATION SKILL AND CULTURAL CHALLENGES

One of the biggest challenges companies face in the digital transformation are skill and cultural challenges within the enterprise. CPV will lighten the workloads for data analysts, but this also means that they will have to increase their data visualization and data processing skills. A CPV road map must address the need for changing skills and perspectives of personnel (see Figure 2). A transformation process that focuses only on technology is headed to failure.

Figure 3: The CPV 4.0 road map with colors aligned to Gartner's Types of Analytics Capabilities (2017) terminology [9].



STEPS TO PHARMA 4.0™ VISION FOR CPV

For some, Pharma 4.0™ concepts can feel visionary and too future focused. We encourage starting small and anchoring the basis for the CPV data strategy in the risk to the product or patient. While remaining focused on the end vision, we recommend starting with a single product, with the aim to scale an enterprise system for process performance monitoring and control.

Using the road map in Figure 3, we describe some of the processes that need to be in place from pharmaceutical quality system (PQS), culture and skills (C&S), and information technology (IT) system and technology perspectives.

Automate Univariate CQA/CPP Reporting

Using this reporting has many benefits: Compliance with regulatory expectations, an increase in productivity, and the visibility and early detectability of product quality performance. Further, relevant data for reports are easily available for CPV practitioners because the documentation doesn't require further formatting or adaption. CQA dashboards with signal alerts automate the periodical refresh of this data. Automating the end-to-end process enables GxP reporting for CPV reports and annual product quality review (APQR). Prerequisites for this step include:

- Personnel are skilled in statistics and statistical process control concepts (C&S)
- A continuous quality improvement culture exists (C&S)
- The integrity of the captured data is assured (e.g., systems validated) (PQS)
- Continual improvement of process performance and product quality ICH Q10 (PQS)
- Automated data gathering and contextualization infrastructure is in place (e.g., data lake, historian) (IT)
- All relevant systems integrated provide information to the infrastructure (IT)

Build Models to Understand Multivariate Relationships

This step enables acquiring deeper process knowledge and achieving earlier detection of problems and potential causes. It will create data connections that support adding process parameters and materials attributes for the less-capable CQAs and building genealogies. It will allow offline multivariate models to understand contribution causes of observed variation and multivariate anomaly detection will complement the lagging signal alerting. Prerequisites for this step include:

- Personnel within the CPV team have advanced statistical skills (C&S)
- A data-driven culture exists in the enterprise (C&S)
- A multivariate (statistical) model life cycle management quality procedure is in place (PQS)
- Knowledge management throughout the life cycle ensures science- and risk-based justifications for model relationships (PQS)
- Integration of multivariate statistical software for contribution analysis and batch progression (IT)

Use Online Predictive Models

These models deliver more robust processes, which enhance productivity and reduce cost. Predictive models allow a move to multivariate monitoring to online/real-time analytics (continuous process verification, as briefly described previously). Prerequisite:

- Advanced analytics, simulation, and data science skills in individuals within the CPV team (C&S)

CONCLUSION

The survey discussed here reveals that manufacturing companies are improving their CPV processes by digitalizing their data-gathering processes and using human teams that have data analysis knowledge. The survey showed that most pharmaceutical manufacturing companies leverage these procedures to gain

knowledge and create more robust manufacturing processes. Moving to a fully automated CPV has many benefits, from reducing time to complete CPV to enhancing productivity. For example, automating the first univariate CQA/CPP reports will enhance compliance and online predictive models will enhance productivity and reduce costs.

However, a fully automated CPV is more than a project: it is a journey. Many steps must be completed before a fully automated CPV is up and running, and each step has its own challenges and benefits. To deploy systems capable of gathering data automatically requires an entire IT infrastructure; adaptive process based on automated controls require digital twins and advanced artificial intelligence algorithms; and building multivariate models that will provide a higher process understanding requires a data-driven culture. The road map to CPV shows that the path is not easy or quick, but once implemented, the benefits in productivity and efficiency go far beyond compliance.

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About the authors

Mark O'Connor recently transitioned to the role of Technical Lead and Production Start-up Manager for a new primary packing facility in AstraZeneca in the UK. He will lead the multidisciplinary team responsible for the validation and associated operations start-up activities for a state-of-the-art aseptic syringe assembly line through to stable commercial supply. Previously, Mark was the global lead for continued process verification and the lead author for the cross-functional quality standards in AZ. He managed the process maturity, led the associated data strategy, and chaired the global network for AZ's production facilities. Mark has an MSc in analytical chemistry and is a Six Sigma certified Black Belt. He has delivered presentations at ISPE conferences, co-chairs the PAT & Lifecycle Control Strategy CoP, and is a member of the process validation team. He has been an ISPE member since 2018.

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OPERATION WARP SPEED:
A View from the Inside

By Carlo de Notaristefani, Dr Ing

Operation Warp Speed coordinated US government support of the pharmaceutical industry's effort to develop and deliver vaccines and therapeutics across the United States to fight the COVID-19 pandemic. This article provides an inside look at the work done by this team to address the threat posed by COVID-19.

Starting in May 2020, teams from the US Department of Health and Human Services (HHS) and the US Department of Defense (DoD) acted as enablers, using the resources of the US government to accelerate development as well as creation and mobilization of the capacity to manufacture at scale. Between November and December 2020, two vaccines and two antibody treatments received Emergency Use Authorization (EUA) from the US Food and Drug Administration (FDA). Within hours after notification from the FDA, the distribution and administration of the vaccines began. By the end of Q1 2021, a third vaccine had received EUA, and over 200 million doses had already been delivered for administration, a timeline never before achieved in history.

Nothing unites humans like a common enemy, the saying goes. When the pandemic surged into global awareness at the beginning of 2020, it was not unexpected, yet the world was utterly unprepared for it.

Other viral threats had emerged in the past, and somehow faded away. Governments and nongovernmental organizations had reacted, made vows to never again be caught unprepared, and then failed to follow up with resources and plans to ensure it would not happen again.

Countries around the world reacted differently to the appearance of COVID-19. From outright denial and minimization to full deployment of the containment measures used over past centuries, lockdowns were rolled out in many places with dramatic consequences for the economy and the welfare of large swaths of the global population.

Much is being written on the implications of these measures, and some of the other financial measures implemented at the time. We had to resort to these instruments because we were reacting late; we had no proactive plan in place. But as we reacted, two things happened that made a significant difference in the course of this pandemic as compared to those that preceded it: the scientific community came together to fight this threat through science and innovation, and governments around the world mobilized to support it.

PANDEMIC BEGINNING

At the end of 2019, I had just retired from my position as Executive Vice President of Operations for a large global pharmaceutical manufacturer, with plans for easing into advisory or board roles and enjoying more time sailing and biking. However, the evolution of the pandemic made my retirement plans less viable.

My first contact with the US government project to fight the pandemic occurred one morning in April 2020, while I was biking empty roads in New Jersey, which was a rare situation I had not experienced since the great financial crisis of 2008.

I received two calls, the first from Bob Kadlec, Assistant Director at HHS for Preparedness and Response, and the second from Alex Azar, Secretary of HHS. They described how the US government had determined that the best way to fight the pandemic was to mobilize the public resources of the government and the scientific innovation and the entrepreneurial spirit of the industry in order to pull out all stops and accelerate the development of safe and effective vaccines and any other treatment we could develop.

They compared this effort to the Manhattan Project, which aimed to end World War II, and they asked about my availability to participate, advise, and coordinate all aspects of the project related to the manufacturing. This proposal was a dream come true: not only had I been given the opportunity to do something for the

industry and my country, which have both given me so much, but I also had a real shot at escaping the boredom of lockdown and retirement. Being in the fortunate position of having control of my time, I gave my full commitment and that's how my experience with Operation Warp Speed started.

OPERATION WARP SPEED

Over the following few weeks, the structure of this project was better defined and an overall leader was appointed. Moncef Slaoui, a former GSK R&D executive with significant vaccine development experience and a successful industry track record, was named Chief Scientific Advisor and overall program lead. The lead of all US government resources was General Gustave Perna, a four-star general who had been leading US Army Logistics, an enormous organization, and who had deep supply chain knowledge.

Slaoui and Perna built an incredible partnership throughout the time they worked together leading the operation, and shaped the culture and the team spirit that ultimately made everything possible. This was a culture of fact-based and data-driven decisions, empowerment with accountability, and personal commitment, starting from the leadership. Perna used to say that "as long as something is not illegal, immoral or unethical, we will find a way to make it happen." And he certainly did.

I credit this culture of teamwork, transparency, and accountability, together with a governance process aligned with best practices, as a key driver of the operation's success. Debates and disagreements were allowed, but at the end each decision was made based on data and owned by the team. Key decisions were escalated to a board chaired by the Secretary of HHS and the Secretary of Defense with participation from the White House, the National Institutes for Health (NIH), the FDA, the Centers for Disease Control and Prevention (CDC), the Assistant Secretary for Preparedness and Response (ASPR), and Operation Warp Speed leadership. This board met weekly to be updated on progress, endorse recommendations for critical decisions, and provide support with resources as needed.

A lot of work was happening behind the scenes, of course, to gain the political endorsement and the funding for the operation, and a special credit goes to Azar and his Deputy Chief of Staff Paul Mango for successfully bringing it forward and shielding the operation from external noise.

The name Operation Warp Speed (OWS) was selected, and on a sunny morning on 15 May 2020, we were in the Rose Garden at the White House for the official announcement. The mission of the operation was clear: deliver at least one safe and effective vaccine, manufactured at scale, and distributed to 64 jurisdictions before year-end 2020.

Not many people believed at that time that this could be possible, and to be perfectly honest, we did not have a clear path defined at that point. But we had fully committed to making it happen.

We were assigned some offices on the seventh floor of the HHS building in Washington, DC, and started to immediately work on the strategy, structure, and key "business processes" in industry terms or "battle rhythm" in army jargon. Most of the HHS building was empty because people were working remotely, but the OWS team was there in person every day, traveling to clinical and manufacturing sites as needed.

The mission was translated into a plan over the following few weeks, and the critical milestones identified, while the work to compress the timeline started. We needed an EUA for a vaccine in less than 12 months from the identification of the viral genetic sequence. This level of compressed timing had never been attempted in the history of vaccine development and it was obvious that we could not handle this in the usual way.

THE DEVELOPMENT

The global effort to develop a vaccine for COVID-19 started on 10 January 2020, when a Chinese virology team posted the genetic sequence of the virus on a global public health site. Several pharmaceutical companies immediately started designing a vaccine, using many of the available platform technologies, either proven or innovative. A few days later, two companies who had been developing a pioneering new technology, mRNA, had designed their first vaccine candidate: Moderna in the US and BioNTech in Germany.

This first step had to be followed by an enormous amount of work to confirm the safety and effectiveness of each vaccine, culminating in a successful phase 3 human clinical trial on over 30,000 patients. At the same time, companies had less than 11 months to build a supply chain able to deliver between 50 and 100 million doses per month of each successful vaccine, while all the infrastructure to administer that level of inoculations was simultaneously being prepared.

It was evident that no company could have possibly accomplished all of that, regardless of how brilliant their scientists or manufacturing executives. We were in the middle of a pandemic, and supply chains everywhere were heavily disrupted. Pharmaceutical companies were already challenged in trying to maintain existing supply of necessary life-saving drugs amidst shortages in materials and the impact of fear and lockdowns on their employees and operations. Hospitals were beginning to see the impact of the surge in COVID-19-related hospitalizations: how would clinical trials be managed in that environment?

What made the accelerated delivery time possible for the vaccines was the decision by OWS to focus on being an enabler of industry innovation and execution without trying to control all aspects of the execution itself.

In effect, the US government was underwriting the development and manufacturing risk for a number of vaccines and antibody treatments. Companies could start executing activities in parallel, because they no longer had to minimize those risks.

By agreeing in advance to purchase a very large number of doses of vaccine, before having evidence of safety and effectiveness, the US government removed the biggest financial risk for the industry, effectively pulling out all the stops that would typically slow down development and manufacturing. The same approach was taken with monoclonal antibody therapies.

This was extremely impactful, especially when combined with targeted support actions to remove key constraints and accelerate clinical development and supply chain setup and manufacturing.

The first key decision to make was how many vaccines to support, and which ones. There was no shortage of opinions, of course, mostly coalescing around two viewpoints: the first for maximizing the number of programs supported, in order to maximize the probability of success. The second was to focus on a limited number of platform technologies—and a limited number of programs by technology—in order to not lose focus and disperse the energy and attention of the operation. Ultimately, the second viewpoint prevailed, together with the recommendation to select three platform technologies (mRNA, viral vector, and protein sub-unit) and two programs per platform (Pfizer-BioNTech and Moderna, J&J and AstraZeneca, Sanofi and Novavax).

On the therapeutics side, the Regeneron and Eli Lilly antibody cocktails were initially selected, but screening for additional candidates to support (also in different therapeutic segments, such as small molecule antiviral) continued throughout the program. This ultimately led to identifying and supporting another antibody from AstraZeneca, as well as the Merck-Ridgeback and Pfizer antivirals.

The level of support required by these companies was different, of course, due to their varying size and resource availability. But the hurdles they were facing were comparable.

We set up a multifunctional team to work in close contact with each company as a single point of contact and channel for all communications. This allowed for timely and transparent communication, and included all key functional experts (clinical, development, regulatory, quality, and manufacturing).

The acceleration of the clinical program required the activation of a very large number of clinical centers, strategically selected to provide the necessary mix of patient age groups, ethnicity, and risk profiles to ensure that the safety and effectiveness profile could be appropriately assessed. Leveraging the NIH network was instrumental for that purpose. Ongoing monitoring of the enrollment allowed for course corrections when in some cases numerical enrollment for patient subgroups were behind schedule.

MANUFACTURING

From a manufacturing perspective, the hurdles were enormous. The board had requested that all vaccines be manufactured in the US, including both the antigen and the fill finish process, and that to the greatest extent possible, we use components and raw materials also manufactured in the US. While this was certainly a reasonable strategy to minimize risk in a pandemic setting, it had to face the reality that there was no readily available capacity at that scale for producing vaccines and antibodies in the US. After all, we did not know which vaccine or antibody would prove successful in the clinical trials, and so we wanted to set up enough capacity for each one to independently supply the entire US population. If more than one program was going to be successful, the world could have certainly used the excess doses.

We surveyed the industry contract development and manufacturing companies CDMOs and manufacturers to identify all available capacity that could be immediately available to us, or modified and retrofitted within the time frame we had available. It was amazing to see how many companies, large and small, responded to our requests and came forward with creative proposals on how they could support the operation. It was an outstanding demonstration of mobilization against a common enemy and commercial rivalries were set aside.

The operation worked with the US Department of Justice (DOJ) to enable the exchange of capacity information between manufacturers, with the purpose of assessing potential manufacturing collaborations for COVID-19 treatments. The DOJ issued an opinion on 23 July 2020, stating that such exchanges of information for the purpose of increasing supply of COVID-19 therapies would not harm but help consumers, opening the door for collaborations between Genentech and Regeneron, Amgen and Eli Lilly, and Merck and J&J.

However, there wasn't enough existing capacity for viral vector and protein sub-unit vaccine production in the US. We had to build it, and time wasn't on our side.

The Biomedical Advanced Research and Development Authority (BARDA) within the Office of the Assistant Secretary for Preparedness and Response in HHS had developed partnerships with two companies, and started construction of general-purpose capacity to manufacture biodefense countermeasures over the past several years. That capacity had never been finalized or started up, and had never received regulatory approval. The facilities existed, but we lacked most of the equipment and there was no organization to operate them.

We focused on the effort to retrofit, accelerate construction, and qualify those facilities while hiring and training the necessary personnel. These two facilities were assigned to viral vector and protein sub-unit programs, and additional facilities were onboarded to supplement capacity. In all, five plants in the US supported those four programs, with two of the five plants shared by two programs each. It was not an ideal situation, but it could work.

Initial assessments of these facilities pointed to the lack of experience in their staff as the major risk to execution, and not surprisingly, that was indeed the biggest challenge the program initially encountered from a manufacturing standpoint. To successfully manufacture any product, you need the process, the equipment, the materials, and a trained organization. The one thing we struggled with the most to accelerate was the selection, hiring, and training across the board in all of the facilities involved.

Both Moderna and Pfizer had already started building their own capacity for vaccine production, and luckily, the manufacturing capacity for these vaccines can be built faster than classical bioreactor capacity, so construction and qualification could be completed within the timeframe we had available.

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The general supply chain disruptions we all experienced during the pandemic did not spare the pharmaceutical supply chains. The industry was facing shortages of everything, which made keeping the regular drug supply very challenging. On top of that, we required equipment, capacity, and components to manufacture several billion doses of vaccines.

The US government had put agreements in place to support expansion of capacity in critical components early as part of the general pandemic response plan, and we took full advantage of that. Many times we deployed a provision in the Defense Production Act (DPA), which allows the government to request priority fulfillment of its orders to the government and its contractors. This provision was administered by the DoD personnel in OWS. Material procured under the DPA can only be used to fulfill government orders and must be used in the US.

This was a very powerful tool, and we were extremely careful in its use, monitoring not only the delivery to OWS contractors but also the impact that this prioritization was having within the broad pharmaceutical supply chain. We worked in close contact with the FDA Drug Shortage Staff within the Center for Drugs and Evaluation and Research (CDER) to find alternative sources for every situation that could have led to potential shortages, and I can honestly say we prevented many crises this way.

Fill-finish capacity was already in short supply and at a premium in the US before the pandemic, and we leveraged multiple companies to enlist enough capacity to support the OWS programs. Several companies had expansion plans in place, mostly started before the pandemic, and we helped them accelerate readiness of the new capacity.

That involved mobilizing the US Army Corps of Engineers to support construction, using the DPA to accelerate deliveries of equipment and construction efforts, dispatching US Army cargo planes for deliveries, and providing logistic support for shipments of equipment and components, at a time when cargo capacity was limited around the world. When we needed the support of foreign technicians for the qualification and startup of filling lines or other critical equipment, we worked with the Department of State to ensure the timely issuance of visas.

During Labor Day weekend 2020, a convoy of trucks carrying oversize HVAC units to one of the factories was stopped, and we were risking start-up delays of three days. We prevented that by organizing special permits with the Departments of Transportation of the four states being crossed by the convoy, along with state patrol escorts.

We monitored all the activities, providing support as needed when risks to the execution schedule were identified, coordinating with the DoD and other government agencies.

Early in the program, we made a decision to install a "person in the plant" in each critical node of our supply chain where the antigen was manufactured and the fill finish was happening. This proved to be very valuable, not only for providing real-time insights on progress and issues, but also to improve trust and communication.

> The scientific community came together to fight this threat through science and innovation, and governments around the world mobilized to support it.

These individuals were majors from the DoD and expert supply chain professionals. We briefly trained them on the uniqueness of vaccine manufacturing, and they were dispatched at a moment's notice for a nine-month assignment. These individuals all deserve a lot of credit for their selfless service and for having helped reduce the impact of the many issues that normally occur during a startup.

Ultimately, 14 plants (many with more than one filling line) supported the fill-finish activities for the six vaccines and two antibodies, and a few more plants were involved in ancillary activities.

DISTRIBUTION AND ADMINISTRATION

Distribution of the vaccines was flawlessly organized by the DoD logistics team with OWS. The criteria to allocate and distribute the vaccine were decided by the board. Distribution had to be fair and equitable and was based on the population of each of the 64 states and jurisdictions we needed to supply. We partnered with McKesson, UPS, and FedEx to establish distribution centers and a next-day air delivery system to ensure chain of custody as well as cold-chain integrity. Each jurisdiction administration point could order vaccines for next-day delivery on the mainland US and 48- to 72-hour delivery for the other jurisdictions.

A logistics "war room" and control tower were set up on the second floor of the HHS building, and a system to collect data on inventory and immunization from all states and jurisdictions was developed in record time. This system was called Tiberius, and it allowed visibility and a single source of information for all logistics operations. As Perna used to say, it allowed us to "see ourselves." After having personally seen implementions of IT systems in large corporations for many years, I have to say that this system greatly exceeded my expectations, both in terms of capabilities and time to deployment.

The team also had to provide each vaccine administration center with all the ancillary materials needed for a successful vaccination campaign. This included syringes—which were

different for different vaccines gloves—sanitizing pads, CDC vaccine cards and other items, in quantities to match the number of doses shipped. For every vaccine supply chain, there was a matching supply chain to provide the kits customized for that specific vaccine.

From a logistics perspective, the most critical vaccine was the Pfizer product, which had to be stored in dry ice at -80° C. Each shipper contained a GPS monitor that allowed tracking in real time, and a resupply process for dry ice. Nothing was left to chance.

Beyond providing resources and support for development and manufacturing, the government ensured an unprecedented level of access and flexibility from regulators. The Center for Biologics Evaluation and Research, the FDA division responsible for vaccine review, allowed companies to execute rolling submissions and the review to proceed in parallel with the submission. This flexibility, however, did not extend to any requirement for the quality and safety of the vaccines: At no point in time did I see any compromise on those critical aspects.

In addition to the clinical package with the phase 3 data including the safety follow-up, the submission package needed to include data from the validation lots. And, assuming success, we also wanted to be in a position to have inventory available and start the immunization campaign as soon as the FDA completed their review and issued the EUA.

That put manufacturing squarely on the critical path: During fall 2020, we were completing equipment qualifications, going into engineering runs, followed back-to-back by validation, and then stockpiling. The schedule did not allow for much inventory buildup in preparation for approval, and it was a startup, after all, with all the risks interconnected. In every plant, people were working extended shifts and weekends in order to meet deadlines, with tremendous personal commitment despite the risks.

By the end of 2020, we had about 30 million doses already shipped or ready to ship, with many more at different stages in the manufacturing process, and we had clear visibility to an acceleration in supply to support an acceleration in vaccine administration, which was already close to about 1 million doses per day with a target to get to 3 million doses per day very quickly. Manufacturing activities continued uninterrupted throughout the holidays. Many people at the sites told me they had not taken a day off in many months, and they did not plan to take any until there was assurance of ample availability of doses. That is real commitment!

Of course, as in every startup, not everything was smooth sailing. We were always running hand to mouth with materials, and any issue with the quality of a component would have had an immediate impact on the manufacturing schedule. The Army logistics team was tracking all shipments in real time, and at times we had to invite some CEOs to phone conferences with Perna when we saw a risk to a delivery date. Some equipment failed, and we had to rush replacements, and so did some of the materials. But when you look at the sheer size of the manufacturing operation, these were really small issues that had no material impact on our ability to deliver.

CONCLUSION

Was everything really successful, and what did we learn from it? These are the questions I am most often asked and I have pondered quite a bit.

If you look strictly at the mission OWS took on, it was certainly successfully accomplished, with two safe and effective vaccines approved before the end of the year, and a third one by the end of Q1 2021. Of the six vaccines, five have obtained approval in the US or Europe, and they have been administered in several countries. The sixth has recently announced positive clinical results, and it will soon be submitted for approval. That is a remarkable achievement for our industry and for science, and it is already making a difference in the world.

How should we rate our manufacturing performance? I keep asking myself what we could have done differently to ensure even better outcomes in volumes and timing. I've concluded that beyond having manufacturing capacity available and ready to use when the pandemic started, I cannot think of anything else that could have made a difference in this situation.

I also wish we had taken a more forceful approach to the one site that failed to deliver, which caused delays to two programs. But even then, this would not have changed the situation for the first two months of supply.

What have I learned from this experience? The short answer is: a lot! First, I have been reminded once more that leadership truly matters. Thanks to the impactful leadership of Slaoui, Perna, and many others in the companies and organizations we worked with, along with those at HHS and DoD, thousands of people selflessly dedicated themselves to fighting the pandemic, setting aside personal priorities, and focusing 100% on this mission.

I have also learned firsthand that the industry alone, and the government alone, could not have achieved what we did. You need both, with the best that each can bring to the table, to make it happen.

And finally, I have learned how critical it is to prepare for the next pandemic. Because there will be another one. We don't know when and where it will emerge, but it will. That, we can all count on.

About the author

Carlo de Notaristefani, Dr Ing, is an international operations senior executive with global technical, operational, and P&L experience. He has deep expertise in designing and operating global supply chains in complex regulatory environments, leading accretive M&A activity, and devising and executing value-creating strategies in global markets. He serves on the board of several pharma and CMO companies, and advises companies and investors. In May 2020, Carlo joined Operation Warp Speed/Federal Covid Response, the US government initiative to support acceleration of development and supply of COVID-19 vaccines and therapeutics, as the lead advisor for Manufacturing and Supply Chain. He has collaborated with the sponsors, suppliers, and CDMOs to ensure the fast scale up of manufacturing and distribution for the US. In Carlo's most recent corporate position, he was Executive VP of Operations at Teva Pharmaceuticals, Inc. Carlo retired from this position at the beginning of 2020. Before joining Teva in 2012, Carlo was the President, Technical Operations and Global Support Functions for Bristol Myers Squibb between 2004 and 2011.

PANDEMIC PROGRESS:

Industry's Journey From 2020 to Today

By Wendy Haines

In 2020, the world was grappling with how to slow the spread of the SARS-CoV-2 virus and appropriately treat people who had the COVID-19 infection without approved therapies or vaccines. In two years, there are multiple vaccines and treatments along with great knowledge about the virus—and about how the industry mobilized, partnered, and achieved tremendous strides in addressing the global pandemic.

Healthcare professionals were able to share information in real time about what courses of treatments seemed to work, the signs and symptoms people were experiencing, and what underlying health conditions contributed to a more severe COVID-19 infection. Similarly, the drug industry, through unique collaborations with competitors, worked in concert to supply the global market with vaccines and therapies. Unprecedented speed to market was achieved with drug companies working closely with health authorities to provide status of trial results and partnering with logistics companies to deliver vaccines, which required shipment at an extremely low temperature. Government entities worked together to create a priority for administration of vaccines, mask mandates, and social distancing to curb the spread of COVID-19.

ATTACKING THE VIRUS

An enormous amount of literature and research has been conducted on coronaviruses because they cause the common cold in addition to the outbreaks of Severe Acute Respiratory Syndrome (SARS) and Middle Eastern Respiratory Syndrome (MERS), the other two novel coronavirus infections [1–3]. The viral envelope of coronaviruses is composed of four major viral structural protein components: spike (S) protein, membrane (M) protein, nucleocapsid (N), and the envelope (E) protein [4]. The M protein provides the virion envelope shape and is the most abundant constituent of coronaviruses; the main function of the N protein is to bind the viral RNA; and the E protein is a minor constituent of virions and is an integral membrane protein [4].

The majority of the drug companies designed vaccines and therapies that targeted the S protein of the SARS-CoV-2 virus. The S protein is a type 1 trans-membrane glycoprotein that is expressed on the surface of coronaviruses (CoV) and is responsible for receptor binding and virion entry into the cells [5]. Minor differences in CoV S protein structure and function correlates with striking changes in CoV tropism (ability to infect different cell types) and virulence [5, 6]. Additionally, CoV S protein binds to its host receptor, angiotensin-converting enzyme 2 (ACE2), and fuses the host and viral membrane [7].

To understand if detection methods, treatments, and vaccine efficiency were effective as new variants of SARS-CoV2 emerge, the US Department of Health and Human Services (HHS) created the SARS-CoV2 Interagency Group (SIG) composed of multiple federal agencies, including divisions of the National Institute of Health (NIH),the Centers for Disease Control and Prevention (CDC), and the Food and Drug Administration (FDA) [8]. The SIG developed a variant classification to monitor variants in the US and to raise awareness regarding evidence of increased transmissibility, if detection methods are not as effective, and if current countermeasures (i.e., vaccines and therapies) are not as effective [10]. The World Health Organization (WHO) maintains a global dashboard to show confirmed COVID-19 cases, deaths, public health and social measures (PHSM); technical guidance, vaccines, treatments, and tests; and research and response [9]. Health authorities' websites around the world have information about the COVID-19 pandemic, such as the European Medicines Agency (EMA), Health Canada, and the Brazilian Health Regulatory Agency (ANVISA), to access information such as approved countermeasures.

Table 1: WHO COVID-19 variant labels.

Source: CDC, December 2021

WHO Label	Variant of Concern (VOC)	Variant of Interest (VOI)	Variants Being Monitored (VBM)
Alpha	Dec 29, 2020		Sept 21, 2021
Beta	Dec 29, 2020		Sept 21, 2021
Gamma	Dec 29, 2020		Sept 21, 2021
Delta & Omicron	VOC		
Epsilon	Mar 19, 2021	Feb 26, 2021	Sept 21, 2021
Eta		Feb 26, 2021	Sept 21, 2021
Iota		Feb 26, 2021	Sept 21, 2021
Kappa		May 7, 2021	Sept 21, 2021
N/A (B.1.617.3)		May 7, 2021	Sept 21, 2021
Zeta		Feb 26, 2021	Sept 21, 2021
Mu			Sept 21, 2021

At the time of this writing, there are currently only SARS-CoV2 variants being monitored (VBM), variants of interests (VOI), and variants of concern (VOC), but there are no variants of high concern (VOHC) (see Table 1). A VOHC designation means that prevention measures or medical countermeasures have clear evidence of significantly reduced effectiveness relative to the circulating variants of SARS-CoV2 [10]. Specifically, the use of rapid virus genomic sequencing data with phenotypic data allows evaluation of the effectiveness of COVID-19 tests, treatments, and vaccines approved or authorized for use in the US against the emerging variants [11]. The CDC provides weekly estimates of proportions of circulating variants to permit timely public health action via Nowcast [11].

At first, health care providers treated COVID-19 patients based on their symptoms prior to having approved therapies and vaccines. In order to ensure COVID-19 therapies and vaccines were available to the world population in a timely manner, health authorities used conditional approval, such as the FDA's Emergency Use Authorization (EUA), which grants the FDA the authority to protect public health against "chemical, biological, radiological, and nuclear (CBRN) threats including infectious diseases, by facilitating the availability and use of medical countermeasures (MCMs) needed during public health emergencies" [12].

THE FIRST VACCINES

The mRNA (messenger ribonucleic acid) vaccines received conditional approval and then gained full approval by the FDA. mRNA are single-stranded molecules that instruct human bodies to make proteins. mRNA vaccines contain three main types of ingredients: mRNA, lipids, and salts and sugars [13]. The mRNA used in both the Comirnaty (BNT162b2) vaccine manufactured by Pfizer, Inc. and BioNtech and the Spikevax (mRNA-1273) vaccine manufactured by ModernaTX, Inc., is a modified nucleoside mRNA encoding the S protein of SARS-CoV-2. This instructs the body to assemble a harmless piece of protein from the virus that causes COVID-19 [13]. The protein that is produced activates the immune system to recognize COVID-19 infection in the future. In general, the lipids (fat) work in concert to enable mRNA entry into cells and the salts and sugars help ensure vaccine stability while the vaccine is manufactured, frozen, shipped, and stored until administered [13].

THE NEXT VACCINES

Viral-vector-based vaccines, such as the Janssen Pharmaceuticals Companies of Johnson & Johnson COVID-19 vaccine (JNJ-78436735), are composed of viral vector, and sugars, salts, acid, and acid stabilizers [13]. A recombinant, replication-incompetent Ad26 (adenovirus) vector that encodes a stabilized variant of the SARS-CoV-2 S protein instructs the body to build a harmless piece of protein from the virus that causes COVID-19 [13]. Similar to the mRNA vaccines, the sugars, salts, acid, and acid stabilizers in viral-vector-based vaccines help ensure vaccine stability while the vaccine is manufactured, shipped, and stored until administered [13].

As of 23 February 2022, Sanofi and GSK are seeking regulatory approval, including with both the FDA and the EMA, of their protein-based COVID-19 vaccine [14]. The Sanofi and GSK COVID-19 vaccine is composed of 10 µg antigen formulation of SARS-CoV-2 adjuvanted recombinant protein-based vaccine + GSK's AS03 [14]. As with the mRNA and viral-vector-based COVID-19 vaccines, the protein-based COVID-19 vaccines tell the body to produce an immune response against SARS-CoV-2 S protein and fight a COVID-19 infection [15].

MISUNDERSTANDINGS ABOUT VACCINES

There has been confusion and misunderstanding around how vaccines function, specifically, why the COVID-19 vaccines do not prevent infection in vaccinated people. Essentially, vaccines

provide the body with a "memory" to recognize a virus that the body has been vaccinated against to mount an immune response to fight the virus in the future. None of the approved mRNA or viral-vector-based COVID-19 vaccines claim to have 100% effectiveness in preventing COVID-19 infection. However, COVID-19 vaccinations have been shown to reduce the severity of infection.

Another point of misunderstanding and misinformation revolved around the adverse events or side effects after a COVID-19 vaccine. The most common adverse events from vaccines, not just COVID-19 vaccines, are injection site reactions: pain, redness, and swelling. Because the purpose of a vaccination is to elicit an immune response to a viral infection, one may experience side effects such as fever, chills, and aches as the body is building immunity against SARS-CoV-2. These adverse events are not long-lasting and will subside. As with any medicinal product, a very small percentage of people can have an anaphylactic, or an allergic, reaction, but this is rare. Additional, very rare events after COVID-19 vaccinations include thrombosis with thrombocytopenia myocarditis and pericarditis, and Guillain-Barré syndrome [16].

ALTERNATE THERAPIES

With the start of the global pandemic, health care providers were treating COVID-19 infected patients based on their symptoms. Early in the pandemic, there was news discussing the use of convalescent plasma. Convalescent plasma is obtained from donors who have recovered from COVID-19, and the plasma may contain antibodies to SARS-COV-2 that could suppress the virus and elicit an inflammatory response. In February 2021, the FDA revised the EUA for convalescent plasma to limit authorization to only high-titer COVID-19 convalescent plasma and only to treat hospitalized patients with COVID-19 early in disease course or in patients hospitalized with impaired humoral immunity [17]. High-titer and low-titer plasma refer to the number of antibodies present in a person's plasma against COVID-19. Convalescent plasma, also known as serum therapy, goes back about 130 years and has been used as a first course of treatment when there is an epidemic or pandemic, according to Dr. Josh Sharfstein, Vice Dean for Public Health Practice and Community Engagement at Johns Hopkins [18].

Front-line workers and health care professionals sought other types of therapies to help patients with COVID-19 at the start of the pandemic. Immunomodulators were investigated to see if these types of products would be effective against COVID-19 infections and the list of immunomodulators that the COVID-19 Treatment Guidelines Panel recommends is a noticeably short list compared to the list of immunomodulators not recommended for the treatment of COVID-19 [19]. Anti-viral medications, such as HIV protease inhibitors, hydroxychloroquine, and chloroquine and/or azithromycin, were evaluated, but the COVID-19 Treatment Guidelines Panel recommends against the use of these to treat COVID-19 [20]. Ivermectin is an FDA-approved antiparasitic product used to treat several tropical diseases, such as scabies, onchocerciasis, and helminthiases, but is not approved to treat viral infections [21]. There are mixed results pertaining to the use of ivermectin and COVID-19 treatment: some reports showing no benefits or worsening of disease after ivermectin use and others showing greater reduction in inflammatory markers, shorter time to viral clearance, or lower mortality rates in patients who received ivermectin than in patients who received similar drugs or placebo [21]. The COVID-19 Treatment Guidelines Panel stated there was insufficient data to recommend for or against use of ivermectin for COVID-19 infection [20].

Remdesivir is an FDA-approved COVID-19 nucleotide prodrug that is administered intravenously in a hospital or health care setting and its mechanism of action is to bind to viral RNA-dependent RNA polymerase and inhibit viral replication through premature termination of RNA transcription [20].

Monoclonal antibody (mAb) treatments against SARS-CoV-2 have received EUA from the FDA, such as ritonavir-boosted nirmatrelvir (Paxlovid) and molnupiravir [20]. The COVID-19 Treatment Guidelines Panel's recommendation in order of preference for treating non-hospitalized patients with COVID-19 follows: ritonavir-boosted nirmatrelvir (Paxlovid), sotrovimab, remdesivir, and molnupiravir. Hospitalized patients with COVID-19 infections are recommended to receive remdesivir with or without immunomodulators based on the patients' conditions [20].

CONCLUSION

We all hope that the world continues to collaborate with universities, institutes, and competitor companies to deliver life-saving medicines to the global population. With the pandemic, we have all seen the importance of educating the world on drug products, how they work, and potential side effects so that people can make health-based decisions with information that is easily understood regardless of education background or the field one works in. Our goal in the pharmaceutical industry is to be in the business of improving people's quality of life.

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About the author

Wendy Haines is the Director of Toxicology and Laboratory Services at PharmEng Technology, and has over 25 years of toxicology experience. She has BS degrees in pharmaceutical sciences and biology from Campbell University, a PhD in toxicology from the University of North Carolina, Chapel Hill, and is a board-certified toxicologist (DABT). She impacted human health laws at the Environmental Protection Agency (EPA) in 1997, worked on the Genome Project between the EPA and the National Institutes of Health, and later conducted her PhD at the EPA performing directed research for the Office of Pesticides. She was a study director and oversaw preclinical trials at a contract laboratory, and was a consulting research toxicologist for the National Toxicology Program. Wendy has performed toxicological safety evaluations of almost 300 different drug products. She is Past President of ISPE CaSA, Past Chair of the International YP Committee, and is a member of the *Pharmaceutical Engineering* Committee (PEC). Wendy has been an ISPE member since 1996.

A Diverse Workforce Enables Businesses to Succeed

By Joydeep Ganguly


Joydeep Ganguly

The lack of diversity in the pharmaceutical engineering industry is widely recognized. Less well understood is why change is so hard to achieve. From my years of work in this space, and through observation of ongoing efforts to embrace diversity in all forms, I have developed a hypothesis: Progress is stifled because we as a society wrongly believe diversity and inclusion efforts are nice-to-have peripheral strategies to an organization's mission. Ultimately, we need to recognize that diversity is a business must-have, a driver of our bottom line, and a key element that will allow us to adapt to our industry's changing demands.

A diverse workforce, when coupled with an inclusive culture that reshapes the traditional power structures within an organization, produces strong business results and we've seen this firsthand at Gilead Sciences. The more widely this tenet is understood, the quicker our workforces will reflect society, and the better equipped our businesses will be to meet the challenges of tomorrow.

NEW BUSINESS TRENDS ARE REDEFINING JOBS

The pandemic has accelerated trends that are reshaping pharmaceutical engineering. Companies and organizations must incorporate new skillsets and perspectives to meet these changing needs.

For example, leadership was once based solely on technical prowess. Now, leaders must have superb social intelligence, and apply adaptive, interdisciplinary thinking and a design mindset to achieve business success. Technical depth remains a requirement but is no longer a primary qualification for the job. In addition, partnership models that were solely transactional in nature now depend on trust between parties, requiring an entirely new set of skills to allow for improved connection and collaboration.

These new business trends travel across the workforce, too: Digital fluency is now a requirement for almost all workers; environmental sustainability is a factor in decisions touching nearly all areas of an organization; and the implementation of smart infrastructure means entire workforces must be upskilled to maintain and manage the new, digitally enabled and connected infrastructure.

How can businesses adapt to these new demands? Though challenging to implement, the answer is simple: by employing a diverse workforce.

THE STRENGTH OF A DIVERSE WORKFORCE

Numerous studies have demonstrated that diverse companies are more productive, competitive, and innovative than their less diverse counterparts [1]. In part, they perform at a higher level due to the collaboration between people from different backgrounds, which opens up new ways of thinking and working.

Different lived experiences can help frame a better and wider range of scientific questions, which then lead to stronger innovation and better decision-making. And, of course, equitable and just environments enable people to do their best work.

At Gilead, we see this every day. Our inclusion and diversity initiatives are ambitious and strive to touch every aspect of Gilead's operations, with the goal of embedding these as values into everyone's daily work.

This comprehensive approach has led to transformative change in our organization: More than 50% of my leadership team are women, which has led to richer perspectives as we look to solve tough problems, and eventually has led to better business outcomes. In addition, more than 7,200 of our roughly 13,500 employees belong to at least one of six employee resource groups (ERGs): Gilead Leadership Organization of Black Employees (GLOBE); The Pride Alliance; Women at Gilead; Gileados: Latinos at Gilead Sciences; Gilead Veterans Engagement Team (GVET); and Gilead Asian Interest Network (GAIN). These ERGs support recruiting, professional development, culture building, business impact, and community cultivation.

Other programs create change by focusing on diversifying the workforce. Our multi-year Advancing Black Leadership Strategy sets representation goals, creates internal and external talent pipelines, and builds the capabilities of people managers. The complementary program Blueprint for Change invests in long-term partnerships with historically Black colleges and universities and Hispanic-serving institutions to increase our Black and Latino workforce by forging long-lasting relationships and opening pathways for hiring.

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PARTNERING WITH ISPE FOUNDATION INTERNSHIP PROGRAM

To amplify these efforts, I was fortunate to partner with the ISPE Foundation to create the ISPE Foundation Diversity Internship Program, with Gilead serving as the program's inaugural partner in 2020.

This five-year partnership is off to a fantastic start. Together we are identifying undergraduate or graduate students from underrepresented populations and connecting them with opportunities in the pharmaceutical and biotechnology industries.

Gilead hosts two summer interns called fellows who complete a 12-week program that includes a capstone project in the form of an article, whitepaper, or presentation. I'm pleased to share that Gilead's first fellow is now a full-time employee, an indication of the program's early success.

The ISPE Foundation fellows supplement Gilead's existing internship program, producing the largest 2021 summer intern cohort for the Corporate Operations organization. All interns were women and came to Gilead from different universities with varying STEM specialties. They were entrusted to work on impactful projects, supporting our engineering, sustainability and environment, and health and safety programs. This partnership is an impactful, new benefit to Gilead as a whole and my team specifically and is a testament to the value of our longstanding relationship with ISPE. And as the industry continues to evolve in reaction to new business trends and changes in the workforce, I believe that ISPE, and the relationships and discussions it generates, will continue to play a central role.

DIVERSITY BENEFITS TO BUSINESS OPERATIONS

As ISPE and other groups make strides toward a more diverse industry, I'm proud to be in a position to confirm that a diverse workforce has a tangible impact on our business.

Thanks to our workforce, we are positioned to pivot as times change, embracing new ways of working and keeping pace with the evolution of our industry. Our multi-background teams are creative, asking new questions and developing innovative solutions. And importantly, at Gilead we couldn't fulfill our vision of creating a healthier world for all people without knowledge of the needs of communities of all types, in all places.

By creating an environment that places equal value on the contributions, ideas, and perspectives of each employee, we empower each other to achieve great things at Gilead. Diversity gives us a leg up to recruit top talent, who will choose to work at a company with a thriving, inclusive culture.

So far, our continued investments in inclusion and diversity have led to external recognition that captures the attention of our investors and potential employees. These accolades include Best Employer for Diversity by Forbes; a five-star company rating by the Hispanic Association on Corporate Responsibility; a perfect 100 score for policies and practices related to LGBTQ+ employees from the Human Rights Campaign Corporate Equality Index; and a top 25 ranking on the 2020 Working Mother 100 Best Companies list.

We're proud of our achievements and hope that our efforts to increase inclusion and diversity in our workforce are adopted more broadly across the industry.

CONTINUING THE MOMENTUM

Much progress has been made, but of course, there is still much to be done. Black, Indigenous, and Brown people; women; and LGBTQ+ people continue to be underrepresented in STEM fields. The pharmaceutical engineering industry has an opportunity to lead change by creating more opportunities for these groups. To protect the health of our industry, we must continue increasing representation and investing in talent from diverse backgrounds.

There are passionate and brilliant engineers and future engineers that our industry needs. We must seek them out if we truly want to drive change and pioneer solutions that will better global health. Together, we will all be more successful in creating a healthier world.

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Joydeep Ganguly is Senior Vice President, Corporate Operations, at Gilead Sciences. He is accountable for several strategic functions, including corporate engineering, corporate real estate, capital planning, sustainability, risk management, and global procurement. Prior to Gilead, Joydeep spent 10 years at Biogen in roles of increasing responsibility in technical operations. A thought leader in the operations space, Joydeep has published and presented extensively about operations strategy, bioprocess optimization, and digital transformation. He was recognized by the National Diversity Council as a top 50 Diverse Leader in California, and was awarded the annual Leadership excellence award by the California Diversity Council. Joydeep serves on the Board of Directors for the Bay Area Council, Gilead Foundation, Science from Scientists, and NC State University's Supply Chain Research Consortium. Joydeep earned an MS in electrical engineering from the University of Notre Dame, an MBA from NC State University, and is completing a master's degree in healthcare management at Cornell University. He has been an ISPE member since 2016.

ISPE BRIEFS

New ISPE Guides Explore ATMPs and Update Guidance on CTCs

Released in November 2021, the *ISPE Guide: Advanced Therapy Medicinal Products (ATMPs)–Autologous Cell Therapy* focuses on manufacturing facility development and design for autologous cell therapies for parenteral use. This guide provides an overview of the critical aspects of ATMP facility design as well as the key relationship between current process/facility attribute alignment and how that changes in the ATMP space.

ISPE BRIEFS

"The growing number of autologous products that are entering the pipeline is evidence of the growth potential of this therapeutic approach. The science has promised this for years; it is now delivering on the promise, and it gives new promise and hope to patients that have rare conditions or diseases. It is a game changer," said Guide Lead Jeff Odum, CPIP, Practice Leader, ATMPs and Biologics, Genesis AEC. "The product-process relationship for ATMPs is very different from the traditional cell culture-based approach that most people are familiar with. And because the ATMP space has its roots in the academic/hospital environment in a much smaller scale, the application of GMPs to the overall manufacturing operations is a different challenge."

While the guide focuses on autologous cell therapies, it provides content that may be applicable to other types of ATMPs. Written by a team of experts in the ATMP field, this is the only guide of its kind in the industry about the development and design of ATMP manufacturing facilities.

Published in December 2021, the Second Edition of the *ISPE Good Practice Guide: Controlled Temperature Chamber–Commissioning and Qualification, Mapping and Monitoring* provides guidance on the life cycle management of GMP-controlled temperature chambers from creating a user requirements document to decommissioning a unit. Originally published in 2016, the guide has been revised to align with current industry practice, particularly with respect to the *ISPE Baseline® Guide: Commissioning and Qualification (Second Edition)*, and presents a cost-effective way of demonstrating and maintaining compliance.

"Whether you are new to the business of storing samples, a university looking for answers for small scale storage, or have been doing this for years and are going through the process of benchmarking to assure alignment with the industry, this guide provides the information and 'real world' examples of successful practices being used today, right now, to safely store samples and to meet compliance objectives with many regulatory agencies," said Guide Co-Lead Dean Rainbolt, Technical Applications Manager/Controlled Temperature Technologies Division, Thermo Fisher Scientific. "This guide will help you save time and money by not having to reinvent the wheel and provides you with a strong starting point to building most any sample storage operation."

The controlled temperature chambers discussed in this guide range from purchased commercial off-the-shelf items, such as freezers and refrigerated delivery vehicles, to walk-in cold rooms and walk-in freezers, to custom-built units such as warehouses. The risk-based approaches covered include commissioning, temperature mapping, and periodic review, along with examples and sample templates.

For more information about all ISPE Guidance Documents, visit ISPE.org/publications/guidance-documents

—Marcy Sanford, ISPE Publications Coordinator

Meet the ISPE STAFF

BILL MOJICA

In each issue of *Pharmaceutical Engineering®*, we introduce a member of the ISPE staff who provides ISPE members with key information and services. Meet Bill Mojica, Director of Development & Foundation Operations, ISPE Foundation.

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

Identify, cultivate, and steward individual donors and corporations to support the ISPE Foundation. Build awareness of our mission and initiatives. Being new to the industry, I am challenged to increase my knowledge base on all things pharma.

What do you love about your job?

I love meeting new people. Fundraising is based on relationship building. Therefore, I have the unique opportunity to meet folks from around the world who are dedicated to saving lives. I am blessed to work with an incredibly talented and passionate team at ISPE.

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

I've been a high school football coach for over 30 years. It is an honor to mentor young men and teach the game I've loved my entire life. I also play drums in various bands around Baltimore, Maryland, and my wife and I love to travel!

MOVING FROM CLEANROOM to Isolation Technology for ATMPs

By Marco Fadda, MS Eng

Advanced therapy medicinal products (ATMPs) pose specific manufacturing challenges beyond those typically addressed by pharmaceutical chemistry. Often in current ATMP applications, a change in approach is introduced at some point in the development process out of convenience or necessity, which then results in a change in technology. This article analyzes the possibility of transferring a cell and gene therapy (C&GT) process from the cleanroom approach to an environment based on isolation technology or, in other words, of moving the process from an open space manipulation to a closed and segregated space concept.

The development of C&GT applications raises several questions about the options available for production environments. Although many C&GT processes originated from cleanroom technology, it is reasonable to assume that the time has come to use more efficient production methods.

The aim is to improve quality assurance and efficiency in production of C&GT products, thus generating an impetus to contain costs while improving application possibilities and availability for eventual users. Isolation technology represents an improvement in this field and has proved effective in many other pharmaceutical chemistry applications. Transitioning a C&GT process from a staffed cleanroom—with operators in sterile scrubs working in Grade B environments under biosafety cabinets (BSCs)—to a closed and segregated environment—with operators working from the outside—has challenged operators and process engineers to find the best method to reproduce an established and validated process. In this article, we summarize the main differences between the two approaches, discuss the main problems that emerged, and provide several possible solutions for a smooth and faultless process transition.

ATMP APPLICATIONS

Often in current ATMP applications, at some point in the development process, a change in approach is introduced for reasons of convenience or necessity, which then results in a change in technology. Many of the current in-development processes at the preclinical stage started in an academic environment, dealing with open processes in BSC, with highly operator-centric manufacturing. When the progresses manifest the need of a transition to early clinical production, we need to look at upgrading to a more robust, technology-based, closed platform [1].

In the past, the open cleanroom approach was dominant and prevalent, but the production of ATMPs requires different technologies, isolation technology in particular. It has been encouraged and recommended by authorities [1] because it offers better quality assurance in production (in particular, stability of the environmental conditions, lower levels of contamination, and availability of environmental data) and because it reduces costs [3–5].

In this case study, we analyzed the possibility of transferring a C&GT process from the cleanroom approach to an environment based on isolation technology. In moving the process from an open space manipulation to a closed and segregated space concept, it became clear that it is not possible to simply replicate the whole process. Instead, the task required, depending on the different situations, adaptation of the procedures and tools.

We will analyze this process change here, offering the reader the considerations we encountered and the solutions adopted. In some cases, these solutions consist of having a replacement procedure. In other cases, we needed to develop new technologies to facilitate adapting the open-environment procedure into one with comparable performance in the segregated approach.

As extensively reported in several publications [1, 6, 8, 10], ATMPs pose specific manufacturing challenges, going beyond those typically addressed by pharmaceutical chemistry. While out of scope of this article, these differences include working with living cells, which means dealing with contamination along with many other factors, which we file under "cell characterization."

Finally, we must ensure that the preparation we deliver to patients has the right potency, e.g., when correctly administered, it has the intended result. Because we are dealing with living cells, this can be affected by different factors, including manufacturing, delivery, and transportation. Given the relatively short life of these products, C&GTs require tight coordination between physicians and manufacturers, as products are often manufactured for individual patients, and changes in timing can impact physicians' treatment decisions [6–8].

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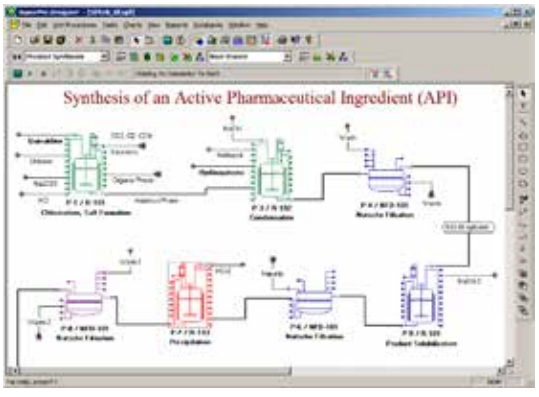

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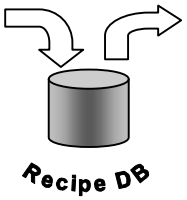

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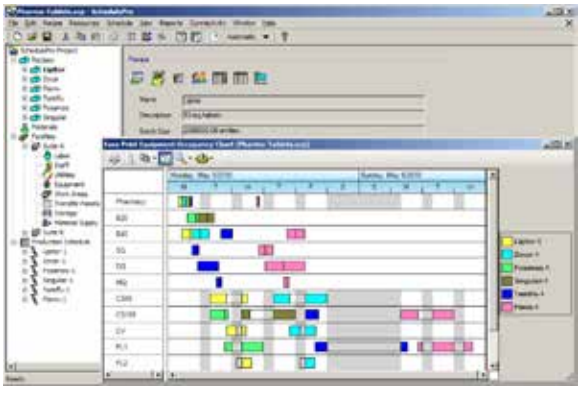

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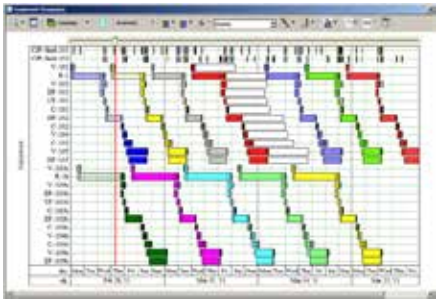

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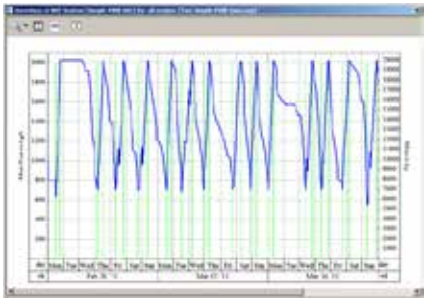

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We know from experience that the development process of C&GT products is often not complete in the initial phases of the project and is subject to several improvements, modifications, and integrations while in process. Therefore we need to also adapt our manufacturing processes to the results obtained during the development itself.

The 5- to 10-year future of the product should also be considered. When production starts, capacity consists of a handful of patients per year. But if the therapy is successful, production capacity must be increased to meet demand.

According to Walters-Nelson, "The biggest issue we tend to see as you start to get into commercial manufacture relates to the increase in patient population" [1].

This increase leads to a demand to either scale up, if the process is autologous, or scale out, if the process is allogeneic. Other concerns include how to ensure scalability of your process is not introducing a linear increase of the workforce, or of the footprint of the facility. As noted by Walters-Nelson, "If you're going to a 1,000, 2,000 or 5,000 patients per year facility and you are looking at linear expansion, you don't want to have to grow your facility five-, six-, ten-fold to accommodate demand. You must think about how to do manufacturing in a more efficient manner" [1].

PROJECT BACKGROUND

Most considerations reported here are part of work completed assisting a customer with an existing laboratory working in a Grade B environment who wanted to extend the operations but move to an approach based on isolators and a Grade C cleanroom. According to regulations [1, 11], isolators can run in Grade D cleanrooms, but the customer already had a Grade C cleanroom available, so there was no need to perform additional work to downgrade the classification.

The company is a private organization working with umbilical cord blood collection and is classified as a cord blood bank. It follows FACT standards [9] and is one of a limited number of companies to have this accreditation. Being in Switzerland, it is authorized for medical practice under Swissmedic, the Swiss National Certification Agency. The authorization also covers mesenchymal stromal cells (MSC) manufacturing.

TECHNICAL CHALLENGES AND CHOICES

In this case study, we relate the transition from the open environment to a closed environment. In the open environment, after several steps of clothing changes with increasing cleanliness, sterile-gowned operators come to a Grade B environment, in an open space, and directly handle products under BSC. In the closed environment, isolators are placed in a Grade C/D background, and operators never come in direct contact with products, which are kept inside the closed Grade A segregated environment and manipulated with the use of suitable glove ports.

The regulatory framework is well known; all national regulatory bodies have issued recommendations on the manufacturing of ATMPs [11, 12]. In Europe, the reference documents are EudraLex–Volume 4–Good Manufacturing Practice (GMP) Guidelines [11] together with EU regulations concerning Pharmaceutical Aseptic Manufacturing [1], which Swissmedic is adopting in Switzerland.

The customer in our case study wanted to change their approach to reduce risk of contamination and cross contamination, achieve flexibility and procedural simplification (e.g., easier access, no more sterile gowning, simplified validation, fast and reliable cleaning), and save money on operational expenses [4, 5]. With moving to a closed technology, several operations and construction details had to be adapted or newly introduced to match the different requirements of this new approach.

Finally, the customer had expectations for final product quality and plant throughput with respect to the space occupied (sometimes referred as batches per year per sqm of surface occupied), with the possibility that operations could be expanded or modified in the future. Further, the product cost had to be kept as low as possible to facilitate patient access and to support process commercialization [10].

ANALYSIS

To analyze the impact of the proposed technology on the production process, we focus our attention on aspects concerned with the following:

- Gloves
- Material management
- Sampling, product delivery, and waste management
- Innovation
- Automation

Gloves

Gloves are a critical point to consider when switching between an open environment and closed environment. Isolator gloves are often cumbersome: they are thicker than cleanroom gloves currently used, users claim to experience a loss of sensitivity, users worry isolator gloves could slow activities, etc. The thickness of isolator gloves is necessary because they must be able to withstand regular hydrogen peroxide decontamination runs: they must be resistant to the biocide agent and thick enough to retain their resistance to punctures and tears through successive decontaminations. Typical isolator gloves thicknesses are 0.4 mm and 0.6 mm. In our experience in the pharmaceutical industry, we find that chlorosulfonated polyethylene (CSM) gloves with 0.4 mm thickness achieve the best compromise between sufficient flexibility and dexterity and resistance to vapor phase hydrogen peroxide (VPHP) decontamination.

Our experience verifies the claim that there is reduced sensitivity when using the isolator gloves; however, this tends to diminish and then disappear as operators are trained with their use. A typical training session involves the repetitive use of commonly used devices in successive sessions and involving all operations. Initial training sessions can be simulated without the products, freeing operators from responsibility and letting them concentrate on achieving the right dexterity.

Figure 1: Effect of training on speed of user manipulation with CSM vs. surgical gloves.

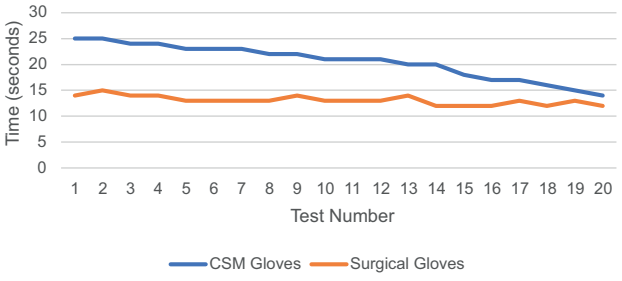


Table 1: Materials used in ATMP processes.

Material	Packing	Physical Condition
Pipettes and pipette tips	Plastic wrapping	Dry
Flasks	Plastic wrapping	Dry
Bottles of cell culture media	Unwrapped	Dry/room temperature
Tubes	Wrapped	Dry
Cryovials (empty)	Plastic wrapping	Dry
Cryovials (filled)	Unwrapped	Wet/frozen
Microscope slides	Packed	Dry
IV Bag	Unpacked	Room temperature or 4°C

To overcome the inevitable differences between the sterile surgical-type glove used in grade B cleanrooms and the 0.4-mm-thick isolator glove, we set up a mock training session with the following operations:

- Picking up and unscrewing the cap of a 2 ml cryovial (Corning product number 430659)
- Pipetting the content
- Screwing on the cap of the cryovial
- Unscrewing the cap of a prefilled Falcon 50 (REF 352098)
- Diluting the pipetted content in the Falcon 50
- Screwing on the cap of the Falcon 50

Average results from the training activities are shown in Figure 1.

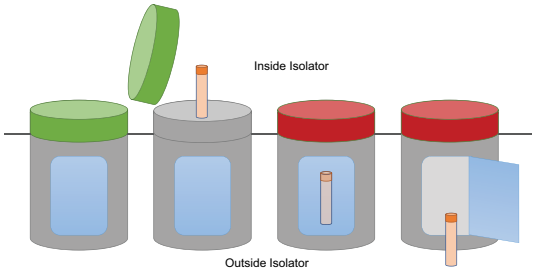
From this, we verify that although there may be some difficulties using the CSM gloves in the beginning, after a set training time, operations run in comparable time and users obtain a comparable dexterity. We have estimated this training time in the operating setup as one week, including repeated simulation of the single operations as well as full process runs.

Material Management

Different materials are needed to carry out ATMP processes. Table 1 shows a sample, not exhaustive, list. These materials can be classified according to their nature and the physical condition they arrive in. As shown in the table, materials may be wrapped (and sometimes double wrapped), unwrapped, at room temperature, frozen, etc.

Materials are introduced to a Grade A cleanroom through a succession of material airlocks and a series of decontamination passages using air flushes and suitable disinfectant agents. Typical decontamination while working in isolators is to use an airlock with a decontamination cycle based on hydrogen peroxide vapors. Materials are introduced in the airlock through the front door and the cycle starts. When finished, the interlock between the main chamber and the airlock is released, and the materials can be passed into the processing chamber. A typical decontamination run can take 25 to 45 minutes, depending on the internal load of the chamber. Hydrogen peroxide cycles follow predetermined recipes, set during performance qualification of the equipment.

Figure 2: Working principle of small transfer hatches.



Due to the different nature of the materials and the different conditions under which the materials are presented, in an isolator environment, an appropriate differentiated strategy may need to be used for material introduction, combining hydrogen peroxide decontamination and safe manual cleaning. In the first step, in a laminar airflow pre-chamber equipped with gloves, laminar flow is used to clean the material and the operator performs a suitable spraying with a sporicidal in the first run. In a second step, the operator passes the material to the airlock (center), waits for reestablishment of Grade A–level cleanliness (with a laminar airflow speed of 0.45m/s, we have in that pre-chamber a safe recovery time of a couple of minutes, as checked with particle counter during validation), and then the material is passed to the processing chamber. All these operations have been validated by the validation team, during system acceptance, including correct pressure cascades (main chamber > pre-chamber > laminar airflow).

Whether working in a cleanroom or in an isolator, a clear supply plan for consumables and ancillary materials is mandatory. When working in a cleanroom, the space allows keeping significant stock, so you can pick up items requested by the process. A typical way to solve this issue in an isolator environment is to provide a storage area where basic working stock is located. This will

help avoid too many replenishments during the course of the process, which mitigates any risk of external contamination.

Sampling, Product Delivery, and Waste

A common activity when running an ATMP process involves collecting samples for in-process controls. Depending on the nature of the final product, a similar activity also has to be run at the end of the procedure for product delivery. Given the different nature of the products that could be developed as ATMPs, blood bags, vials, or other standard or customized containers for tissues all deserve a different approach for packaging and product exit. In the cleanroom, the typical way of realizing the output of finished products is to reverse the process of product input, but the isolator's compact working area provides the possibility to separate them and maintain a unidirectional flow of materials and process.

Sampling

Sampling is an essential operation to in process controls (IPC). It is very similar to product exit, except that sample aliquots are small quantities often contained in vials or in specific instruments cartridges aseptically filled inside the isolator.

Many options are available to accomplish the operations mentioned previously. One option is to use a series of small, single-use transfer hatches. The hatches face the Grade A environment before being used. Once filled with sample, they are locked by a sealing gasket (a red light indicates the hatch cannot be opened). A second opening—interlocked with the first one—faces the Grade D/C environment outside the isolator. From there, the sample is picked up for further processing (see Figure 2).

Another option consists of using pass-through boxes (also called "mouse holes") for easy product exit. The final option is to use continuous liners and a form of rapid transfer ports (RTPs), which can be connected and disconnected due to their sterile connection mechanism. On the isolator side (i.e., in the Grade A environment), it appears as a traditional RTP. The beta container is replaced by a sterile polyethylene long tube, folded into itself several times. The object to extract is placed on the bottom of the tube, as shown in Figure 3 (1, 2). Then the tube is elongated from outside, as shown in Figure 3 (3), and welded or crimped to seal it with respect to the internal environment. The bottom part is then cut away together with the sample/product to be taken out, as shown in Figure 3 (4).

Waste management

Waste management differs a lot between the two approaches and deserves special attention. Waste management has strict rules that must be respected, and it tends to occupy a lot of the available space, drastically reducing the capability of having free working space available. Moreover, it is a potential source of particles, which impacts what may otherwise be a safe and clean environment, increasing the intrinsic risk of failures.

The types of waste can be different: it can be liquid waste used with culture media and plasticware. Typically, you produce a lot of plasticware during a C&GT process; some is clean and some is potentially contaminated, e.g., used flasks, tubes, pipettes.

In cleanrooms, there are different bins available to stow the materials while the batch is in process. In isolators, specific solutions have been implemented to keep waste under control. A dedicated collection chamber, is connected to the main chamber by a passage, and it behaves as an exit chamber, with all the interlocking and decontamination capabilities.

Once filled, it can be emptied and further used, providing hydrogen peroxide features. One of the best waste solutions is the continuous liner already discussed for samples. For liquid waste, there typically are vacuum pumps and a sealed bin in the technical area, which can be sent to directly disposal, or specific bottles to collect the whole batch liquid waste to be disposed at the end of the process.

Figure 3: Sterile continuous liner schematic working principle.

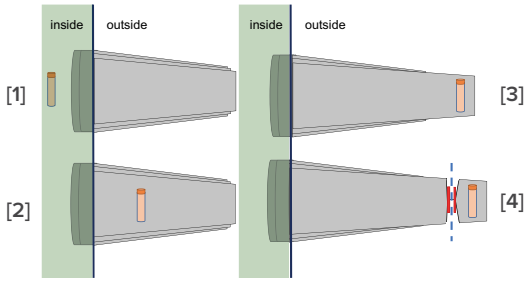
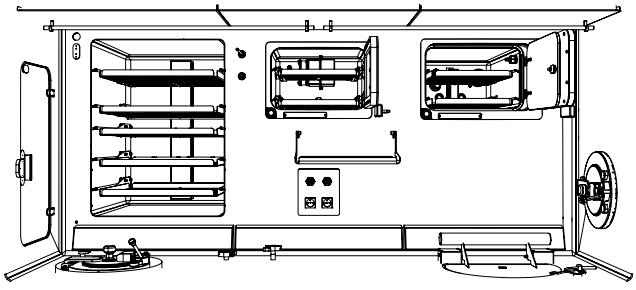


Figure 4: A typical configuration of an isolator for C&GT.



Innovation

The isolator approach forces innovation and suggests improvements in space management and in device integration. Isolators force an efficient use of the available Grade A space, so movable trays have been introduced, to allow alternative use of the workbench, as well as an intensive use of the back and the lateral walls (which is not allowed in a BSC). These are all fundamental steps in gaining space, as shown in Figure 4.

Different devices used for cell processing can be integrated, even commercial devices such as a commercial centrifuge. This type of device integration keeps operators out of the Grade A working space and eliminates useless parts in the device itself

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Figure 5: Integrated device (centrifuge).

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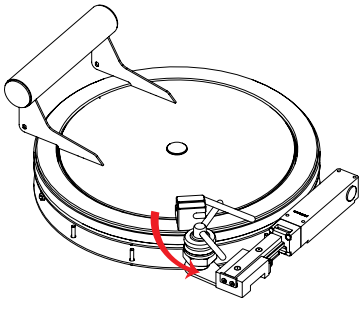

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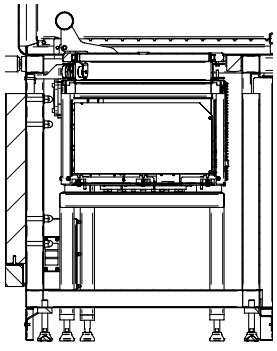

5d

(e.g., the engine and the electronics of the centrifuge). This is a fundamental step for space management, for heat management, and to avoid having moving parts inside the Grade A working space wherever possible.

In Figure 5 (a, b, c, and d), the integrated device (a centrifuge) is the sole bucket, with rotor facing the Grade A environment. The original lid has been removed and adapted. The centrifuge body, engine, and electronics are under the workbench, and the devise is coupled with a shock absorber rubber band (white) and an inflatable gasket to seal the lid while in operation.

Automation

An additional benefit in the use of isolators is the possibilities coming from the integration of different kinds of automation. Isolators are native-software-controlled machines that offer the addition of different levels of interactions: at the lower level, there are sensors and monitoring systems; at the same level, there are other isolators and related equipment; and at a higher level, there are operator interfaces (e.g., standard operating procedures [SOP] monitors and company enterprise resource planners [ERP]).

As an example, we worked with the architecture of the controlling system of a plant with three isolators, internal incubators, refrigerators, freezers, and centrifuges; a set of 144 external mobile incubators (and corresponding automatic transport system); and 20 VPHP generators.

Dedicated communication between resources has been foreseen to allow local data exchange and coordination of activities, so the VPHP generators talk with isolators, the isolators talk together and with incubators, the automatic transport system (FMS – Flex Management Software) talks with incubators and isolators. By accessing the common communication bus, the different components of the system talk with high-level software interfaces and databases, like SOP monitors and company ERP.

DISCUSSION

Isolation has proven to be an efficient and reliable technology in many fields of the pharmaceutical business, and its use is now widely accepted. Its application in C&GT is still limited, compared to traditional pharmaceutical environments, but the situation is changing and more C&GT applications are added daily to the number of those working according to isolation technology [14].

We have reviewed the basics of integrating a C&GT process born in cleanroom under isolation technology, and we have demonstrated the possibility of successful carrying out the process, together with the necessary steps, tools, and adaptations the isolators need to have for managing complex processes in a similar way to C&GT [13].

An increased use of isolation technology in C&GT is introducing additional challenges, both in terms of new manufacturing technologies to be integrated, and in terms of different ancillary operations to be managed and performed. At present, the main manual activities have been "moved" from an open approach to the closed approach under isolators, and we discussed the difficulties encountered but also the positive outcomes of the analysis performed on the single tasks and the solutions adopted for a smooth and flawless transition. We believe that the next step will be the integration of C&GT in dedicated production processes under isolation technology, where the positive benefits of the same (improved assurance of

quality, reduced footprint, increased sustainability) can be integrated with the benefits of automation.

This discussion shows that complex processes can be operated in an isolator under Class A conditions with resultant improvements in quality assurance and the potential for reducing operating costs. Not discussed yet is that isolators have the potential to be more portable than cleanrooms, which are very challenging to make portable. This presents a completely new opportunity, as today C&GT manufacturing is mainly centralized in a relative few number of plants. This is a great advantage for isolators allowing manufacture of C&GT products to be carried out closer to clinic sites and making speed of manufacture faster.

CONCLUSION

Although historically many C&GT projects have been initiated in cleanrooms, isolation technology is now mature enough to allow its use in C&GT applications. In fact, several processes can now be successfully transferred under it. These two approaches are different, and many aspects need to be evaluated. For example, there are no fixed rules, except those coming from regulatory bodies, and no lasting and constant situations because they can change from time to time or from product to product.

The proper application of an in-depth process, pharmaceutical engineering knowledge, and robust regulation can lead to the solution and reinforce the potential superiority of the closed environment approach. The implementation is not simple, but many issues, as described here, have already been addressed and there is a validated solution available.

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Marco Fadda, MS Eng, is with COMECER SPA, Italy. He began his professional life as a researcher, part of a team dedicated to investigating the quality of bone cutting using robotic held tools, and the corresponding surgical planning and execution processes. Subsequently he moved to a series of companies dedicated to medical robotics, performing development, training customers or staff, and supporting robot-assisted orthopedic procedures. He served as an executive for several brands of the medical device industry, with particular focus in understanding medical needs and transforming them into augmentations to support medical procedures and tools. Since 2014, he is dedicated to the development of aseptic solutions for managing cellular products. The primary focus is applying the principles of isolation technology to this branch of the medical field, aiming at performing research and production of ATMPs under GMP conditions, while continuing to work toward a simplification of the production processes to achieve a wider acceptance of these products.

ACCELERATING BIOPHARMACEUTICAL VIRTUAL FATS IN A PANDEMIC

By Ajay Babu Pazhayattil, Kishorkumar Kotini, Mythri Kodidela, and Mike Scribner

Heightened awareness, due to the pandemic, of the need for domestic manufacturing capacity has rejuvenated the biopharmaceutical manufacturing industry and resulted in new commissioning projects. However, cross-country/continental travel restrictions and social distancing–based work protocols during the first two years of the pandemic necessitated adopting unique commissioning approaches. Developing standardized factory acceptance test (FAT) execution approaches fit for the current times can allow for consistency across equipment vendors and their biopharmaceutical clients. This article describes pragmatic best practices that would support the momentum for new domestic manufacturing facilities.

Assessment of the emerging R&D trend from 2018 to 2021 (see Figure 1) indicates a growing tendency to develop new parenteral delivery formulations and a dipping pipeline for oral dosage delivery forms [1].

The biopharmaceutical research and development (R&D) sector continues to grow year over year. US firms are the primary investors in biopharmaceutical R&D, with global share of more than 46% [1]. The US is also the world's largest biopharmaceutical market, generating more than 33% of global revenue. Despite a strong R&D sector in the US, outsourcing of formulation development and commercial manufacturing has become an industry norm. This allows innovators to focus on discovering and developing value stream R&D pipelines. But with this competition, it has become standard for commercial development and manufacturing organizations to look for opportunities to lower costs.

One measure devised by innovators and service providers is moving commercial manufacturing activities to countries that offer lower wages and lower indirect costs [2]. Identifying this trend as a national security risk, the US Food and Drug Administration introduced a number of effective regulatory policy initiatives to accelerate reshoring and increasing domestic manufacturing capacity [3]. The increasing pipeline of parenteral dosage forms, combined with domestic R&D investments and the supply security concerns, provides new renovation and expansion opportunities for domestic vendors to capture biopharmaceutical clients. Awareness of the expectations and availability of the desired tools can enhance virtual FAT execution readiness, in turn meeting the critical biopharmaceutical capital project timelines.

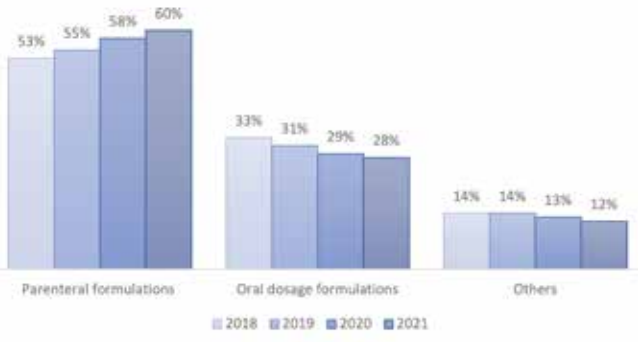
A REGULATORY PERSPECTIVE

In April 2021, the FDA published guidance on remote interactive assessment of manufacturing facilities [4], which was implemented without prior public consultation due to the pandemic. The guidance highlights the regulator's flexibility in adopting special mechanisms during unusual circumstances. The guidance identifies three phases for a remote interactive evaluation: planning, conducting, and concluding.

Planning

The planning phase considers the type of assessment, the facility risk, and the site's ability to share live video, documents, and computer screens. The phase identifies the FDA's and the site's points of contact and collects background information to effectively coordinate remote assessment.

Figure 1: Emerging R&D pipeline.



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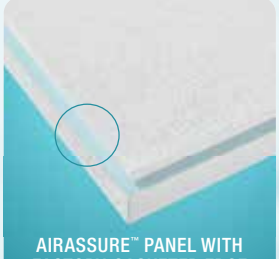

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Conducting

While conducting the interactive assessment, the regulator may request documents, electronic systems visibility, and the use of live-streamed or prerecorded video to examine the facility or data. The regulator may schedule interviews, evaluate corrective actions, and provide online updates. The regulator expects that the remote connection (such as internet connectivity, image quality, cameras) used is continuous, except for temporary issues that can be resolved in a timely fashion.

Capable technologies are expected to be employed for remote viewing and evaluation of critical operations such as aseptic practices, equipment cleaning, setup, material weighing, dispensing, instrumentation, sampling, and testing. The FDA identified three IT platforms—Microsoft Teams, Zoom, and Adobe Connect—for remote assessments. Some of the reviewed documents may be requested in advance.

The expectation is that the information is provided in electronic format or that access is provided for remote screen sharing so that the documents can be efficiently assessed during a live session. Secure protocols to send documents are provided by the regulator. Where a paper format document is requested, the expectation is to send it to the requestor as a scanned and searchable PDF file.

Concluding

The concluding phase culminates in a closeout meeting with observations (where applicable) where the regulator may determine the need for follow-up surveillance activities. The regulator, as a representative of the agency, can use the remote assessment outcome for regulatory decision-making.

FAT CHALLENGES

As in the case of regulators, biopharmaceutical manufacturers commissioning new facilities face a similar logistical challenge with equipment vendors. Conducting on-site FATs at vendor locations is not always feasible during a pandemic. Design and functional features—such as size, utilities, controls, cleaning, contamination, integrity (data and system), safety, operations, capability, components, quality, installation, drawings, integration, and claims—need to be verified early enough to ensure that the unit meets the organization's business and GMP needs.

In addition to ensuring they follow CFR section 211.42, the GMPs further mandate verification and adequacy of equipment construction (CFR 211.65); equipment cleaning and maintenance (CFR 211.67); automatic, mechanical, and electronic equipment (CFR 211.68); and filters (CFR 211.72). FAT is, therefore, a critical step in the commissioning phase because it provides documented evidence that a piece of equipment or system has been adequately tested at the equipment manufacturer's facility and performs to the biopharmaceutical manufacturer's expectations prior to its delivery.

The interactions during FAT can identify vendor GMP deficiencies so that early measures can be put in place. Typically, the biopharmaceutical company's technical teams are present at vendor sites for the hands-on FAT assessment phase of commissioning: a difficult proposition during a pandemic. The emergence of virtual cross-functional teams—consisting of project managers, project engineers, consultants, contractors, subject matter experts, and vendors—with members across different time zones further complicates the on-site execution of FAT, a critical commissioning stage. Therefore, developing a systematic remote assessment approach modeled in line with the FDA guidance approach described above is ideal.

> With the appropriate tools and controls, the goals of FAT can be effectively met despite being virtual in nature.

FAT testing and documentation provide early insight into whether the vendor can meet the biopharmaceutical client's contractual points and system requirements. The FAT allows for making timely corrections, helps avoid returns, and minimizes component upgrades on final installation. Successful completion of FAT is a precondition to shipment. Involvement with the vendor allows for the biopharmaceutical client's technical team to understand specifics of the critical system operation, potential challenges, safety hazards, and details such as disassembly/reassembly. A FAT also allows for seamless site acceptance testing (SAT): The initial FAT testing outcome often drives the downstream SAT requirements. FAT test cases, where justified, can also be adopted for qualification.

A FAT has prerequisites such as an in-place vendor quality plan, user requirement specification (URS), functional specifications, and design specifications. As part of the FAT, vendor documentation is verified; this can include, but is not limited to, operation and maintenance manuals, a component list with catalog cut sheets, diagrams, certifications, materials of construction, and inspection records.

The activities part of a FAT can be broadly categorized into review of prerequisites for FAT, verification of supporting documents and inspection records to meet FAT protocol requirements, functional test checks, documentation of corrective measures for identified deficiency findings , and closure and shipment [5, 6].

MODEL FOR A VIRTUAL FAT

Based on practical application, a sterilizer example table (see Table 1) was developed to identify best practices in accomplishing each of

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the FAT needs through virtual execution. A similar approach can be applied for other systems such as that of complex filling lines and packaging systems. The closure timeline for each FAT phase (planning, conducting, and concluding), document control, and data integrity/governance requirements can be developed as part of the commissioning strategy. The preliminary plan can be agreed upon with the vendor prior to issuing a firm purchase order.

The methods of substantiation during a virtual FAT execution need to be predetermined, in addition to having a preapproved FAT protocol. Where necessary and applicable, the following need to be

Table 1: Execution of virtual FAT example.

FAT Requirements/Tasks	Completed During (Phase)	Remote Execution/Interactive Tools	Evidence
Review prerequisites			
Vendor approval	Planning	Compile internally and procure from vendor using a secured shared folder. Verify prior to start of FAT and document the verification. Examples of commercially available cloud-based secure 21 CFR Part 1–compliant shared storage solutions: Egnyte, Box, MS Teams.	Electronic PDF document
Purchase agreement			
Commissioning plan			
URS			
Functional specifications			
Hardware design specifications			
Software design specifications			
Installation and operating manuals			
Software manual			
Maintenance manual			
Component data sheets			
Component manufacturer information			
FAT protocol			
FAT execution plan			
Participants list			
Verify supporting documents and inspection records meet FAT protocol requirements			
P&ID and general arrangement drawings	Conducting	Vendor to provide the documents in a secured shared folder to review as part of FAT execution.	Electronic PDF document
Electrical schematics			
Pressure vessel dossier			
Welding inspection records (welding quality procedures, weld logs, welder certification, visual/boroscopic/ radiographic inspection photos or videos)			
Material of construction certification and roughness reports			
Test instrument qualification and calibration certificates			
Safety valve certificates			
Declarations			
Controller configuration specification			
Critical instrument calibration certificates			
Roughness reports			
Welding endoscopic check report			
Passivation certificate			
FAT test methods			
Hydraulic pressure test reports			
Slope check reports			
Software qualification package			
Compliance certificates			

FAT Requirements/Tasks	Completed During (Phase)	Remote Execution/Interactive Tools	Evidence
Perform prefunctional test checks			
Check test instrument calibration and qualification status	Conducting	Vendor to submit the completed documentation in the secured shared folder. Verify prior to start of FAT test cases and document the verification.	PDF of calibration and qualification records
Verify operator safety elements		Vendor to submit to secured shared folder the time/date stamped video recordings. Verify prior to start of FAT test cases and document the verification.	Live video streaming and recording
Document FAT installation conditions		Vendor to submit the completed documentation to the secured shared folder along with time/date stamped video recordings. Verify prior to start of FAT test cases and document the verification. Example of a commercially available live video streaming and recording application: MS Teams.	Live video streaming and recording PDF of the executed protocol
Verify access to filter, sample valves, gauges, and perimeter			
Verify all piping components are correctly fitted and labeled			
Check piping insulations			
Check utility loops, connections, and readings			
Perform dimensional and surface checks: chamber, doors, and panels			
Verify instrumentation displays, e.g., manometer			
Check nameplates/U stamps			
Check components			
Verify system dimensions			
Check doors and panels			
Confirm electrical options			
Check electrical cabinets with markings and inspection certificate			
Check that wiring diagram and as-built matches			
Confirm hydraulic options			
Confirm accessories options			
Confirm cabinet options			
Verify rails, load, and height			
Check internal and external trolley specs			
Check P&ID, general arrangement, and electrical schematic diagram vs. as-built			
Perform FAT functional tests			
Check internal and external trolley braking system	Conducting	Vendor to submit the completed documentation to the secured shared folder along with time/date stamped video recordings.	Live video streaming and recording PDF of the executed test
Verify loading and unloading			
Check chamber vacuum leak rate test			
Conduct safety systems challenges: emergency buttons, level sensors, start, interlock, opening/closing		Vendor to submit the completed documentation to the secured shared folder along with time/date stamped video and screen recordings. Examples of commercially available remote access and recording solution: MS Teams and Zoom.	Live control system screen sharing to verify parameters and recording Client and vendor have access to control system for performing challenge/test Live video streaming and recording PDF of the executed test
Cycle functional tests to verify cycles reflect the setup parameters and no alarms are activated: vacuum leak rate test, pressure leak rate test, F0/time-based sterilization cycles, chamber air brake filter sterilization cycles			
Perform software test cases			
Confirm empty chamber temperature mapping and loaded chamber temperature mapping (terminal sterilizer)			

Table Continues

Continued

Table 1: Execution of virtual FAT example.

FAT Requirements/Tasks	Completed During (Phase)	Remote Execution/Interactive Tools	Evidence
Address identified deficiencies, findings, and corrective measures			
Revisit test failures needing redesign and retesting	Concluding	Vendor to submit the completed documentation to the secured shared folder.	PDF documents
Perform tests that could not be executed at FAT location			
Make modifications to meet URS requirements			
Add sensors and monitoring devices			
Complete other minor punch list items before shipment			
Fix documentation errors			Revised approved PDF documents
Identify new design, develop internal quality test, and reperform FAT	Planning > Conducting > Concluding	Not applicable	New FAT
Finalize retest requirements after corrective actions	Conducting > Concluding	Vendor to submit the completed documentation to the secured shared folder along with time/date stamped video and screen recordings (as required).	Approved retest PDF documents
Confirm closure and shipment details			
Conduct closure session	Concluding	Client and vendor to record the event and store in a secured folder.	Live video streaming and recording
Verify closure of punch list item		Vendor to submit the completed documentation to the secured shared folder.	Electronic PDF document
Confirm final shipment packaging configuration			
Verify shipping mode/conditions/storage impact			
Verify adequacy of packaging components			
Approve FAT and shipment		Vendor to share the approved document through the secured shared folder. Example of a commercially available 21 CFR Part 11 compliant document management software: MasterControl	Electronic PDF document

Notes: 1. Once reviewed, the final approved documents and evidences are available in the biopharmaceutical client's qualified document management system. 2. Records, videos, screen recordings, and interviews documented/shared should be attributable, legible, contemporaneous, original, and accurate (ALCOA) and adhere to industry standards for data integrity.

Figure 2: Example of online smoke test video used as supporting evidence.

specified for each FAT task: a combination of live video, recordings, control system screen sharing, and remote access to verify setup parameters; real-time remote monitoring of operating parameters; and contemporaneous documentation. The biopharmaceutical client's team is responsible for the data integrity/governance of the collected evidences. Figures 2–3 provide examples of supporting evidence used when successfully executing FAT in a remote setting.

EMERGING TECHNOLOGIES

Deploying new virtual technologies can enhance remote FATs. Digital twin is a technology that can simulate testing of multiple variants while reducing any material waste. Digital twin technology can permit virtual commissioning [7], has been helpful in exposing defects early, and has enhanced engineering efficiency by almost 30% [8]. Although some augmented reality and virtual reality hardware are still evolving for use in cleanrooms, they can be effectively used in unclassified areas such as an equipment vendor's FAT test floors. The technology can be used to provide

Figure 3: Example of spray coverage image and clean in place (CIP) execution image used as supporting evidence.

assisted remote training to a biopharmaceutical client's technical teams to familiarize them with equipment components, teach them troubleshooting techniques, and demonstrate equipment operation prior to taking part in FAT execution. Pharma 4.0™ machine learning and artificial intelligence sensors are being integrated into equipment so that process optimization and monitoring can be achieved once in use. And the same sensors and process modeling software can play a key role while remotely assessing equipment drift during FAT trials.

CONCLUSION

The approaches discussed in this article can be applied to downstream commissioning steps such as SAT and qualification. One of the goals of FAT is to ensure that the equipment is evaluated at the vendor site prior to shipment and delivery. Completion of the predefined test cases corroborates compliance with URS/functional specifications. Although virtual solutions exists for both document assessments (such as certificates and P&ID) and functional tests, organizations may consider FAT for complex systems. Higher levels of interaction with vendor subject matter experts and the opportunity to have early hands-on training during an on-site visit can be invaluable. Therefore, it is important that during the virtual execution, the vendor provides access to their key technical personnel, gives sufficient opportunity to discuss details, and clarifies features.

A well-conducted virtual FAT eliminates traveling during a pandemic while saving on the associated expenses (capital expenditures, or CAPEX). With the appropriate tools and controls, the goals of FAT can be effectively met despite being virtual in nature. The several FAT executions that we conducted using the model discussed here have further established that a well-planned application of virtual tools and data governance policies can be comparable to an in-person execution. The FAT report becomes the basis of determining the on-site SAT protocol requirements on receipt and the extent of the SAT/qualification test executions.

The checks and verifications performed during FAT can be used to support qualification activities, and they do not need to be repeated, provided there is risk-based justification that the functionality will not be affected by any subsequent activities prior to acceptance and release [5]. The additional practices discussed can prove advantageous for biopharmaceutical organizations as they immediately convert the otherwise tacit equipment knowledge into codified explicit knowledge for downstream use. A key goal while developing a virtual FAT program should be to preserve conformity with internal procedures, industry standards, and regulatory guidelines.

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MATHEMATICAL MODELS
in Experimental Design and Scale-Up

By Johannes Möller, Dr Ing, and Ralf Pörtner, Dr Ing

The implementation of a mammalian cell-based biopharmaceutical manufacturing process demands robust methods for knowledge handling, from early-stage development and technology transfer to production scale. Mathematical process modeling can summarize this knowledge as the relationships of critical quality attributes to critical process parameters using mathematical equations and sound statistics [1, 2].

In this article, the term "mathematical model" refers to a system of ordinary differential equations describing the timely progression of process state variables, such as cell, glucose, or product concentration. Please refer to [3] and [4] for more insights into this model class.

Based on our experience in the field of bioprocess development and optimization, mathematical modeling has multiple advantages because it can:

- Be used in novel computational tools to deepen process understanding during pharmaceutical process development, which can be applied during the process and product life cycles [5]
- Evaluate manufacturing data of already established processes to identify unknown dependencies (i.e., data mining) [1, 2]
- Be a decision-making tool during routine manufacturing, e.g., to plan operator capacity or to evaluate batch-to-batch variability [6]
- Capture knowledge during the life cycle of the process, including the prediction of defects and transferability during the product life cycle [6]
- Virtually evaluate new configurations and feeding regimes prior to experimental testing [5, 6]
- Show the validity of the process during technology transfer [7]
- Decrease the development costs for experimental design and determine fast and efficient cell expansion, resulting in accelerated time to the clinic [8]

Physical laws and a metabolic understanding of the biotechnological system are the basis for using mathematical modeling to represent the bioprocess. Several mathematical models of varying complexity for bioprocess control and optimization have been previously described in the literature [1–3]. However, to our knowledge, mathematical process models have been seldom used in industrial practice.

Disadvantages of mathematical modeling are ensuring that the necessary internal resources are available to work and handle them in a regulated environment. Well-trained staff with backgrounds in GMP, computer systems, and statistics with a clear technological focus are needed. Even then, the setup of a mathematical model can take several months and requires deep immersion into the process. Moreover, the qualification of model-based systems is challenging and not standard because it must verify the performance of the model with respect to product quality and process robustness. The operators and technical staff have extensive experience within their respective processes, but the translation of this experience into a computational tool may face personal reservations and not be well received.

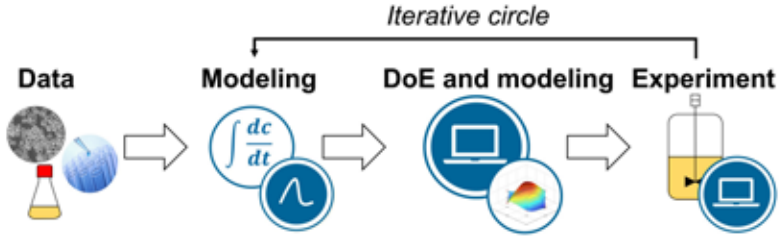
Nevertheless, novel efforts for the application of mathematical models have been described for upstream and downstream processing [9, 10]. The general difference between mathematical models is the structure of the underlying algorithms, which are specific to their intended use. Off-the-shelf software tools for the mathematical modeling of biomanufacturing processes are not commercially available because the complexity of the models used relies on a different number of measurements, available data, and computational power.

Our view on the use of mathematical models in the design of experiments and the evaluation of process transfer and scale-up is described as follows.

MATHEMATICAL MODELING AND DESIGN OF EXPERIMENTS

The early-stage development of novel bioprocesses (upstream) at laboratory scale is mainly based on the experience of the research team involved and the performance of the cell line screened for production. For fed-batch processes, the first steps in process development partly comprise media adjustments and the investigation of the most appropriate feeding regime for the platform technologies used. During this phase, mathematical process models can summarize the metabolic dependencies, e.g., glucose consumption for cell growth and viability or the effects of supplementation on the glycoprofile [11].

Figure 1: General workflow for the application of model-assisted DoE (mDoE).



By using standard cell lines and media, the expected growth characteristic is efficiently transferred into a mathematical process model [12]. This mathematical model can be combined with design of experiment (DoE) methods, which show great potential for the development of process strategies and media supplementation [13].

In an intensified DoE method (iDoE), the factors in the planned experiments are changed within each individual experiment, and the model is then used to analyze the results. Due to the complexity of such staged experimental results, the process analysis is enhanced by the model [14].

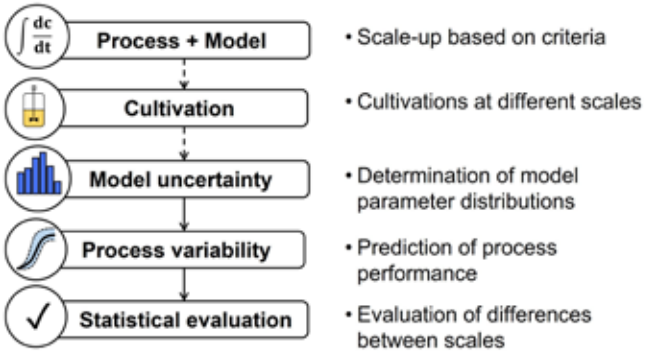
In model-based DoE (mbDoE), experiments are planned to properly identify the mathematical model and its parameters [15]. In model-assisted DoE (mDoE), a process-related target (i.e., maximum product concentration) is efficiently optimized using a low number of experiments, and the model assists in the evaluation and recommendation of DoE designs [12, 16]. The use of these mDoE results in typical savings of 40%–80% in the number of experiments, depending on the specific study [12, 15, 16].

For all methods, the available data and the known cellular effects obtained from screening studies or media test experiments can be used as the basis for setting up cause and effect relationships for cell growth, metabolism, and productivity.

An exemplary workflow for mDoE involves multiple steps (Figure 1) [5, 6]. First, the objective of the study (i.e., maximization of product concentration) should be well defined. Then, the biotechnological system is mathematically modeled based on the identified cause and effect relationships, and an mDoE is planned. Typically, two to four influencing variables are chosen with consideration of the technological constraints present in the production scale. The space for equipment operation is usually well known due to extensive qualification/validation activities, and optimizations are within narrow technology-related borders.

After planning the experiments, they are performed at laboratory/pilot scale, preferably using a scaled-down model of the manufacturing process. If the experimental data are available and the aim of the study is fulfilled, the data are included in the mathematical model, and it is transferred to production, together with the process settings. If the aim is not fulfilled, the data are used to adapt the process understanding in the form of the mathematical model, and new iterative experiments are planned.

Figure 2: Model-assisted workflow for the evaluation of the dynamics of bioprocesses at different scales [5, 6].



By using universally understood principles (i.e., mathematical model), the experimental strategy can be enhanced, which could lead to reduced experimentation (mDoE/iDoE) and/or better factor understanding (mbDoE).

EVALUATION OF PROCESS TRANSFER AND SCALE-UP

After process development, the bioprocess, including its process strategy, is transferred to pilot or production scale. Currently, scale-up and scale-down of the derived process knowledge between different departments within a company are challenging because of varying process performance and cellular changes [5, 6, 17]. For scale-up criteria, hydrodynamic states such as power input per volume are often defined as constant between the different scales, even if a hydrodynamic characterization is not available at each scale [18].

Additionally, a hydrodynamic scale-up procedure does not consider the dynamics of the bioprocess itself. It is not ensured that the previously developed process strategy is scaled up sufficiently and that the process dynamics stay constant during scale-up. In other words, how could the growth behavior and productivity be ensured from the smaller to larger scale?

Mathematical process models are key to compare and evaluate the process dynamics between different scales (Figure 2).

The development of process strategies requires fast methods to plan experiments and ensure efficient process transfer and scale-up.

Starting with the developed process and the mathematical model, scale-up is performed using known hydrodynamic criteria and experience of the bioreactors. Then, cultivations are performed at the different scales, and the same mathematical model is used to describe these cultivations considering experimental variations and analytical deviations. The model parameter distributions are derived to predict batch-to-batch variability and potential out-of-trends. Furthermore, the average and expected specification limits of the in-process controls are simulated. At the end, the individual model parameter distributions are statistically evaluated to identify if the process dynamics are the same between the tested scales. The same process dynamics are ensured if no changes in the parameter distributions are identified. Otherwise, if the parameters differ significantly, a validation of the process strategy is recommended using advanced DoE methods, which were introduced previously [7]. This approach provides a novel, knowledge-driven decision-making tool for bioprocess scale-up and scale-down to guarantee the same process performance from a few milliliters to production scale.

CONCLUSION

The development of process strategies requires fast methods to plan experiments and ensure efficient process transfer and scale-up. This article described the use of mDoE methods to consider well-known biological effects in the planning of experiments. This approach results in a reduced amount of laboratory work. Furthermore, a workflow was highlighted to evaluate process transfer and scale-up/scale-down using mathematical process models. The introduced approaches provide novel knowledge-driven decision-making tools for bioprocess development and implementation.

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INDEX

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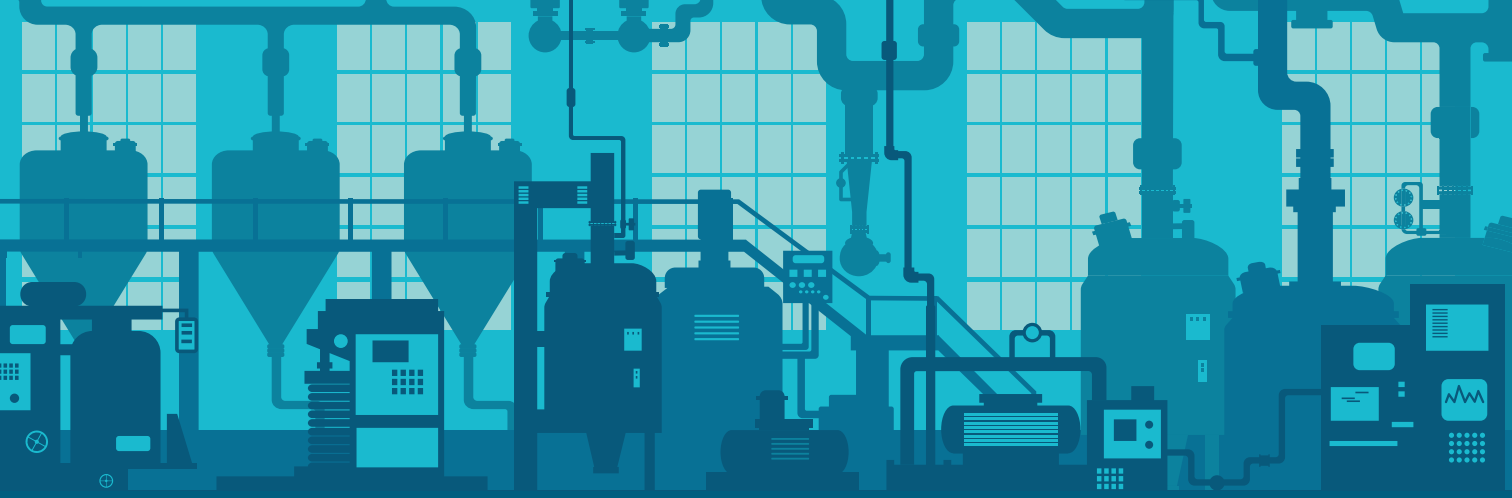

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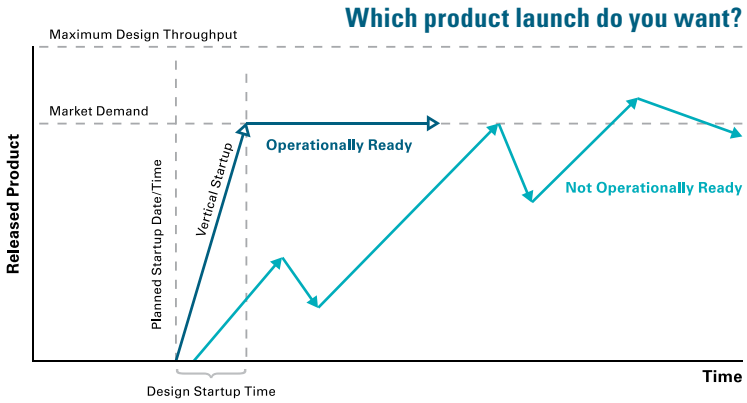

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