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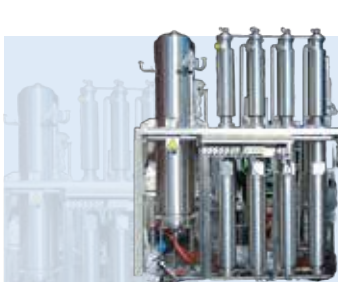

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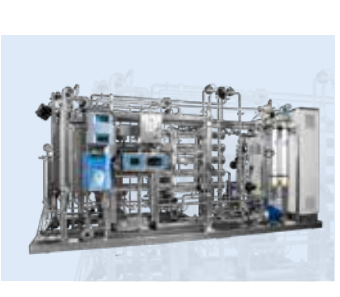

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By Scott W. Billman


Scott W. Billman

ATMPs and Biotech in 2024

It is hard to believe that we are halfway through the year for the ISPE programs and the Board of Directors in 2024. We have continued to progress through the 2023–2025 ISPE Strategic Plan with engagement from Chapters, Affiliates, the ISPE Foundation, and ISPE committees and volunteers.

The professional society was built and is run by its amazing volunteers. ISPE's communities of practice (CoPs), training, and guidance documents come from the dedication and energy of the volunteer membership. All the Chapter, Affiliate, and international leadership and committee chairs are volunteers who dedicate their free time to support and share their knowledge across the membership. In each issue, we spotlight some of those volunteer members. Please make sure to check out those articles in this issue.

NEW GUIDANCE

The biopharmaceutical issue of *Pharmaceutical Engineering®* is always a publication filled with interesting articles. Biopharmaceutical manufacturing and the challenges and advances in that area have been at the core of ISPE and throughout the history of our trainings, publications, and discussions. You will find several articles on advanced therapy medicinal products (ATMPs) in this issue of PE. They range in topics across the basic discovery, technical steps in manufacturing, and how to document and manage risk in the manufacturing of these therapies.

Biopharmaceutical topics in this issue include the basic discovery, technical steps in manufacturing, and how to document and manage risk in the manufacturing of these therapies.

At the beginning of 2024 ISPE published two new guides in this area: the *ISPE Guide: ATMPs - Allogeneic Cell Therapy* and the *ISPE Guide: ATMPs - Recombinant AAV Comparability & Lifecycle Management*. These guides are in addition to the original *ISPE Guide: ATMPs - Autologous Cell Therapy*. At the end of 2023, the third revision of the *ISPE Baseline® Guide Vol 6: Biopharmaceutical Manufacturing Facilities* was published. In addition, ISPE has developed training courses in the areas of biotechnology and ATMPs. These trainings come from our dedicated volunteers and through the biotechnology and ATMPs CoPs.

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The 2024 ISPE Biotechnology Conference will be held in Boston, Massachusetts, 17–18 June.

2024 CONFERENCES

The 2024 ISPE Europe Annual Conference in Lisbon, Portugal, was another great forum for our membership to get together and share their thoughts on the industry. We were able to hear industry experts speak on topics like digital transformation projects, artificial intelligence (AI) use cases, sustainability, and perspectives from regulators. Through the ISPE Foundation Grant program, we again sent students and recent graduates to the conference, free of charge, to engage with ISPE membership and learn more about the industry. It is only through the generous donations from members and corporate sponsors that we can continue to grow this program. It has been an invaluable benefit to those who have been able to participate.

We will once again come together to discuss biotechnology and ATMPs at the 2024 ISPE Biotechnology Conference in Boston, Massachusetts, 17–18 June. This will be a place for our membership to get together and engage on these topics, and many more. We will have sessions across the spectrum of biotech technologies, facilities, manufacturing, AI, and sustainability.

I have been amazed at the variety of topics and the level of expertise and interaction I have seen at the local and international conferences and events this year. As a longtime member and volunteer with ISPE, this year has seemed to be full of new and exciting topics. The continued advancement of our digital journey, and the growing use of AI, is a topic generating a lot of buzz and engagement.

Hearing how others in the industry are thinking about this and discussing use cases and the future potential has been great. I look forward to more interaction with the membership on topics like AI, Annex 1, and biopharmaceutical manufacturing as the year continues. I hope you enjoy the articles in this issue, and I look forward to talking with you at an upcoming conference.

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

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By Vivien Santillan


Vivien Santillan

AN ERA OF INNOVATION AND EMERGING TECHNOLOGIES

The emergence of new modalities and innovations on drug development and research, such as advanced therapy medicinal products (ATMPs) and personalized and precise therapies, presents new opportunities for the treatment and management of diseases and injuries. As these innovations continue to evolve, the regulatory landscape likewise evolves and this has led to the production of higher-quality, safer, and more efficacious medicines.

ATMPs: CHALLENGES AND SOLUTIONS

Recent studies indicate that investment in ATMPs is expected to spawn growth in terms of the establishment of research facilities and related infrastructure. However, challenges in manufacturing sector flexibility are expected as the industry adapts to the new and emerging technologies. These challenges include standardization, interoperability, integration of legacy systems to new technologies, regulation, and security, among others. It is therefore imperative that these factors be given serious consideration along with the perceived improvements, efficiencies, and benefits.

Among the equally important aspects that can bring about effective technology diffusion and adaptation are capacity development in human resources, improvements in infrastructure and research facilities, education, and knowledge management, which must be supported by relevant and responsive government regulatory policies.

Of these, human resource capacity development is where an organization has direct control and influence. In recent times, it is no longer sufficient to have a workforce with appropriate skill sets. The global landscape requires the organization to empower the same workforce not only with knowledge on technology innovations but with awareness of market and social developments as well. This is where the organization can have meaningful impact.

MAKING A DIFFERENCE WITH ISPE WOMEN IN PHARMA®

ISPE is acknowledged as a forerunner in scientific, technical, and regulatory advancement throughout the entire pharmaceutical life cycle. As a global leader, ISPE offers its members different platforms to obtain technical proficiency. It is also a great resource for training and workshop requirements in the industry. Consistent to the demands of the global market, ISPE members are trusted to provide relevant and responsive solutions and perspectives to the ever-changing landscape of the pharmaceutical industry.

Adapting to change and enabling the organization for continuous improvement will lay the foundation for an engaged and responsive workforce.

Women in Pharma is a community within ISPE that provides a forum for collaborations on technical and career advancement topics that aims to balance the needs for personal and professional growth. Its programs include mentorship of its members, promoting safe space for meaningful conversations, and fostering partnerships, among others. This community offers a venue to pursue personal development through building relationships to create social impact. It also seeks out opportunities to lead and make a difference to shape the future of pharma. It is cognizant of the important role that the workforce plays in organizations and endeavors to leverage diversity, equity, and inclusion to drive operational excellence within the workplace.

Adapting to change and enabling the organization for continuous improvement will lay the foundation for an engaged and responsive workforce. Organizations must not only have an awareness of this dynamic but should also be mindful of its essential requisites. The benefits of a workforce with the necessary skill sets and a well-rounded perspective of the needs of the market will redound not only to the organization, but to the industry as well. This is where ISPE and Women in Pharma can help. Let us connect, collaborate, and inspire our workforce and the future generations to adapt by continuously seeking knowledge.

Vivien E. Santillan is Regional Director for Asia at Novatek International and the 2023–2024 Chair of the Women in Pharma International Steering Committee. She has been a member of ISPE since 2012.

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By Monique L. Sprueill


Monique L. Sprueill

ISPE OPPORTUNITIES FOR GROWTH IN 2024

It is an exciting time to be an ISPE Emerging Leader! With conferences, professional development support, mentorship, and other opportunities, joining ISPE as an Emerging Leader can help boost your career and expand your network.

ISPE CONFERENCES

The 2024 ISPE Europe Annual Conference in Lisbon, Portugal, was amazing. As part of the Professional Development Grant Program, approximately 15 students and Emerging Leaders were sponsored by the ISPE Foundation. Travel, accommodations, conference fee, and membership dues (as needed) were covered for grant recipients. Students and recent graduates collaborated and networked during the Hackathon. They built lasting relationships and made connections that may lead to future opportunities.

The Professional Development Grant application process recently opened for the 2024 ISPE Annual Meeting & Expo. The conference will take place in Orlando, Florida. Visit www.ispefoundation.org and submit your application for the Professional Development Grant. Award recipients will be notified in the summer, starting in July.

As we approach the 2024 ISPE Biotechnology Conference in June, there are additional opportunities to gain or enhance skills. Workshops are offered that will highlight new technologies, innovative methods, and state-of-the-art facilities. ISPE members are performing work that will result in better outcomes for and extend the life of patients. As Emerging Leaders, you are an integral part of shaping the future of this industry.

BIOLOGICS, CELL AND GENE THERAPIES, AND ATMPS

Biologics, cell and gene therapies, and advanced therapy medicinal products (ATMPs) will continue to grow and expand to address the needs of patients. ISPE Communities of Practice (CoPs) host forums for industry professionals to discuss advancement, challenges, and lessons learned. These programs allow participants to gain knowledge that will enhance job performance, resulting in more visibility, and open the door to new experiences.

ISPE MENTORSHIPS AND OPPORTUNITIES

Are you trying to navigate your career and need some guidance? Are you dealing with a difficult work-related situation and not sure how to manage it? Looking to broaden your understanding of the industry on an international level? Are you thinking about taking a course or getting a certification? ISPE's Women in Pharma® sponsors a mentor program, Mentor ISPE, that introduces Emerging Leaders to professionals who can help with career development and promotion.

In addition to the Professional Development Grant, the Foundation also provides access to scholarships and internship programs. Donations to the Foundation are used to help students and Emerging Leaders gain skills, experience, and visibility that will drive professional growth. Learn more at www.ispefoundation.org

Join ISPE as an Emerging Leader to help boost your career and expand your network. You can network with other professionals, gain a mentor, and take your career to the next level.

Some key advantages of joining Emerging Leaders are:

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

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

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

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

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

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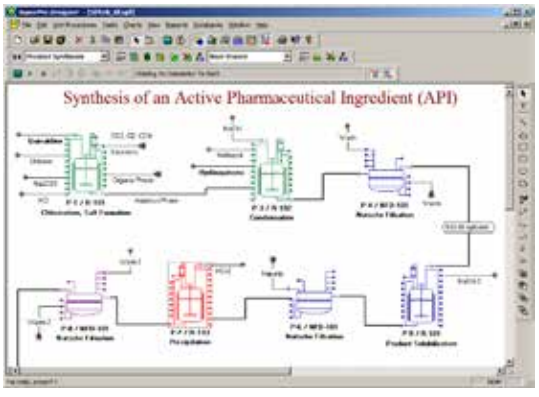

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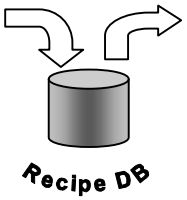

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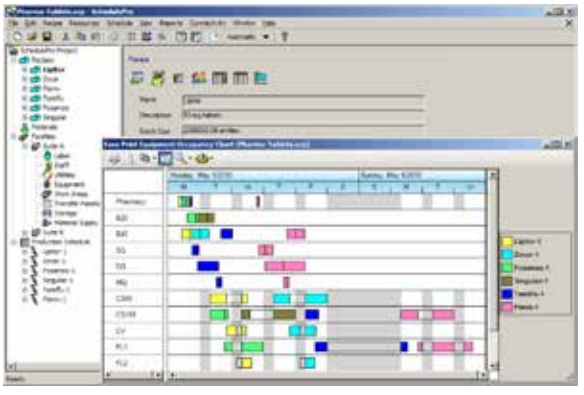

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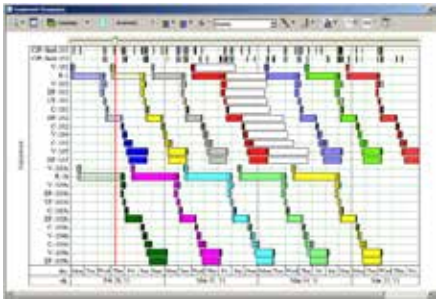

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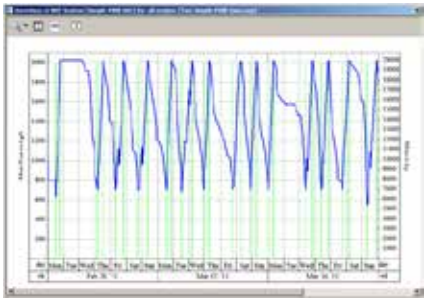

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SchedulePro is a versatile production planning, scheduling, and resource management tool. It generates feasible production schedules for multi-product facilities that do not violate constraints related to the limited availability of equipment, labor,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

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FRONT-END DESIGN of Personalized Medicine Facilities

By Sean Tully and Tom Bannon

The commercialization of personalized medicine has ushered in demand for a new type of facility—personalized medicine facilities—which can produce thousands of small-scale batches per year. There are currently only a handful of these sites, but many more are in various stages of design and construction. Designing these personalized medicine facilities presents new challenges, and a different design approach is necessary. Cyclic scheduling can produce high-quality models rapidly and aid collaborative design. A focus on room and zone availability and movements can prevent bottlenecks in corridors, gowning, and airlocks to streamline production.

PERSONALIZED MEDICINE FACILITIES AND BULK DRUG SUBSTANCE PRODUCTION

The industry's collective understanding of personalized medicine facilities is relatively immature, especially when compared to more established platforms for bulk drug substance production. Examples of more established platforms include, but are not limited to, small-molecule chemical active pharmaceutical ingredient (API), monoclonal antibody (mAb), and bacterial fermentation. The processes employed to make personalized therapeutics are also relatively immature, and we see a good deal of flux in process development during design.

CAR T Facilities

Of particular interest are autologous chimeric antigen receptor (CAR) T cell therapies. As of January 2024, there are only six such therapeutics approved by the US Food and Drug Administration (FDA) [1]. Accordingly, there are only a small number of facilities producing these therapies at scale. A large-scale facility would typically be capable of producing 4,000–10,000 patient batches per year.

The focus of this article is on production-scale CART facilities, which produce at least several thousand patient batches per year.

We have completed several front-end designs for large-scale CAR T facilities in recent years. From our experience, we have observed that such facilities require a different design approach than bulk API facilities. In this article, we outline these differences and identify some common pitfalls and key design considerations. Many of the issues relate to the scaled-out nature of production and are equally applicable to other similarly sized gene therapy facilities operating on other modalities.

We have also encountered challenges in creating scheduling models for these facilities using currently available software. In response to this, we have developed a proprietary approach for rapid generation of production scheduling simulations, which we outline in detail.

DESIGN APPROACH

The main high-level difference between the production of bulk drug substances and personalized medicine is in scale, specifically scale-up vs. scale-out. Bulk drug substance production requires large equipment, with reactors in the thousands, or tens of thousands, of liters and with 10 or more batches per year. Personalized medicine produces small-scale batches, typically no more than a few hundred grams, but it produces perhaps ten thousand such batches per year.

With the scaled-up nature of bulk drug substance production, the focus is on equipment sizing, and the general approach is that we design around the needs of the core process equipment. With personalized medicine, considerations such as personnel and material flow, which are usually peripheral to the design of a bulk facility, are of critical importance. The two approaches are contrasted in the following section.

Bulk Drug Substance Approach: Focus on Equipment

As process engineers, we have developed mature procedures for facility design centered on our many years of experience with bulk API facilities. With small-molecule chemical API facilities, designs often accommodate many different short campaigns to make intermediates, with any given reactor used for several different reactions. The complete process to make the drug substance is generally broken up into many subprocesses, with the intermediates bulked and stored in between.

These facility designs often need to account for multiple intermediate production recipes, with a strong focus on the requirements for campaign changeover and line clearance. A great deal of design focus is also centered on utilities, solvent storage, emissions, and waste.

With bulk biologics (e.g., mAb and bacterial fermentation), the focus is generally centered on efficiency and throughput. Batches tend to be run straight through from vial thaw to drug substance formulation. Core equipment tends to be used once per batch. Design challenges revolve around the size and count of upstream trains, and the sizing of downstream equipment, with a focus on balancing equipment size against utilization. The sizing and scheduling of solution preparation is also a key consideration.

Core equipment vs. support equipment

It is important, at this point, to differentiate between core equipment and support equipment. Core equipment is the equipment that is used in the core process and typically has physical contact with the work-in-progress batch. Support equipment comprises utilities, waste management, clean-in-place (CIP) skids, solution preparation and hold vessels, and tank farms.

With bulk facilities, the primary challenge during front-end design is to optimize the sizing and count of the core equipment to meet throughput requirements in an efficient manner. In general, the design of core equipment should not be constrained by any outside factors. Having done this, the design scope widens to encompass the design of support equipment, such as solution preparation and utilities.

In the front-end design of bulk facilities, labor and discrete movements are often not a key design consideration. In general, the core equipment has primacy, and the assumption is that adequate labor will be provided to ensure the process runs smoothly. Changes to labor requirements tend to have a minimal impact on cost and layout, being perhaps limited to some scaling of gowning areas.

Although bulk facilities do include discrete material movements, such as powder containers, movable equipment, and single-use consumables, it is unlikely that the facility will be bottlenecked by logistical concerns.

Risk and redundancy

A final design consideration is a philosophy on risk and redundancy. For bulk facilities, this is primarily an economic consideration: balancing the cost of providing redundancy against the probability and cost of a failed batch due to equipment unavailability or breakdown. In general, for bulk facilities, there tends not to be any redundant core equipment, unless a particular piece of equipment has many units in parallel (such as, occasionally, reactors and bioreactors) or has complex routine maintenance requirements (such as centrifuges). We would typically see some redundancy in clean utilities, solution preparation, and CIP skids.

Bulk drug substance facility design

Bulk drug substance facility design typically proceeds as follows. First, identify overarching design goals and degrees of freedom. Questions in this step can include:

- What are throughput requirements; are they specified in terms of batch quantity or volume or mass of product?
- Are we designing for one or more products?
- Do we need to accommodate process variability, e.g., titer ranges?
- Is a phased design required to meet a demand ramp?
- Are key equipment sizes and counts fixed, or are they a degree of freedom?

Next, prepare parameterized mass balances to size primary equipment. The mass balance should be easy to scale if, e.g., batch size or equipment size is varied. Prepare production schedules to validate and optimize sizing of core equipment. This can be challenging if complex changeover scenarios are a feature, but the task is usually straightforward for single-product facilities because core equipment should not wait for anything.

Next, use the production schedule and mass balance to size utilities and support equipment. This is significantly more challenging than the previous step because non-core equipment often experiences competition from multiple sources.

Finally, we consider support equipment. Consider support vessels first (e.g., solution preparation), followed by cleaning systems, then clean and black utilities.

Personalized Medicine Approach: Focus on Flow

Large-scale personalized medicine production facilities present very different design challenges. Adopting an equipment-focused approach can trip up designers due to the more profound impact of personnel and material flows.

These facilities typically produce thousands of batches per year, perhaps two orders of magnitude more than a typical bulk biologics or chemical API facility. The processes involved are currently very labor-intensive and a typical batch may require over 100 individual consumables, typically packed into kits. Each batch produces perhaps a dozen quality control (QC) samples, giving tens or hundreds of thousands of samples per year. It is clear from the scale of these discrete movements that they will have a much greater impact on facility design than in a bulk facility that makes a few batches per week and relies mainly on piped transfers.

Facility layout

In bulk drug substance facilities, the size and layout of the facility is primarily driven by equipment requirements and adjacencies. In personalized medicine facilities, we still need to accommodate the process equipment, but we are often dealing with

Table 1: A summary of the key differences between bulk drug substance and personalized medicine production facilities.

Comparison	Bulk Drug Substance Facility	Personalized Medicine Facility
Scale	Large process equipment, relatively small count of core process equipment	Mainly benchtop equipment, high degree of scale-out with 10 or more parallel equipment items
Material Transfers	Mainly piped	Mainly discrete movements
Throughput	10–100 batches per year	1,000–10,000 batches per year
QC	Hundreds of tests per year	Thousands or tens of thousands of tests per year
Key Considerations	Equipment sizing, solution preparation, utilities, solvents, and waste	Equipment and suite counts; movement of kits, personnel, samples, and product; and ability to clean rooms and corridors

a mix of benchtop equipment, biosafety cabinets, gloveboxes, and stackable incubators. Of equal importance in a room is a focus on headcount, ergonomics, and staging space.

In personalized medicine facilities, corridors, gowning, and airlocks can become bottlenecks in the process. The ability to deep-clean spaces with sporicidal agents needs to be considered early in the design, as this may prevent personnel from accessing rooms and corridors for several hours a week. If these features are not considered thoroughly throughout the design process, a facility can become bottlenecked by its infrastructure, rather than its core process equipment.

One key degree of freedom, when designing for scaled-out production, is the tradeoff between room size and room quantity. Fewer, larger rooms lead to a more space-efficient design but make it difficult to carry out cleaning. Using an increased number of smaller rooms reduces the likelihood of cross-contamination and reduces the risk of equipment, such as air handling units, failing. However, this strategy also requires more space and complexity and can hamper flexibility. A balance must be struck to arrive at a reasonable design.

Material movements

The impact of discrete material movements can have a profound effect on layout and facility size. Larger rooms may require multiple material air locks (MALs) or personnel air locks (PALs) so that material and personnel movements do not become a production bottleneck. The space required for kitting and movement from non-graded space into the suite can be substantial. As a result, we require data on the scheduling of material movements early in the design process. This usually comes in the form of a bill of materials (BOM), plus a separate BOM for discrete waste streams.

Personalized medicine facility design

Personalized medicine facility design typically proceeds as follows. First, identify overarching design goals and degrees of freedom. Questions in this step can include:

- What are the throughput requirements?
- Do we need to accommodate process variability?
- Is a phased design required to meet a demand ramp?
- What are redundancy requirements (at room, suite, workstation, and equipment levels)?

Next, a BOM and waste BOM should be drawn up (a detailed mass balance is not typically required). Prepare production schedules to validate and optimize count of suites and equipment. Several options may be investigated here, so a structured approach should be taken to allow for multiple models to be maintained simultaneously with minimal duplication of data.

Then, add detail to the production schedule, such as material movements and personnel requirements. Consider room and corridor cleaning requirements and the capacity of MALs, PALs, rooms, corridors, and gowning. Some iteration will be required to arrive at one or more viable solutions.

CAPACITY MODELING

To prove a facility design is viable, a capacity model is required. The aim of a capacity model is to demonstrate how the required throughput can be scheduled on equipment in the facility while ensuring that demands for material movements, labor, and cleaning can be reasonably met. We have considered developing production models using several methods. We found that recipe-based scheduling software is too slow to solve problems, and that discrete-event simulations are too slow to build and their complexity is a barrier to collaboration.

Evaluating Existing Techniques

Recipe-based scheduling software is ubiquitous in the pharmaceutical industry and is widely used to aid in the design of bulk substance production facilities. We have found that this type of software does not perform well when there are many simultaneous batches in process at a given time. Take, for example, a large-scale CAR T facility. If it produces 10,000 batches per year, and a batch takes two weeks to produce, there will be over 400 batches in production at any given time. The number of batches to be scheduled will be even greater than this, 500 or 600 to give a few days of fully occupied steady-state production in the middle of the scheduled campaign.

Even with straightforward models, with zero degrees of freedom, we are seeing solution times running into hours, making this approach intractable for rapid design development. Furthermore, the clash-resolution algorithms in this type of software are of limited efficacy when batches overlap considerably. This is a limitation of the technique, rather than the software; the mathematical

complexity of this form of scheduling tends to make solution times grow exponentially with model size [2].

Discrete-event simulation (DES) can also be used to model large-scale personalized medicine facilities [3]. DESs are structurally very simple [4]:

- A clock starts at time zero and keeps track of current time.
- An event in the model consists of an action and a time.
- A data structure called a "priority queue" keeps track of future events and keeps them in order.
- The model is run by continuously popping the next event from the head of the queue, setting the clock time to the event time, and then executing the event actions. This is repeated until the queue is empty.
- Note that event actions often involve the creation of more events. For example, if the model executes a "start incubation" action, this may add a "finish incubation" event to the queue to be executed in the future.

DES solution times tend to scale linearly with problem size and therefore can deal well with large models. DES software can be used to create incredibly detailed models of personalized medicine facilities, including 2D and 3D dynamic models. Such models tend to be complex to build, requiring a good deal of decision-making about movements and operating rules. Although the models they produce can be powerful tools for optimizing and understanding these facilities, they remain too slow and complex to build (rather than solve) and are accordingly not a good fit for short-duration front-end design.

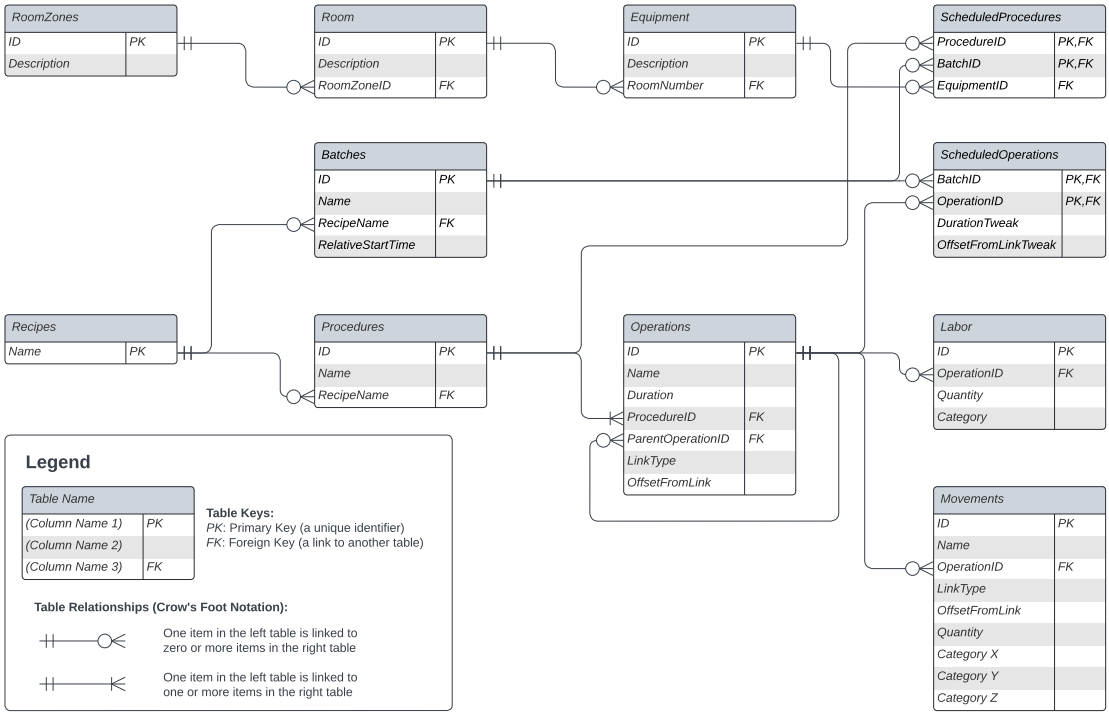
Another important factor is the relatability of the model. Is it in a format that the client can interact with and understand? Is it simple enough to explain and defend in a short presentation? Is it easy to read the input and output data? Because DES is quite unstructured, it can be difficult to explain and characterize a model. It is difficult for a client to see all the data in the model and to understand the rules implemented within.

During front-end design, when there is rapid churn, it is critical to have a model that can be modified in near real time, so that both the designer and the client can coalesce on a workable design. It is our view that DES would represent over-simulation at this phase of design, requiring a great number of philosophical decisions to be made regarding movements, staging, and interactions. DES does remain a valid tool for detailed design or for modeling an existing facility in operation.

A Cyclic Approach to Scheduling

For a large-scale personalized medicine facility, we are generally considering 24/7 production and a few dozen batches per day. It is reasonable to assume, therefore, that every day is scheduled

Figure 1: Input data model entity–relationship diagram.



identically (with adequate downtime each day for cleaning and routine maintenance). Furthermore, we can usually assume that the *n*th batch on any given day will always use the same equipment.

Finally, we are usually in the situation where all process procedures take less than a day (apart from incubation). This allows us to make an important simplification. Instead of looking at a long scheduling horizon of several weeks and hundreds of batches, we need only consider a 24-hour window. This window captures steady-state production, with the assumption that the 24 hours on either side of this window will be identical, and so on.

Borrowing from recipe-based scheduling software, we can define the production recipe, and its durations, but then use modular arithmetic to wrap the schedule around on itself and just focus on this short, repeating window. Note that in principle, the approach could be extended to consider longer or shorter repeating periods (e.g., weeks), with an accompanying increase or decrease in model size.

The Input Data Model

To develop a capacity model on the preceding premise, we must first create an input data model to make sense of data requirements. Consider this to be like a database, with tables of related data. (Indeed, a database is well-suited to capture such data, but it could more easily be built using tables in a spreadsheet or plaintext files.) A high-level data model is shown in Figure 1. The terminology used in this model is based on the ISA-88 standard [5].

A summary of the tables is given next:

Equipment

This can represent a single piece of tagged equipment (e.g., a cell counter) or a collection of equipment (e.g., a workstation including a tube welder, some process equipment, and a cell counter).

Rooms and room zones

These constructs allow us to specify where equipment is, allowing us to plan idle time for cleaning. By grouping rooms into zones, we can see when the entire zone is available to be cleaned.

Recipes

A recipe is the top-level of a set of instructions for how to make a single batch. In a typical model, we may just have a single production recipe (which is run many times per day) and a daily-task recipe (e.g., for daily setup or restocking tasks).

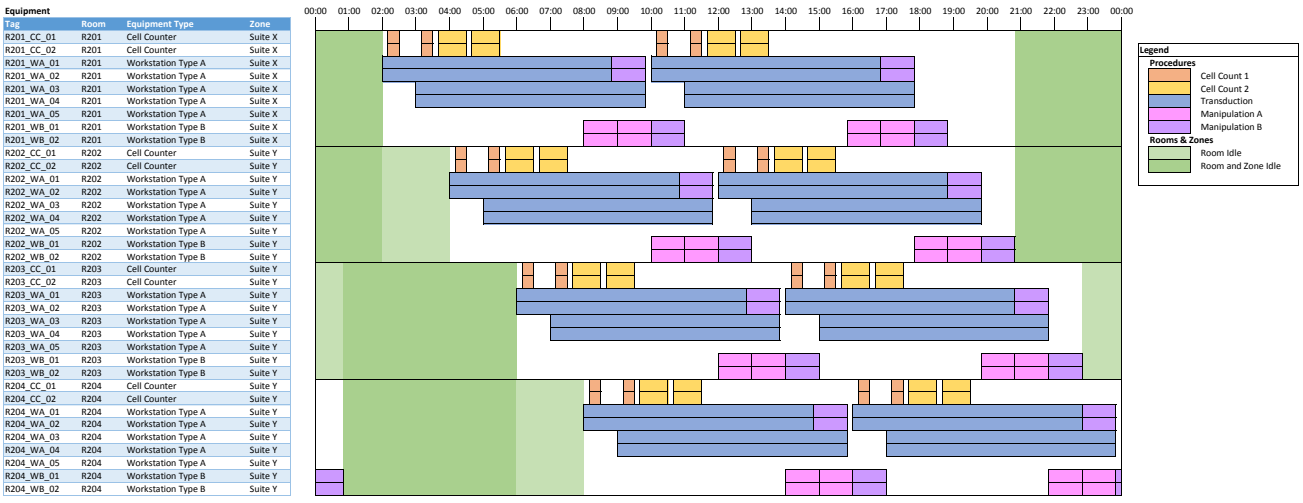
Procedures

Each recipe consists of many procedures (e.g., "activation" or "transduction") that involve constraining a single piece of equipment for their duration.

Operations

These are the building blocks of procedures (e.g., "setup," "mix," "teardown") and can be linked to other operations in various ways. Durations are defined at the operation level. The scheduling

Figure 2: Typical equipment schedule plot shows equipment occupancy as a function of time over a 24-hour period.



Equipment

Tag	Room	Equipment Type	Zone
R201_CC_01	R201	Cell Counter	Suite X
R201_CC_02	R201	Cell Counter	Suite X
R201_WA_01	R201	Workstation Type A	Suite X
R201_WA_02	R201	Workstation Type A	Suite X
R201_WA_03	R201	Workstation Type A	Suite X
R201_WA_04	R201	Workstation Type A	Suite X
R201_WA_05	R201	Workstation Type A	Suite X
R201_WB_01	R201	Workstation Type B	Suite X
R201_WB_02	R201	Workstation Type B	Suite X
R202_CC_01	R202	Cell Counter	Suite Y
R202_CC_02	R202	Cell Counter	Suite Y
R202_WA_01	R202	Workstation Type A	Suite Y
R202_WA_02	R202	Workstation Type A	Suite Y
R202_WA_03	R202	Workstation Type A	Suite Y
R202_WA_04	R202	Workstation Type A	Suite Y
R202_WA_05	R202	Workstation Type A	Suite Y
R202_WB_01	R202	Workstation Type B	Suite Y
R202_WB_02	R202	Workstation Type B	Suite Y
R203_CC_01	R203	Cell Counter	Suite Y
R203_CC_02	R203	Cell Counter	Suite Y
R203_WA_01	R203	Workstation Type A	Suite Y
R203_WA_02	R203	Workstation Type A	Suite Y
R203_WA_03	R203	Workstation Type A	Suite Y
R203_WA_04	R203	Workstation Type A	Suite Y
R203_WA_05	R203	Workstation Type A	Suite Y
R203_WB_01	R203	Workstation Type B	Suite Y
R203_WB_02	R203	Workstation Type B	Suite Y
R204_CC_01	R204	Cell Counter	Suite Y
R204_CC_02	R204	Cell Counter	Suite Y
R204_WA_01	R204	Workstation Type A	Suite Y
R204_WA_02	R204	Workstation Type A	Suite Y
R204_WA_03	R204	Workstation Type A	Suite Y
R204_WA_04	R204	Workstation Type A	Suite Y
R204_WA_05	R204	Workstation Type A	Suite Y
R204_WB_01	R204	Workstation Type B	Suite Y
R204_WB_02	R204	Workstation Type B	Suite Y

of a procedure is calculated from the scheduling of its constituent operations.

Labor

Labor requirements are attached to operations. More than one category of labor may be required for a given operation, and the quantity of each category can be specified.

Movements

Movements are attached to operations and are assumed to be instantaneous. This table is used to track the movement of work-in-progress batches, samples, and kits from the point of view of process demand (i.e., when the process needs a kit or emits a sample). During front-end design, it is unlikely there will be sufficient time to work thorough exactly how each movement is staged. It should be sufficient to track when the movements occur from the point of view of the process, and to consider, for example, hourly averages by room when looking at MAL or corridor utilization.

Batches

Batches are instances of the recipe, scheduled to start at particular times during the 24-hour window, with the assumption that similar batches start at the same time and use the same equipment every day. Our first important degree of freedom is in how batches are scheduled and staggered throughout the day.

Scheduled procedures

This table specifies the equipment required to carry out a particular procedure in a particular daily batch, forming the second major degree of freedom in the model.

Scheduled operations

This table is used to tweak the scheduling of particular batches by, for example, delaying or pulling forward tasks or modifying the duration of tasks by some delta. Ideally, every batch will be scheduled identically relative to its batch start, but occasionally it is useful to have this additional degree of freedom to resolve minor clashes. Incubation durations are usually defined as a range, so some of this rangeability can be used to resolve short-duration clashes.

From the input data model, it should be clear that we have all the data necessary to calculate the exact timing of every procedure, labor requirement, and movement requirement in our repeating 24-hour window. Although we are not going to derive the sort of clash-resolution algorithms found in recipe-based scheduling software, we have found that this is unnecessary.

In any case, such software struggles to resolve clashes in models of this scale. It is possible to create a model in a spreadsheet (without recourse to any macros or scripts) that can fully describe the schedule and highlight clashes visually and calculate almost instantaneously. This allows us to resolve scheduling clashes manually and rapidly by assigning a procedure to different equipment or by delaying or pulling forward an operation.

Outputs

The most important output is a plot showing a clear equipment schedule (for the 24-hour repeating window). This is not something that is possible to do natively with the limited plotting capabilities of spreadsheet software, but we have found an approach using conditional formatting that allows us to create clear plots. This is done by discretizing equipment occupancy into, for example, 5- or 10-minute blocks and coloring in cells (using conditional formatting) to compose the plot. See the example in Figure 2.

In the equipment schedule plot example, each row represents tagged equipment. Colored blocks indicate procedures occurring in equipment. The plot can be filtered by room or equipment type. The available time for cleaning is shown in green; lighter green blocks indicate the room is free and darker green blocks indicate that the room and zone are both free. This allows us to identify

Figure 3: A typical movement chart showing movements in and out of a particular room.

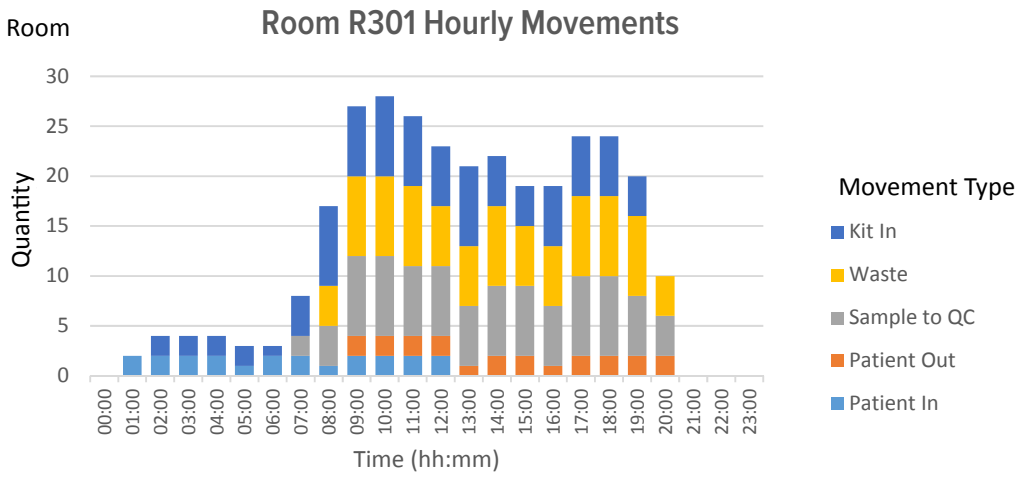
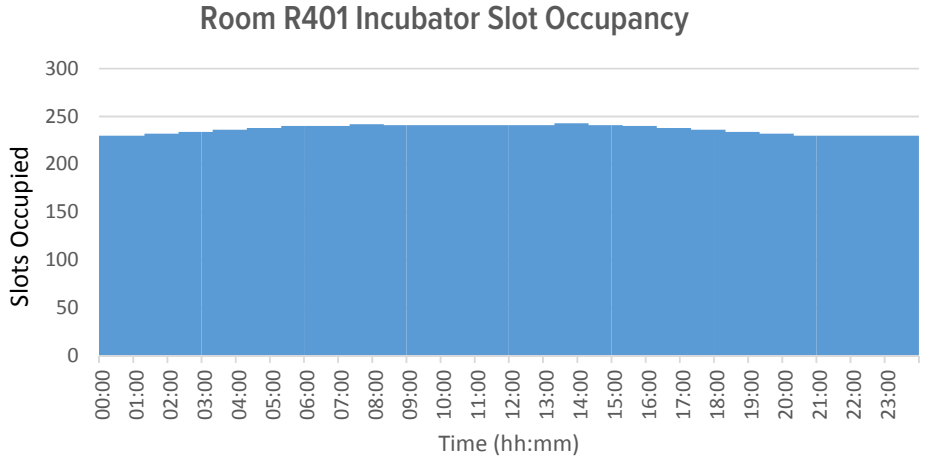


Figure 4: A typical incubator occupancy chart showing the quantity of incubator slots occupied as a function of time.



blocks of time where deep cleans of corridors can be scheduled.

In addition to the scheduling of equipment, the resolved model gives us data on personnel and movement scheduling. We can generate useful graphical outputs from this, such as pivot charts that allow us to see labor requirements by room and/or labor category. Labor demand is linked to operations. Based on the resolved schedule, we can calculate the start and finish times for each use of labor. We can then trend labor demand over time. With labor requirements, we are typically interested in real-time demand to allow us to identify, for example, peaks in room occupancy.

We can also generate similar charts showing movements in and out of rooms by category. Movements are assumed to be instantaneous in the model. Based on the resolved schedule, the time for each movement occurrence is known. With movements, we typically sample over longer periods for the purposes of plotting. For example, we may be interested in the movement counts in each hour, broken down by category, for a particular room.

This longer interval is more appropriate, as the schedule only tells us when the process consumes or emits a material, and we are not at the stage in the design where we are ready to reason about how

exactly kits and waste are ordered, staged, or removed. What we are aiming for is an indication of busy periods in MALs so that we can decide qualitatively if there is broadly sufficient MAL capacity and staging to allow some movements in to occur ahead of time and some movements out to be delayed. A typical movement chart is shown in Figure 3.

We can treat long-duration procedures such as multiday incubation as a special case. Within a room, we count total incubator slot occupancy, rather than trying to model each individual slot within the banks of incubators. This can be displayed as a bar chart or step function plot, as per Figure 4, which shows the quantity of slots occupied as a function of time.

Benefits of Cyclic Scheduling

The following list includes some of the many benefits of cyclic scheduling:

- A well-defined input data model can drive the handover of information from the client in a clear manner.
- Each table in the input data model can be easily implemented in a spreadsheet, giving both the designer and client a resource that is human-readable and easy to check.
- The model resolves in seconds and highlights clashes, enabling rapid design development. (We have found that it is responsive enough to allow updates in real time during design workshops.)
- The equipment schedule plot provides a clear tool to visualize the operation of the facility.
- The ability to visualize room and zone availability aids the development of a cleaning philosophy.
- The ability to plot daily trends in movements and headcount allows constraints in labor, MALs, and kitting to be factored in earlier during the design process.

CONCLUSION

We have highlighted the differences between designing a bulk drug substance production facility and a large-scale personalized medicine facility. In particular, designers need to account for the large number of discrete movements and must allow adequate time in the production schedule for room and corridor cleaning.

Faced with the challenge of designing scaled-out personalized medicine facilities against tight front-end design timelines, we have found that existing methods are a bottleneck to the design process. By developing a modeling philosophy around cyclic scheduling, we can develop high-quality models rapidly. These models are in a format that is easy to comprehend, without stakeholders needing familiarity with complex software packages. This approach aids collaborative design. By focusing on room and zone availability and movements as part of our design, we can preempt bottlenecks particular to personalized medicine facilities.

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POST-APPROVAL CHANGE MANAGEMENT

for Cell and Gene Therapy Products

By Peter Millili, PhD, Andrew Chang, PhD, Stuart Finnie, PhD, and Maria Amaya, PhD

Cell and gene therapy (C&GT) products represent a significant step forward in patient treatment and often offer unique patient benefits. However, product developers face significant hurdles within the regulatory landscape. The tools laid out in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q12 guideline: "Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management" [1] could provide novel ways to manage the regulatory interface for C&GT products in a proactive science- and risk-based manner.

REGULATORY CHALLENGES FOR C&GT PRODUCT DEVELOPERS

Developers of C&GT products face significant complexity within the regulatory framework. This field is relatively new and less established than other traditional biotechnology fields. Therefore, both development and regulatory frameworks are evolving continuously in line with emerging information. This leads to a complex and uncertain regulatory landscape with significant hurdles. Lack of international harmonization across regulatory agencies on approaches to these products adds to the challenges, particularly in the post-approval space. For future development of these products, speed and agility should be considered in the context of this framework.

One possible solution to these challenges is the Post-Approval Change Management Protocol (PACMP) concept, as outlined in the ICH Q12 guideline. This concept could be used in novel ways and leveraged to facilitate the updating of certain product quality attributes, such as product-related impurities specifications, based upon evolving understanding and increased clinical experience and product manufacture. This concept is outlined in this article.

ICH Q12 AND THE PACMP

The ICH started work on a specific guideline to address the issue of life cycle management from a science- and risk-based approach in 2014. This resulted in the ICH Q12 guideline, which reached Step 4 in 2019 and has been in ongoing implementation globally since this time. ICH Q12 sets out to provide a framework for the management of post-approval change and is designed to increase the predictability and transparency of change proposals, both for the license holder and the competent authority.

ICH Q12 introduces several tools for the management of regulatory change. Of particular interest to this discussion is the PACMP. Tools like the PACMP have been available in some jurisdictions for many years, so technically this is not an innovation.

Traditional Post-Approval Change

In a traditional post-approval change interaction, the applicant makes one submission to the agency in which the scope of the change is outlined, including an outline of experimental and confirmatory work necessary to support the change and the data from this work. For a change to a well-characterized biotechnology product, this would entail a description of the change, a risk assessment of the impact of the change, a presentation of the comparability activities and data (as envisaged in ICH Q5E), and data from any stability studies considered necessary.

There are two major issues with this approach. First, logistically, the applicant must wait until all the data is gathered before making a submission to an agency. Given the potential requirement for

stability data, waiting for this data can significantly lengthen the process. Second, the agency reviews both the applicant's strategy for the change and the resulting data corresponding to that strategy at the same time.

Consequently, if the agency has issues with the path the applicant has taken and believes that additional or different experiments are necessary to support the change, this could jeopardize the approvability of the change and lead to significant delays in implementation. This can be especially troublesome in situations where the change is complex or where there is limited guidance.

Post-Approval Change Under the PACMP

With the PACMP, the applicant makes two submissions: one outlining the scope and strategy for evaluation of the change and the supporting work to be performed and a second subsequent submission providing the resulting data from the agreed-upon supporting work. Although this may seem to be double work, this approach offers transparency, predictability, and efficiency over the traditional approach.

First, the submission of the strategy is freed from the need to wait for generation of all the data. Thus, this can be done at any time once the strategy for the change and the required supporting information has been established. Not having to wait for the data constitutes a significant time savings [2]. Second, provided that the data meets the agreed-upon protocol, the subsequent implementing submission is expected to be a lower category of change, usually moving from prior approval category to a notification, providing a significant efficiency once the appropriate results are available.

Finally, and perhaps most important, the applicant and the agency have a chance to discuss and agree on an appropriate package of information to support the change before any significant work has been initiated. Crucially, this agreement is binding, coming as it does from the approval of a regulatory submission. The probability of any agency queries sufficiently major enough to derail the progress of the change is, therefore, markedly reduced so long as the agreed-upon strategy and data package are delivered.

In addition, ICH Q12 makes it clear that the PACMP need not be confined to one change only. Written well and with the appropriate justification, a PACMP has the potential to cover similar changes multiple times for a single product or similar changes across multiple products. PACMPs are increasingly seen as a useful tool by many agencies and almost as a first step into implementing ICH Q12 globally.

Several pilot programs have included the use of PACMPs, and there is increasing interest in PACMPs across many agencies. Indeed, the use of PACMPs as a transparent and efficient regulatory instrument has been reflected in the European Medical Agency's PRIME toolbox [3] as a useful way to manage the kinds of complex changes envisaged in accelerated development scenarios.

OPPORTUNITIES WITH PACMPS

The ICH Q5E guideline "Comparability of Biotechnological/Biological Products" [4] is widely regarded as a reliable framework for assessing comparability in biotechnological and biological products, such as monoclonal antibody therapies. This framework should be applied to C&GT products, using a risk-based approach that considers their unique characteristics.

Use of PACMPs offers a structured and systematic approach to managing changes in product quality attributes, and specifications, over time.

Due to the innovative nature of C&GTs, flexibility is necessary to maintain high-quality standards because traditional methods of demonstrating comparability may not always be appropriate. It is crucial to adapt and tailor the assessment process to effectively address the specific challenges associated with C&GT products, thus ensuring their exceptional standards are upheld.

Use of PACMPs offers a structured and systematic approach to managing changes in product quality attributes, and specifications, over time. This proactive strategy not only allows for adjustments driven by advancements in manufacturing knowledge but also enhances product adaptability to meet evolving regulatory requirements and patient needs. In this article, we propose transformational use of PACMPs for effective management of specification changes for C&GT products.

Specifications

Current state manufacturing processes for autologous chimeric antigen receptor (CAR) T cell products often result in a large degree of nonconforming results. This is due to the inherent variability in the cellular starting material for the process (i.e., patient material including those with significant illness). Initial specifications of these products are often based on limited clinical experience, resulting in the setting of limits that are frequently not reflective of the process capability.

If an out-of-specification (OOS) result is observed for a patient lot, a quality event is initiated with laboratory and manufacturing process elements investigated. Each batch that generates an OOS result has an individual impact assessment performed. In addition to the impact assessment, batches undergo review through relevant safety and quality committees to assess the manufacturing/testing process in conjunction with the medical status of the patient to determine a recommended action plan for batch disposition determination.

At this point, if the product poses a safety concern to the patient, then the batch is not administered. However, if there is a high degree of confidence that the benefit-risk balance favors continuing with the batch, oftentimes a physician is contacted, and options are reviewed for their decision on acceptability of the material. In the event a physician chooses to still administer the

Figure 1: Illustration of EAP with the FDA.

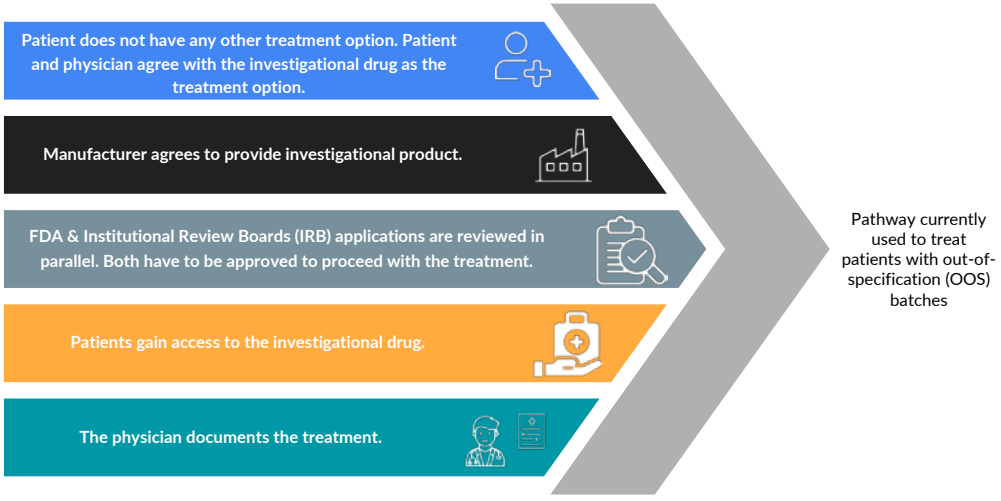
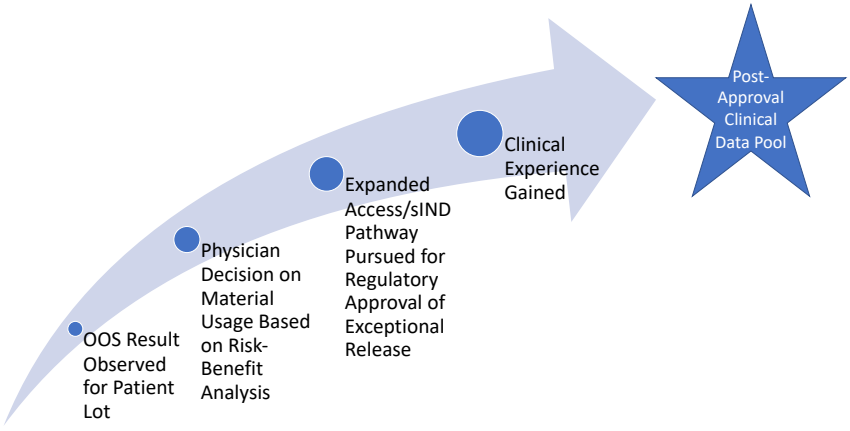


Figure 2: Creation of post-approval clinical data pool from nonconforming autologous CAR T products via EAP/sIND release pathways.



nonconforming product, exceptional release of these batches is often pursued through a single patient clinical protocol (single subject investigational new drug [sIND]) or a managed access or expanded access program (MAP/EAP) of the manufacturer. Such pathways are outlined in 21 CFR 312 Subpart I for "Expanded Access to Investigational Drugs for Treatment Use" [5].

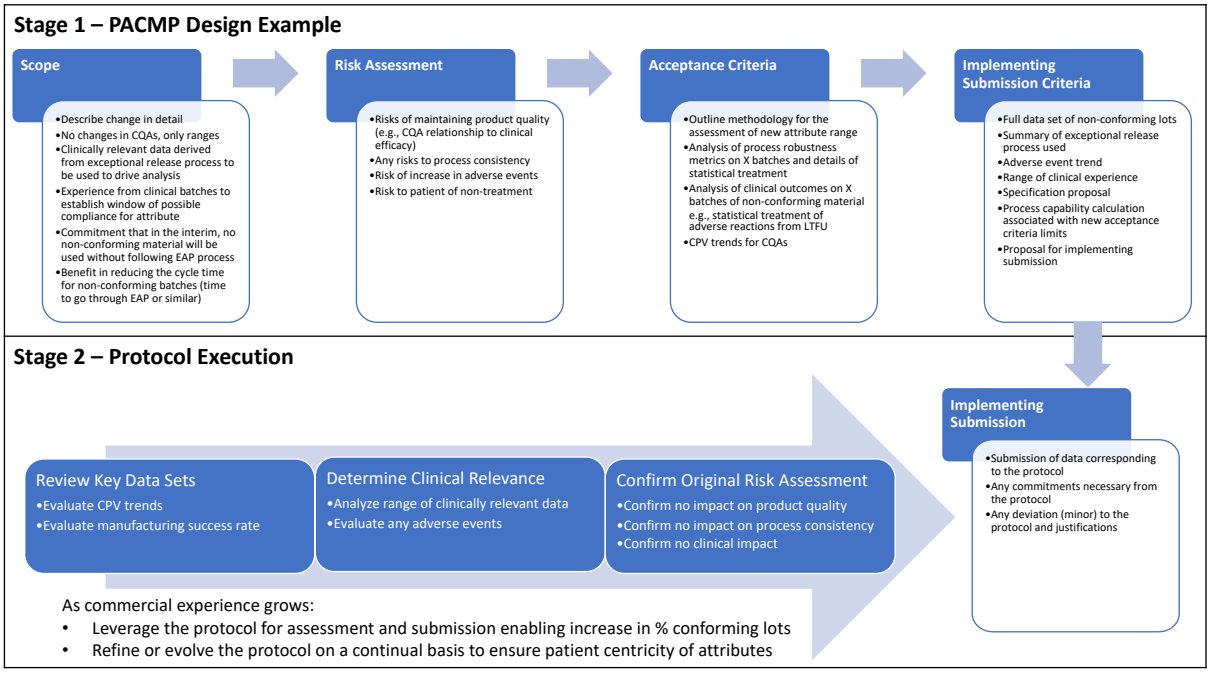
The EAP in the US, summarized in Figure 1, "is a potential pathway for a patient with a serious or immediately life-threatening disease or condition to gain access to an investigational medical product (drug, biologic, or medical device) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available" [6]. Many products in this space are only approved for later lines of treatment, resulting in patient populations that fit this description.

Products that fail the commercial specification can often meet the envelope of specifications used in the clinical investigations, which were the basis for regulatory approval. Additionally, clinical specifications are often established earlier in the product development life cycle and therefore are broader.

As a result, significant effort by companies is often put into the EAP. Through this process, alignment with health care providers (HCPs) and regulators on patient suitability is reconciled with quality/GMP release considerations as quickly as possible to serve the patients in need. Over the course of the product's life cycle, significant data is accumulated for lots outside of the commercial specification. As such, an opportunity presents itself to explore utilization of this data set, where clinically relevant data is accumulated as a direct consequence of continuous process performance and patient need (see Figure 2).

Additionally, the goal of the third stage of process validation is "continual assurance that the process remains in a state of control (the validated state) during commercial manufacture" [7]. An ongoing program to collect and analyze product and process data that relate to product quality must be established [8].

Figure 3: Outline of the proposed PACMP to support specification change for C&GTs.



CPV: continuous process verification; CQA: critical quality attribute

In the instances where exceptional release is pursued for nonconforming CAR T products, a manufacturer can leverage clinically relevant data outside of commercial specification to ultimately expand the specification range of that attribute while demonstrating control. A nonclinical protocol tracking the safety and efficacy performance of these OOS lots can capture this data. This will build the necessary rationale to produce a statistically and/or clinically relevant specification range more reflective of the process capability while demonstrating no patient impact.

A PACMP could be an appropriate way to negotiate changes to specifications leveraging the large and evolving post-approval data gathered on these products. A PACMP could illustrate to an agency how a company intends to use this data to modify the specification. This could be negotiated between the applicant and the agency, and a suitable path forward agreed upon, including the potential to downgrade the implementing submission.

Elements used for specification changes

Having clinically relevant specifications reflective of the true process performance also allows manufacturers to focus resources on more impactful investigations pertaining to true outliers from the process, not marginal OOS events from commercial specifications based on limited data that ultimately have no impact on patient safety and efficacy.

A conceptual outline of a PACMP for this kind of specification change could pull this information together to support a change, as illustrated in Figure 3.

Stage 1 is the design and submission of the protocol proposed for the change. This protocol is structured as follows:

1. Outline the scope of the change in detail. (For example, the scope of the change is limited to the acceptance limit or range for the specification. Critical quality attributes and the analytical methods used for the attribute will not be changed.)
2. Discuss the potential risks in making this change and how these can be mitigated, taking account of the risks and benefits to the patient.
3. Outline the criteria that will be used in the assessment of the change.
4. Propose the contents of the implementing submission and the reporting category.

Stage 2 is the gathering, review, and assessment of the data aligned to the protocol and the subsequent submission of this data to a regulatory agency.

As previously stated, assessing comparability for C&GTs is not simple and can require a combination of both analytical data and some confirmatory data from clinical use. In the PACMP, it would be anticipated that the applicant would illustrate how a justifiable number of batches could be assessed to establish an appropriate range of acceptability. This range of acceptability may be related to either the clinical materials or to a range of OOS material, shown during long term follow-up (LTFU) activities to present low probability of clinical risk to patients. All of this would be outlined with appropriate justification in the PACMP, which is subject to regulatory approval.

Upon accumulation of sufficient data, as agreed on in the PACMP, a specification change (traditionally filed as a prior approval supplement [PAS]) can be pursued as a lower reporting category (i.e., CBE-30). Furthermore, over the course of the product life cycle, as additional data is accumulated as part of the post-approval clinical data pool, additional CBE-30s can be submitted, modifying specifications and enabling a cycle of continuous improvement and understanding of the product.

Given the frequency of nonconforming commercial products in traditional autologous therapies, a future state quality system inclusive of a manufacturing outcomes-based approach is desirable to minimize the need for EAP or sIND avenues. By having clear pathways to establish patient-centric specifications, the burden on sites, HCPs, and patients can be reduced and treatment options can be accelerated.

Furthermore, significant advantages exist pertaining to simplifying the notification process of release for OOS products. By linking this process simplification with a cycle of data collection/specification refinement, great benefit to patients through expanding access to these innovative, lifesaving treatments can be achieved. Future autologous products should consider defining such quality strategies proactively as part of their quality management system (potentially through PACMPs), leveraging risk management principles. Key questions to consider as part of this strategy development include:

- What is the appropriate nonclinical tracking mechanism for patients receiving nonconforming products during LTFU?
- How many data points are needed to justify expansion of commercial specifications?
- The goal of the third stage of process validation is continual assurance that the process remains in a state of control (the validated state) during commercial manufacture. A holistic picture of the manufacturing process and its performance relative to the specifications is needed to justify further modification. What models and/or principles can be applied to further bolster the argument of modifying specifications while maintaining control?
- By implementing a cycle of continuous improvement based on the increasing clinical data pool accrued by nonconformances, how are process changes and improvements being factored in to reduce and ultimately eliminate the need for such a cycle?

Life Cycle Management

The rapid advancement of scientific understanding within the pharmaceutical sector has paved the way for ground-breaking modalities like C&GTs and personalized medicines. However, this surge in innovation is placing increasing strain on the current process of justifying specifications between health authorities and applicants.

The rapid pace of scientific advancements necessitates an alternative approach to effectively navigate the evolving landscape of pharmaceutical development and regulatory processes. Typically, numerous C&GTs are approved for the market with a limited data set and on a small scale. Consequently, changes are bound to occur as more data is gathered about the product, as the manufacturing process is improved, and as the scale of production expands.

The scientific knowledge that the pharmaceutical industry is gaining in the field of C&GTs opens possibilities for increased collaboration between industry and regulators. This collaboration can result in the formulation of specifications that prioritize the quality, safety, and effectiveness of new medicines, ultimately meeting the needs of extremely ill patients.

Additionally, it can play a vital role in establishing resilient supply chains, enhancing the accessibility of these medicines for patients in need. Due to the limited number of clinical lots and process characterization data available during the submission stage of C&GTs, regulators and industry may collaboratively set interim commercial specifications.

These specifications are determined based on the potential risks to patients and are supported by existing knowledge. This approach allows for the launch of the product while ensuring patient safety, with the understanding that further data and refinement will be undertaken as more information becomes available.

The adoption of patient-centric specifications, which incorporate scientific knowledge and insights gained throughout the development and life cycle of a pharmaceutical product as a standard in pharmaceutical manufacturing of C&GTs, offers a dual benefit for both industry and regulators. By aligning the objectives of ensuring quality patient care and optimizing manufacturing efficiency and control, patient-centric specifications contribute to a win-win situation for all stakeholders involved.

The concept of reusing well-designed PACMPs, as discussed in ICH Q12, holds particular significance for C&GTs. These PACMPs can serve as a framework in the absence of specific guidance, providing a general understanding of how comparability will be addressed. Although certain cases may require more specific protocols, having an agreement on broad terms for comparability can still prove to be a valuable tool. This approach promotes efficiency and consistency in assessing and ensuring the comparability of C&GTs throughout their life cycle. The implementation of a PACMP offers several advantages for applicants. It allows them to:

- Define the level of risk associated with a change or multiple changes in relation to patient safety
- Use their knowledge and expertise to demonstrate how the impact of a change can be assessed, providing insights into the management of residual risks
- Determine appropriate tests to be conducted to evaluate the change, as well as establish suitable boundaries for these tests and provide rationale for their selection
- Reach an agreement with the competent authority on the strategy for managing the change, along with the reporting category for subsequent confirming data. This approach fosters certainty for both the applicant and the reviewer, enabling improved planning and execution of changes throughout the product life cycle
- Facilitate continuous improvement to ensure ongoing patient supply

CONCLUSION

C&GTs are a vital and growing part of the modern approach to therapy. The tools outlined in ICH Q12 provide insights into how this post-approval data could be used to facilitate change for these products. In particular, the PACMP could be used to leverage ongoing monitoring data in transparent discussions with agencies and thereby progress changes in an efficient manner, ultimately providing a mechanism to maintain products in a state of control and ensure a continuous supply to patients.

C&GTs are generally produced in small batch quantities, necessitating the production of multiple batches to adequately support early phase clinical trials. As the product advances to the commercialization stage, the demand for C&GT batches significantly rises due to data generated from a larger patient pool, thereby providing opportunities to enhance knowledge on the relationship between product quality attributes and clinical outcomes.

The generation of a substantial database during the life cycle management of C&GTs serves as a crucial resource, enabling the justification of post-approval changes and facilitating the continuous improvement of the product. Moreover, the combination of data from chemistry, manufacturing, and controls (CMC), and patient experience provides compelling evidence that any manufacturing changes do not have an adverse impact on the product.

The establishment of data ecosystems becomes imperative as an extensive volume of data is continuously being gathered, aiming to a future state where correlations between CMC and clinical data can be identified. Implementing suitable data and analytics ecosystems, such as those facilitated by artificial intelligence, will make it feasible to monitor and compare safety, efficacy, and patient benefits with corresponding product quality information. This integrated approach ensures a comprehensive understanding of product performance and supports a high-level analysis to facilitate life cycle management.

The PACMP presents a unique opportunity for collaborative efforts between the industry and regulatory agencies to streamline life cycle management. This initiative aims to identify pertinent CMC and clinical data, fostering the establishment of an effective platform for improved communication between regulators and the industry.

A crucial aspect of this endeavor is to encourage the adoption of industry best practices. This ensures the collection of comprehensive information throughout the product life cycle and establishes strong connections between the data and clinical outcomes. By joining forces, stakeholders can proactively enhance the understanding of product performance, safety, and efficacy, which leads to more efficient and informed decision-making processes.

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IN-SILICO DATA-DRIVEN MECHANISTIC MODEL–ASSISTED Process Validation

By Rui Wheaton, PhD, Ahsan Munir, PhD, Sri Nikhil Gupta Gourisetti, PhD, Austin D. Dixon, PhD, Tyler D. Huber, PhD, Ryan R. Davis, PhD, and Brian To, PhD

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The US Food and Drug Administration (FDA) advocates for the integration of quality by design (QbD) principles throughout the pharmaceutical product development landscape, aiming to elevate both process understanding and product quality. Key challenges to the process control strategy include navigating time- and resource-intensive processes. One solution is digital shadow technology which, when constructed using mechanistic models, offers many benefits throughout the product life cycle.

Successful QbD implementation requires a comprehensive understanding of the intricate relationship between critical quality attributes (CQAs), critical performance indicators (CPIs), key performance indicators (KPIs), and variability in process parameters and raw materials [1].

The essential milestones and objectives for achieving QbD include [2, 3]:

- Defining CQAs, CPIs, and KPIs and their acceptable ranges and identifying process parameters, material attributes, and the ranges that influence them
- Establishing process understanding on how process input parameters impact CQAs, CPIs, and KPIs
- Formulating control strategies and process capability

CHALLENGES TO THE PROCESS CONTROL STRATEGY

One of the most formidable challenges on the path to developing the process control strategy lies in the demanding and resource-intensive nature of wet lab experimental process characterization studies (PCS). At the core of this process, the design of experiments (DOE) emerges as a pivotal tool, empowering the development of process knowledge while uncovering the complex multivariate impact of process parameters to product quality and process performance.

Following the design of these experiments, the lab work commences; the scale of the experimentation is typically quite significant, which reflects the complexity of the process tool. For example, a unit operation with five potential process parameters requires around 50 runs to effectively encompass quadratic effects and multivariate interaction effects. Furthermore, even more runs can be required to define the process parameter range used to define the DOE. These runs entail a substantial time investment. For example, each chromatography unit operation can take approximately five to eight hours to finish.

In addition, extensive resources are also required to generate feed materials for the PCS and qualify analytical methods to test PCS samples. This poses a significant challenge and concern to company resources, considering a complete manufacturing process typically includes six to nine unit operations. In some instances, when a different product or process follows similar pathways, a cost-effective "platform" approach is used to streamline process validation and minimize development expenses. When implementing this approach, it is essential to ensure the common elements identified are truly applicable to various products, without compromising the unique characteristics of each product.

Another hurdle encountered by clinical and commercial manufacturing is impact assessments due to process-related deviations. Historically, root cause analysis and process/product assessment heavily relied on the process knowledge of subject matter experts (SMEs), but it takes time for SMEs to acquire the appropriate knowledge. In some cases, the process experience is tacit knowledge that is difficult to transfer to others. This can be detrimental to the manufacturing process because inaccurate

conclusions may result in additional deviations reoccurring in subsequent cycles or batches if process history and knowledge are not well maintained.

To target these challenges, this article explores the strategic integration of digital shadow technology into various stages of process validation by defining a digital shadow–assisted process validation framework. A highlight of the article is the demonstration of a powerful surrogate model through the fusion of digital shadow technology and statistical methodologies, which enables more efficient and accurate process characterization.

Digital Strategy (Digital Shadow) with In-Silico Models

As the biopharmaceutical industry embraces Industry 4.0, more options are emerging to address these challenges, with the concept of a digital shadow emerging as a disruptive tool. This concept encompasses a system-level, in-silico model that has proven itself as a predictive powerhouse for evaluating process dynamics and performance. Regulatory authorities have also encouraged the integration of mathematical models to support bioprocess development and manufacturing efforts, leading to a surge of studies centered around in-silico models [4].

Statistical and Mechanistic Modeling

Under this concept, two predominant modeling techniques provide the in-silico framework: statistical modeling and mechanistic modeling. Statistical models exhibit exceptional computational efficiency and facilitate automation, thus positioning them as ideal tools for real-time process monitoring and control. However, their predictive scope must be confined to the validated operating space, necessitating a substantial amount of experimental data for model training [5]. In contrast, mechanistic models are rooted in physical and biochemical principles. They have been a standard method in chemical engineering for decades and continue to advance within the biopharmaceutical industry [6, 7].

Mechanistic models afford profound and scientific process understanding derived from principles governed by natural laws. This imparts longevity to their validity and extends their utility beyond the range of the design space used for model calibration. Consequently, mechanistic models emerge as robust tools for process optimization, deviation analysis, scale-up/-down studies, and process characterization [8]. Furthermore, the number of experiments required for model calibration and validation is substantially lower than statistical models, showcasing the additional benefit of efficiency and resource economy.

Surrogate Models

In PCS, statistical analysis plays a crucial role in determining how process input parameters impact CQAs, CPIs, and KPIs. A surrogate model is a combination of both modeling methods. In this approach, a mechanistic model is used to assist in conducting DOE studies alongside laboratory experiments. The result is then input into a statistical model for data analysis, leading to the formulation of prediction expressions for CQAs, CPIs, and KPIs. The surrogate model harnesses the advantages of both modeling methods while mitigating their respective limitations.

As the biopharmaceutical industry embraces Industry 4.0, more options are emerging to address these challenges, with the concept of a digital shadow emerging as a disruptive tool. This concept encompasses a system-level, in-silico model that has proven itself as a predictive powerhouse for evaluating process dynamics and performance.

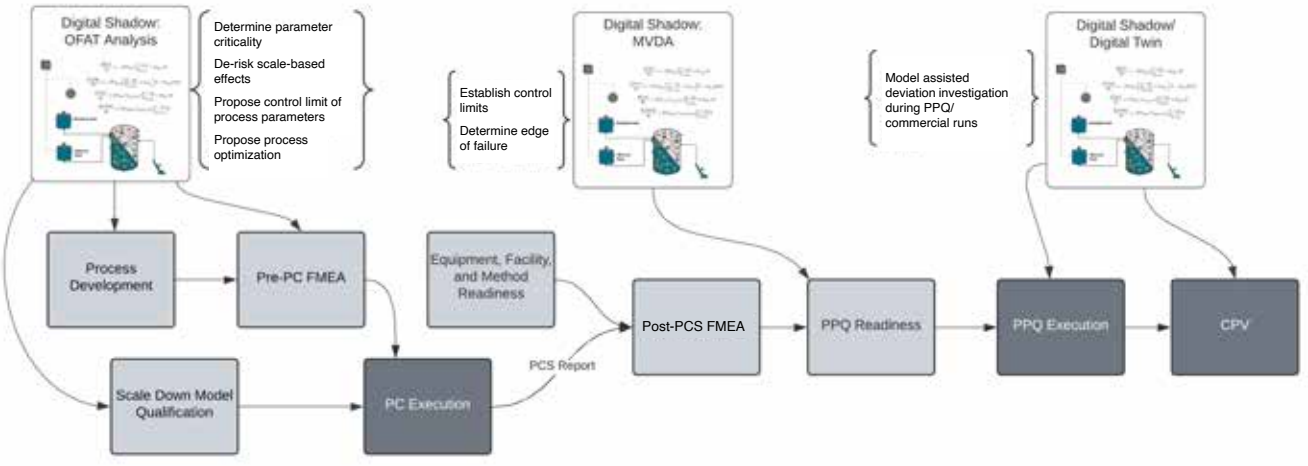
DIGITAL SHADOW–ASSISTED PROCESS VALIDATION

To achieve the milestones in QbD, a robust and systematic process validation framework is imperative and would include [9]:

- Process design with scaled-down models
  - Design production process and process control to ensure that the drug substances/products meet safety, identity, strength, purity, and quality targets
  - Build and maintain process knowledge and understanding
- Process qualification with at-scale runs
  - Demonstrate the process can consistently produce drug substances/products with target product qualities
  - Demonstrate that the commercial manufacturing process can consistently meet the predetermined process performance with the established process control strategy
- Continued process verification during commercial operations
  - Continued assurance that the process remains in a state of control (the validated state) during routine commercial manufacturing.

In many of the previously mentioned steps, a digital shadow can be implemented alongside lab work to significantly reduce the resources needed to improve process understanding and establish process control strategy. We propose a digital shadow–assisted process validation framework, which is shown in Figure 1.

Figure 1: Digital shadow–assisted process validation framework for a cation exchange chromatography (CEX) unit operation.



OFAT: one factor at a time, MVDA: multivariate data analysis, PPQ: process performance qualification, PC: process characterization, FMEA: failure mode and effects analysis, CPV: continuous process verification

The steps in the process validation workflow where digital shadow assistance can be beneficial are highlighted:

- Process characterization: This step includes process development, scale-down model qualification (SDMQ), and pre-process characterization failure mode effect analysis (FMEA). Digital shadow can be employed for process optimization, determining parameter criticality, defining initial process control strategy, and scale-based effects de-risking.
- Process performance qualification (PPQ) readiness: Digital shadow can assist in establishing control limits and identifying edge-of-failure.
- PPQ execution and continuous process verification: Digital shadow can be used for deviation investigations.

Further details on these functions will be elaborated on in the following sections.

USING DIGITAL SHADOW IN PROCESS DESIGN

The first stage of process validation is process design, and a successful validation program depends on information and knowledge from process development, clinical, and/or engineering runs.

Typically, the process design phase involves the following key steps:

1. Identification of critical aspects: Identify CQAs and CPIs/KPIs and their corresponding specification limits.
2. Parameter mapping: Identify the potential critical process parameters, key process parameters, critical material attributes, and key material attributes.
3. Model scaling: Design a scale-down model (SDM) and demonstrate that it is representative to the eventual operations at the commercial scale.
4. Design of experiments: Formulate a comprehensive DOE and execute it with the qualified SDM.
5. Statistical insight: Employ statistical analyses to identify the criticalities and relationship of the process parameters.
6. Control strategy formulation: Develop the control strategy based on outcomes of the DOE and process knowledge.

Defining the In-silico Model for a CEX Unit Operation

In the digital shadow–assisted process design, the in-silico model needs to be defined. The steps for defining the model are shown in Figure 2.

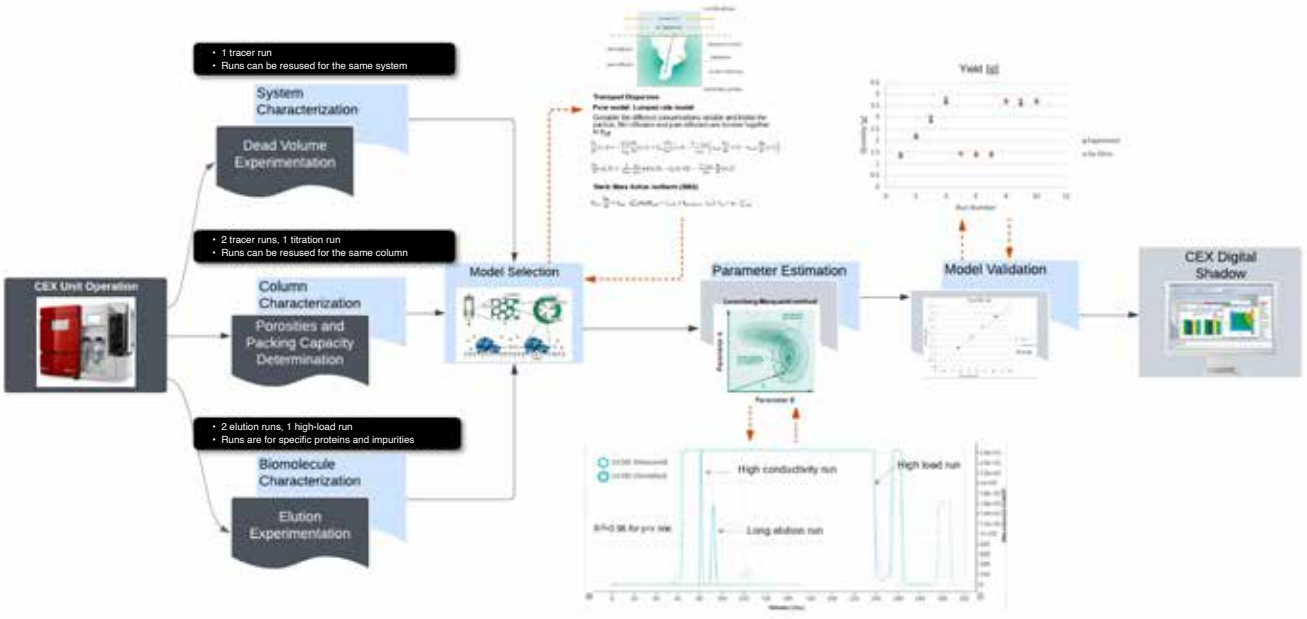
1. System, column, and biomolecule characterization: Several initial experiments are needed as the first step to gain system-, column-, and biomolecule-level understanding.
2. Model selection: The complexity of the model is subsequently determined by specifying the mass transfer assumptions in the mobile phase and stationary phase. This step will determine the calculation time and model accuracy.
3. Parameter estimation: Experimental results are used to calibrate/train the model through parameter estimation.
4. Model validation: A new set of experiments is used for model validation by running the model with the corresponding process parameters (e.g., load capacity, impurity concentration) and comparing simulation results and experimental data (e.g., yield, purity).

Unit operation characterization

In chromatography, three levels of unit operation characterization need to be done for model calibration and validation:

1. System-level characterization: One tracer run is needed for dead volume calculation.

Figure 2: Steps for digital shadow development shown for a CEX unit operation.



2. Column-level characterization: Two tracer runs are needed for the porosity determination and one titration run is needed for ionic capacity.
3. Biomolecule-level characterization: In most cases, two elution runs and one high-load run are needed for isotherm parameter calibration.

Of all the experiments required, the tracer runs can be performed rapidly and do not need to be repeated for different products, assuming that the same system and columns are used. The elution runs, however, are unique to different products and impurities as they provide information on the physiochemical interactions of the protein and resin.

As the application of mechanistic models is not constrained by the model calibration design space, experiments conducted under any process condition can be used for model validation. For instance, experimental runs conducted during the process development stage can be directly applied, eliminating the need for additional experiments.

Following the validation of the model, it transforms into the digital shadow for this unit operation. A complete digital shadow–assisted process characterization platform is shown in Figure 3.

Digital Shadow–Assisted Process Characterization

After the digital shadow is set up, it can be employed to offer recommendations for the DOE design space with initial runs. Subsequently, an I-optimal DOE is structured to capture both the quadratic and interactive effects of process parameters. The digital shadow is then used to execute the experiments within the DOE.

Building a Surrogate Model

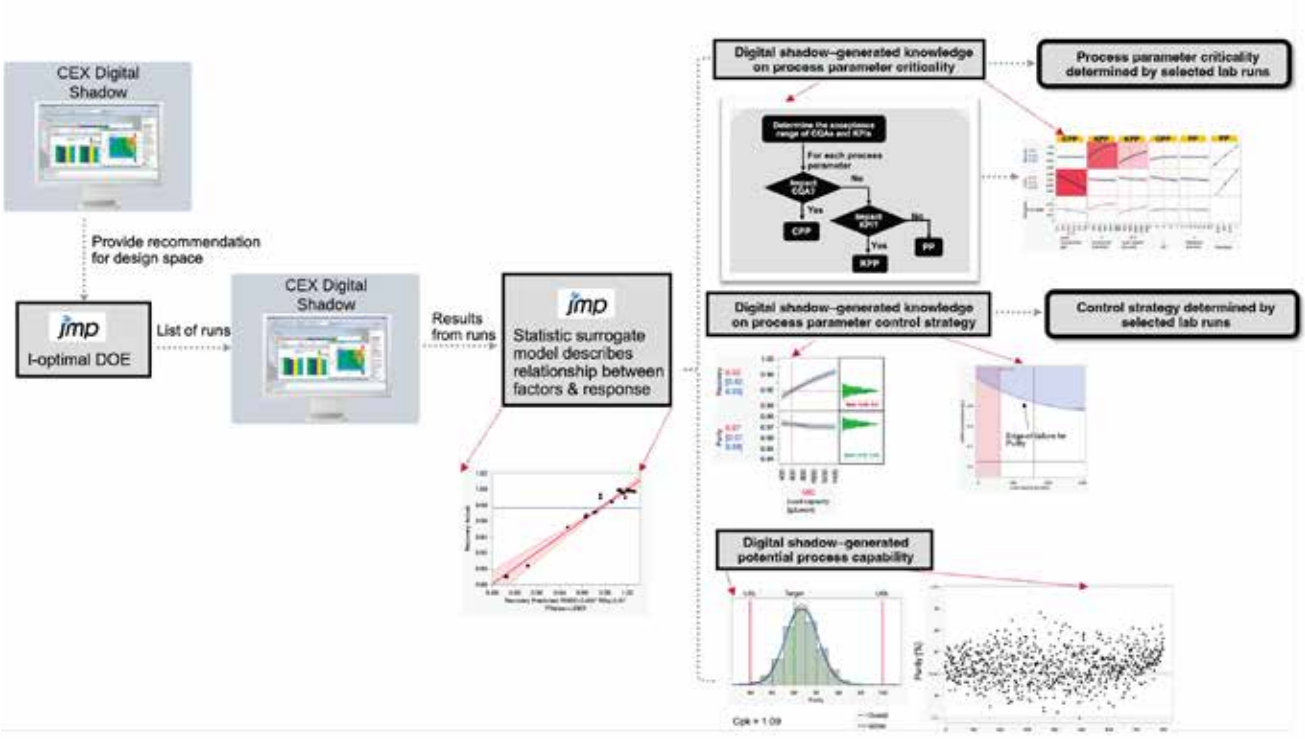
The results from the in-silico runs can be used to build a surrogate model with statistical methods that describe the relationship between the process parameters and, hence, how the process responds to variations in process input parameters. With this in-silico process, the criticality of the process parameters on performance and quality attributes can be evaluated. This approach provides mechanistic understanding for optimizing lab experiment selection, enabling efficient acquisition of valuable results with a minimal number of lab experiments.

The surrogate model can also be used to predict the proven acceptable ranges of the critical process parameters and key process parameters, and then the predicted proven acceptable ranges are confirmed with lab experiments. On top of the impact of single parameters, the surrogate model can also reveal the significance of multivariate interactions. In situations where significant impacts are identified, an edge-of-failure analysis can be carried out. Lab experiments can then be conducted at the identified edge-of-failure parameters to confirm the outcomes from the surrogate model and to make the final refinements to the control strategies. With this approach, the amount of effort, cost, and time needed to develop the process validation control strategy can be reduced by 75% compared to a pure lab-based approach [10].

Expected Process Capability Analysis

Upon finalization of the control strategy, the digital shadow can also be used to generate an expected process capability analysis. Employing the Monte-Carlo method, a series of random runs with different combinations of process parameter values within the control strategy can be generated and evaluated with the digital

Figure 3: Digital shadow–assisted process characterization platform.



shadow. The outcomes from these runs will then be used to conduct a comprehensive process capability assessment.

BENEFITS OF EXECUTING PCS WITH DIGITAL SHADOW

Executing PCS with the assistance of digital shadow is expeditious. With the knowledge gained from in-silico runs, the amount of lab work can be significantly reduced, and the in-silico run time is negligible. Typically, a model-assisted DOE can reduce 40%–80% of experiments needed in the upstream domain [11]. This provides a significant advantage compared to the conventional practice today that exclusively relies on resource-intensive wet lab experiments for the entire DOE design space.

Oftentimes, PCS works in industry are constrained by limited resources, resulting in a DOE with low statistical power. This, in turn, necessitates more runs during PPQ. However, with the help of digital shadow, the quality of the DOE can be significantly improved with the same resource level, ultimately reducing the number of runs required for PPQ. In cases where a "platform" approach is employed, the digital shadow is also a cost-effective and time-saving tool to identify the commonalities and unique properties of new products.

DIGITAL SHADOW IN PROCESS DESIGN AND SCALE-DOWN MODEL QUALIFICATION

SDMQ is critical for process characterizations. Traditionally, both lab-scale and at-scale runs would be performed and data from both scales is analyzed statistically to assess any scale-induced disparities.

With the digital shadow–assisted SDMQ, a digital model for commercial-scale unit operation needs to be defined. As the process scale changes, there are direct impacts on the fluid dynamic effects caused by differences in equipment geometries. To illustrate in the context of chromatography, columns with identical bed height and smaller inner diameter are normally used as SDMs. In this scenario, column differences (like wall effects, or flow distribution and radial dispersion effect differences) and system differences (like pressure profile or precolumn dispersion and system flow path differences) may lead to different column performance such as peak shape, step yield, and impurity clearance.

It is important to recognize that although fluid dynamic effects are scale dependent, thermodynamic elements (such as protein-resin adsorption isotherms) remain invariant. As a result, while implementing a mechanistic-based digital shadow, the adsorption model parameters derived from lab-scale calibration experiments can be directly transferred to the commercial scale, requiring only the calibration runs to characterize system and column levels [12, 13].

In the case of an observation of discrepancies during chromatography SDMQ, an offset is commonly applied to the SDM. The defined digital shadow with both scales can then assist in the mechanistic understanding of the scaling impact reflected by the

offset parameter. One example is from the study by Benner et al [14]. It uses a mechanistic model to elucidate the impact of scale on elution pool volume by systematically analyzing the mass transfer phenomenon under different scales. Leveraging the Peclet number (Pe), the study yielded a fundamental insight of relative significance of axial dispersion vs. convection across different scales.

DIGITAL SHADOW IN PPQ AND CONTINUED PROCESS VERIFICATION

Process-related deviations that occur during PPQ runs and routine commercial manufacturing could impact product quality and/or process performance. For example, in chromatography, factors including column life cycle and process variation can lead to atypical chromatograms, resulting in poor product purity or yield [15]. In instances of such deviations, the root cause must be identified swiftly to facilitate corrections in subsequent cycles or batches.

Following the process design, a digital shadow for the commercial unit operation has already been built and validated. Once validated, the digital shadow can be used to support process and/or product impact assessments, which are important elements in process-related deviation investigations. The first step of root cause analysis (RCA) is implementing a tool like a fishbone analysis to identify the potential parameters that might be the underlying cause of the deviation. After the parameters are identified, an inverse modeling method can be employed. This involves systematically altering these identified parameters within the digital shadow to align with the observed unit operation performance thus discerning which factor or factors potentially led to the deviation [16].

Furthermore, deviations occurring in a unit operation may stem from variances originating from a preceding unit operation. As a library of digital shadows of distinct unit operations are established for the process, they can be interlinked into an end-to-end, process-level digital shadow. This model can be employed to evaluate how the process parameters of one unit operation influence the outcomes of another. The same inverse modeling method can be used to identify root causes in the connected digital shadow.

RCA is a vital part of continuous process improvement, aimed at identifying and addressing underlying inefficiencies or weaknesses that hinder process optimization and product quality. One of the primary objectives of RCA is the implementation of corrective and preventive actions (CAPAs), which serve to address immediate issues and prevent their recurrence.

Through the application of CAPAs, a more stable and dependable manufacturing process is created. Furthermore, the process understanding gained during RCA, particularly when using the digital shadow for RCA, paved the way for ongoing process refinement. This understanding can be extrapolated not only to rectify the deviating processes but also to enhance other processes, thereby facilitating continuous enhancements.

CONCLUSION

A digital shadow constructed using mechanistic models offers many benefits and advantages across various stages of the product life cycle. Once the model is established and validated, its utility spans the entirety of the process validation cycle and commercial production, creating a rigorous scientific approach with improved mechanistic understandings. This results in an elevated assurance of product quality while significantly reducing the cost of goods sold (COGS).

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CONTINUOUS BUFFER MANAGEMENT SYSTEM:

Large-Scale Buffer Preparation

By Zuwei Jin, PhD

Although traditional tank farm systems have long been the cornerstone of buffer preparation, they face challenges that have grown with the expansion of processing scale in the industry [1–4]. This article explores the concept of the continuous buffer management system (CBMS) as an alternative to traditional buffer tank farm methods. We analyze the historical progression of buffer preparation, highlight the advantages and challenges of the CBMS, and present an overview of its hardware components, system design, and process control strategies to demonstrate the viability of the CBMS as a robust and cost-effective solution for biopharmaceutical buffer management at production scale.

In the realm of biopharmaceutical downstream processing, the continuous pursuit of technological advancements has given rise to innovative approaches that redefine conventional practices. One such transformative development could be the CBMS, a revolutionary departure from traditional tank farm methods. We explore the multifaceted landscape of the CBMS, shedding light on its inception, evolution, and transformative impact within the biopharmaceutical industry.

Recognizing the limitations of these conventional methods, the introduction of inline dilution skid technology marked a significant leap toward more streamlined and efficient buffer management [2]. However, it was the CBMS that truly set the stage for a possible paradigm shift in how buffers are prepared and used in the biopharmaceutical industry. A CBMS is essentially a dynamic form of a buffer tank farm. Instead of using large hold vessels, it uses much smaller vessels called relay tanks (usually less than one-tenth the size of the hold vessels). These are filled by an inline mixing/dilution-based skid, enabling many economic and operational benefits [5].

This article aims to illuminate the path that led to the emergence of a CBMS as a possible disruptive force in the field. By going back to its historical development, we trace the evolution of buffer preparation technology. Our exploration will unveil the economic and operational benefits that a CBMS offers, providing valuable insights into how this novel approach has the potential to revolutionize buffer preparation support in the processing industry.

THE EVOLUTION OF BUFFER PREPARATION TECHNOLOGY

The evolution of buffer preparation technology within the biopharmaceutical industry has been a dynamic journey, marked by significant transitions from traditional methods to more innovative approaches. There are three main technologies related to this journey, as shown in Figure 1.

Traditional Buffer Tank Farm

In the early stages of biopharmaceutical manufacturing, the prevailing method for buffer preparation was the traditional tank farm system. These systems resembled chemistry laboratories with large-scale vessels akin to oversized beakers and flasks. Buffers were premade and stored in substantial vessels, each designed to accommodate the specific process it supported.

Following each use, these vessels underwent rigorous cleaning-in-place (CIP) and sterilization-in-place (SIP) procedures to ensure product integrity. Although this method serves its purpose, it becomes more challenging to operate as the scale of vessels expands, with some processes requiring vessels as large

Figure 1: Historical perspectives on buffer preparation technology.

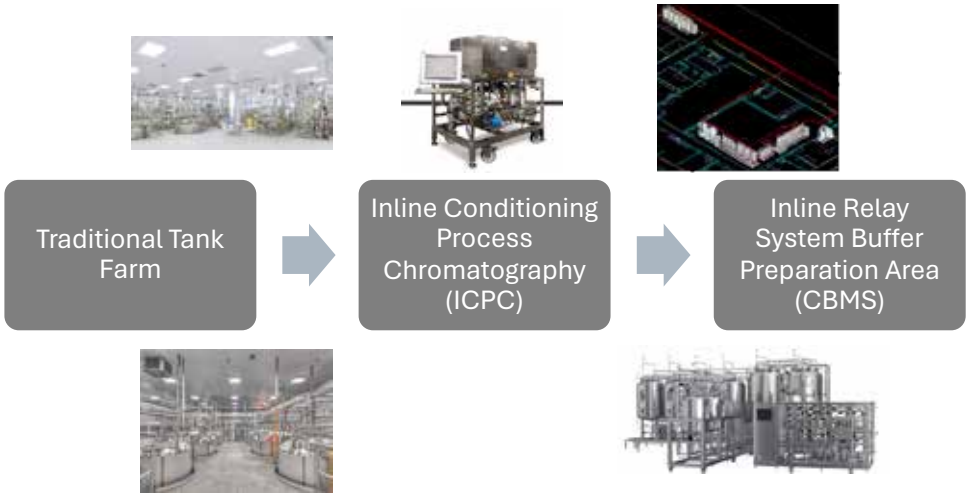


Figure 2: A typical CBMS before delivery.

as 20,000–30,000 liters to support commercial production of chromatography processes [2, 3].

Introduction of Inline Dilution Skids

Approximately 20 years ago, the industry saw a significant shift with the introduction of inline dilution skid technology. This innovative approach aimed to address the limitations of traditional tank farm systems by facilitating the inline mixing of concentrated buffer solutions with a significant volume of water for injection (WFI) at the point of use [3].

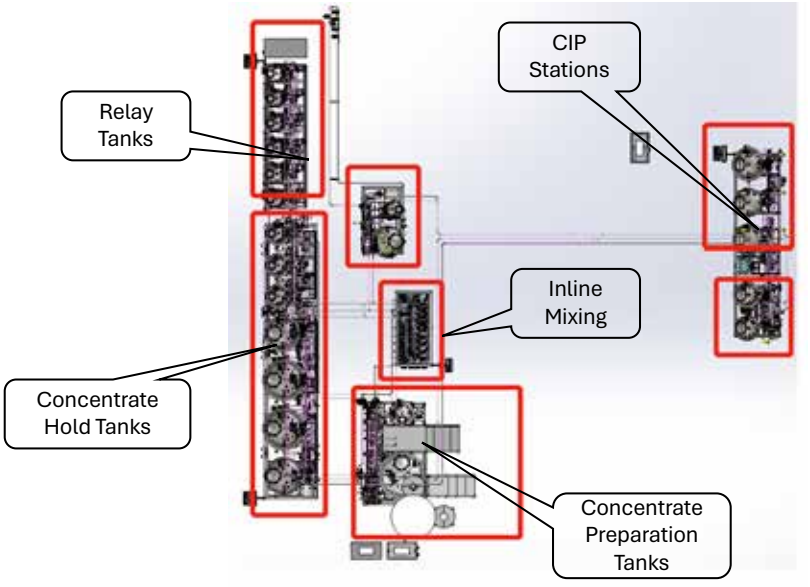
This method marked a departure from the large vessels used in traditional buffer tank farms, replacing them with smaller, more efficient systems. Inline dilution skids allowed for the combination of specific processes with the associated buffer preparation, commonly referred to as inline conditioning process chromatography (ICPC). This marked a notable improvement in efficiency and a reduction in the physical footprint required for buffer preparation, which led to tremendous cost saving [3].

Emergence of the CBMS

The culmination of the evolution of buffer preparation technology has led to the development of the CBMS, as shown in Figure 2. Unlike the preceding inline dilution skids, the CBMS represents a more profound departure from the traditional buffer tank farm concept [5]. Rather than integrating buffer preparation with specific processes, the CBMS uses inline mixing technology to prepare buffers for an entire buffer preparation area.

This is achieved through a series of small vessels known as relay tanks, which can be likened to the shift of playing videos from DVDs to network streaming. In this analogy, traditional tank farms are akin to playing videos from DVDs, while the CBMS operates like a video streaming service. The relay tanks, managed by an inline mixing system, ensure that each vessel remains consistently filled for use. By emulating the functionality of the larger vessels in traditional buffer tank farms, the CBMS allows seamless integration of itself into existing downstream processes. A more in-depth exploration of the benefits and technical aspects of the CBMS as a

Figure 3: Functional modules in a CBMS.



possible transformative solution in biopharmaceutical downstream processing is provided next.

BENEFITS OF THE CBMS

The adoption of the CBMS represents a significant leap forward in biopharmaceutical downstream processing. In this section, we delve into the benefits offered by the CBMS, emphasizing its economic, operational, and potential regulatory advantages over traditional buffer tank farm systems.

Capital Savings

One of the foremost advantages of a CBMS is its potential to revolutionize the economics of buffer preparation in the biopharmaceutical industry. By transitioning from large traditional buffer tank farms to a more compact and efficient CBMS, substantial cost savings can be achieved [1–4, 6] The significantly reduced vessel sizes contribute to a dramatic decrease in capital investment. It is reasonable to expect savings of up to 60% in capital expenditure simply based on the reduction of current GMP (cGMP) space required for the vessels when compared to the traditional buffer tank farm setup [6]. This is a remarkable shift in cost dynamics, allowing biopharmaceutical companies to allocate resources more efficiently.

Operational Savings

Beyond capital savings, a CBMS enhances the operational efficiency of buffer preparation. The smaller vessels, combined with precise inline mixing and control strategies, lead to a considerable reduction in operating costs. The power consumption, reagent usage, and chemical consumption related to CIP and SIP processes are all significantly diminished due to the smaller vessel sizes, resulting in substantial long-term cost savings in the range of 20% to 50% [2, 6, 7].

Enhanced Batch Documentation

A CBMS leverages automation to streamline and minimize manual operations associated with traditional buffer preparation methods. The adoption of a distributed control system (DCS) platform provides better data logging and data integrity, resulting in improved batch documentation. The precise control and real-time monitoring capabilities offered by the CBMS ensure that data related to buffer preparation is more accurate and easily accessible.

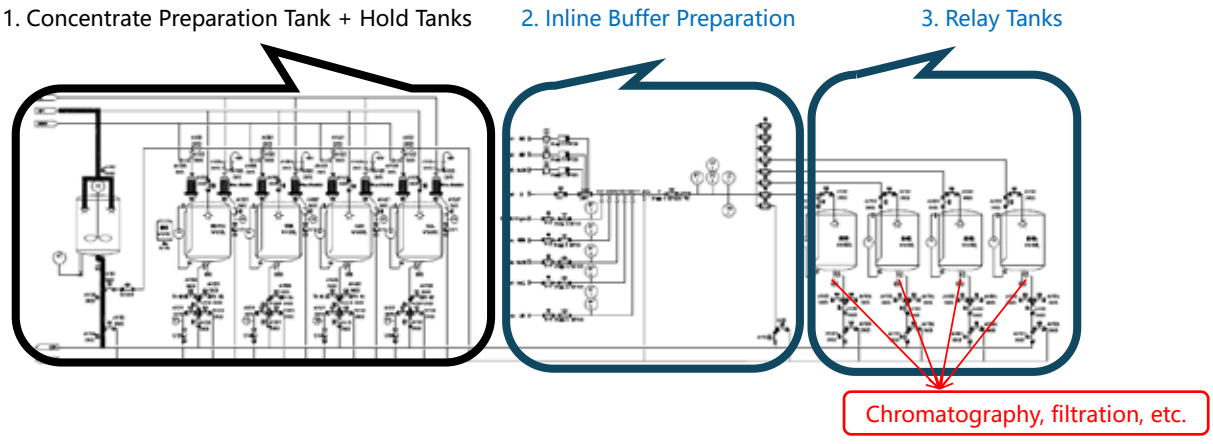
Expansion Versatility

Whether for greenfield projects or the expansion of existing cGMP facilities, a CBMS's small footprint proves an indispensable option for buffer preparation. The CBMS emerges as a versatile and economically advantageous alternative to traditional buffer tank farm systems. Its impact extends beyond cost savings to encompass enhanced operational efficiency, improved batch documentation, and regulatory compliance.

TECHNICAL CHALLENGES OF BUILDING THE CBMS

The development of a CBMS is a relatively complex endeavor that presents several technical challenges especially for the skid manufacturers of many original equipment manufacturers (OEMs). This section outlines these challenges and their intricacies.

Figure 4: Complexity of system design for a CBMS.



System Design

CBMS design encompasses multiple modules, including inline mixing, relay tanks, concentrate hold tanks, and in/out valve matrixes—not to mention devices/IO (input/output) from different vendors, which involves compatibility and integration challenges (see Figure 3). Depending on how concentrates are provided, concentrate prep tanks and CIP stations could also be part of a CBMS. Unlike standard skid-based systems, the CBMS's scale and intricacy make it an overwhelming undertaking for most OEM manufacturers. The management of pumps, valves, flow meters, analytical instruments, pipes, and connectors must also meet stringent hygienic standards such as the American Society of Mechanical Engineers (ASME) standard for Bioprocessing Equipment (BPE) to maintain product integrity and safety [8].

Flow Rate Control

A critical challenge in CBMS development is the precise control of flow rates of each mixing stream in the CBMS. Flow rate accuracy is a pivotal factor in determining the specifications of buffer solutions. Achieving this level of precision in flow rate control necessitates advanced hardware design expertise, fluid dynamics know-how, and an understanding of hygienic principles. In addition to flow control precision at its stabilized state, the flow control loops need to perform in a way that is free from pressure and flow disturbance in the system, which is paramount for practical application of CBMS.

Process Control

Unlike simpler skid-based systems, CBMS involves managing various units and modules, which requires coordination and communication. Each unit in the system must harmoniously interact with others and downstream process units to ensure smooth operation and inter-operations. The complexity arises from the need to manage numerous variables as well as multiple layers of functionality across these units. A more powerful control platform such as a DCS with batch management functionality would be required for a CBMS and innovative control strategies are keys to making a CBMS a practical solution.

Alignment with Plant Layout

The ability to tailor the system to the physical constraints and requirements of a given facility is a crucial aspect of CBMS implementation. Many OEMs lack the engineering capability to adapt such a solution to specific layout of individual plants.

Process Configuration

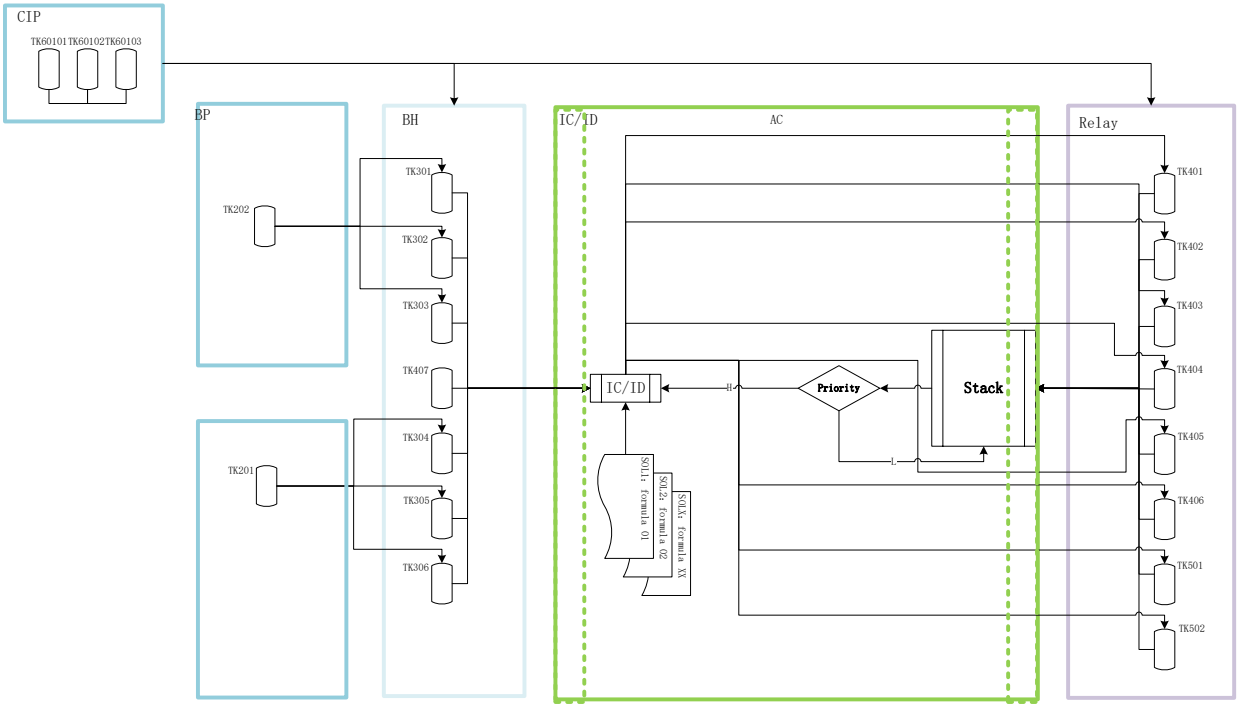
The CBMS's innovative use of relay tanks and the control strategies that enable efficient buffer filling are pivotal to its success. However, these key process concepts were not available until recently. The idea of using relay tanks to decouple buffer preparation from specific processes and the control strategies that ensure reliable buffer filling in multiple relay tanks are a paradigm shift in inline mixing buffer preparation.

The technical challenges associated with building a CBMS are multifaceted and include system complexity, flow rate control, hardware design, process control strategies, plant layout alignment, and the necessity of novel process concepts. Overcoming these challenges has been instrumental in making the CBMS a practical and robust solution.

COMPLEXITY OF SYSTEM AND HARDWARE

The hardware design of the CBMS plays a pivotal role in ensuring the system's effectiveness and reliability [3]. Additional intricate details of the CBMS hardware are discussed in this section.

Figure 5: CBMS running as a service through a S88 batch recipe.



Inline Mixing Module

The core of the CBMS's hardware design is the inline mixing module (see Figure 4). This module leverages advanced technology to blend concentrated buffer components with WFI to create ready-to-use buffer solutions. Ensuring accurate and reliable flow rates is essential for achieving the desired specifications of buffer solutions. Flow control loops—involving a series of diaphragm or rotary lobe pumps, high accuracy mass flow meters, and control devices—are intricately designed to maintain precise flow rates under dynamic conditions.

Inline monitoring instruments such as pH and conductivity meters are usually mandatory to ensure the buffer stays within the specification in real time. Out-of-specification buffer will be diverted to waste immediately and a warning will be issued by the CBMS. Besides inline monitoring, buffer-making performance in inline mixing is usually prevalidated based on the flow rate of each mixing stream for making the buffer. Unlike traditional buffer preparation, tracking of buffer made from the CBMS is based on multiple high-performance mass flowmeters and inline pH and conductivity monitoring.

Concentrate Tanks

The CBMS hardware configuration includes an array of concentrate tanks, each containing different buffer components. These components may encompass 4 moles and 3 moles phosphoric acid, 2 moles citric acid, 2 moles acetic acid, 4 moles sodium chloride, and sodium hydroxide, among others. These tanks hold the concentrated solutions required for buffer preparation. Although single-use bags can be used as concentrate tanks in the CBMS, the tanks are sometimes made of higher alloy materials such as 904L or Hastelloy to accommodate the harsh chemicals.

Relay Tanks

A series of relay tanks play a central role in connecting the CBMS with the downstream process operations. These relay tanks are designed to continuously accommodate various buffer solutions required for the downstream operation the CBMS is supporting. These solutions include wash solutions, regeneration solutions, elution solutions, storage solutions, CIP solutions, and equilibration solutions in a typical chromatography operation. The relay tanks serve as a dynamic reservoir for buffer solutions, ensuring a sustained supply to the downstream processes that the CBMS is set up to support. Relay tanks can be single-use bags as well as stainless steel vessels.

Valve Matrix

The CBMS incorporates a complex valve matrix responsible for managing the flow paths of concentrates and buffer solutions. This intricate network of inlet and outlet valves, involving up to 100 different valves, enables the distribution of buffer solutions

The system and hardware design of the CBMS are engineered to facilitate the precise preparation, distribution, and control of buffer solutions.

to the appropriate relay tanks and downstream processes. Precise and reliable control of these valves is essential to maintaining the integrity of the CBMS and ensuring the buffers reach their intended destinations.

The system and hardware design of the CBMS are engineered to facilitate the precise preparation, distribution, and control of buffer solutions. These elements work in concert to ensure the system's efficiency, maintain the integrity of buffer solutions, and support the overall objectives of biopharmaceutical downstream processing.

KEY PROCESS CONTROL STRATEGY

The success of the CBMS hinges on its robust control platform and well-developed control strategy. In this section, we discuss the intricacies of the CBMS's control strategies and the software platform that underpins its operation.

Software Platform

The CBMS control usually relies on more sophisticated DCSs, which allows oversight of its large number of components through various IOs and many units while also implementing recipe-driven procedural control across multiple units. Ideally, the CBMS control is integrated with the plant downstream DCS through a compact DCS controller, which can be standalone or seamlessly incorporated into a plant's existing DCS.

Process Control Strategies

Given the CBMS's extensive scope, process control strategies are essential for maintaining the synchrony of various units and modules within the CBMS and coordination with downstream processing operations. Besides the equipment-based control for flow rate, tank level, and valve position, batch-level control of functionality must be part of the strategy.

The inter-unit communication between inline-buffer preparation and downstream processing has always been a major practical challenge in plant operation. In many cases, the batch recipe must be so process-specific and complicated that a lot of customization has to be made. The CBMS has, however, basically eliminated this complexity and standardized the batch recipe. This was accomplished by implementing an innovative buffer-filling strategy, which allows a relatively independent boundary of the CBMS in relation to downstream processing [5].

Unit Definition and Standardization

To further reduce the CBMS's inter-unit communication complexity, another critical step is the redefinition and standardization of equipment units within the system [5]. This involves defining units in terms of physical components and also redefining them in the context of batch management, following the S88 standard (shown in Figure 5). By adopting an innovative buffer-filling strategy and standardizing the units within the CBMS, the CBMS can be built as a robust and manageable OEM product.

Batch Recipe

The CBMS leverages batch operation management to set up and oversee buffer preparation. The system runs as a service through a S88 recipe that sets up the buffer-filling service for the relay tanks. Parameters such as buffer ID, flow rate, and total buffer quantities are configured at the beginning of each batch, ensuring that the correct buffer is supplied to the appropriate relay tanks. There is no direct communication required between the CBMS and downstream processing except warnings and alarms.

The CBMS's control platform and strategies are fundamental to its success as a comprehensive buffer management solution. The DCS platform provides the necessary industrial control infrastructure, whereas unit standardization and buffer-filling strategies ensure effective coordination between the CBMS and downstream processing. These elements empower the CBMS to deliver consistent and reliable buffer preparation to the downstream operations it supports as if the CBMS were the traditional buffer tank farm.

TECHNICAL DETAIL OF BUFFER FILLING

As discussed previously, one of the pivotal aspects of the CBMS is its buffer-filling strategy. The CBMS does not need to directly communicate with downstream processing. The CBMS manages to fill the right buffer for the right tank at the right time by responding to tank liquid level and buffer priority. This development significantly simplified the batch-level control logic between the CBMS and downstream processing. In this section, we shed more light on its key concepts and principles.

Liquid-Level-Based Filling

The CBMS employs a liquid-level-based strategy to govern the filling of relay tanks [5]. Each relay tank is assigned with different liquid levels that correspond to specific flow rates for buffer filling. These liquid levels trigger the system to initiate, stop, or alarm the filling process.

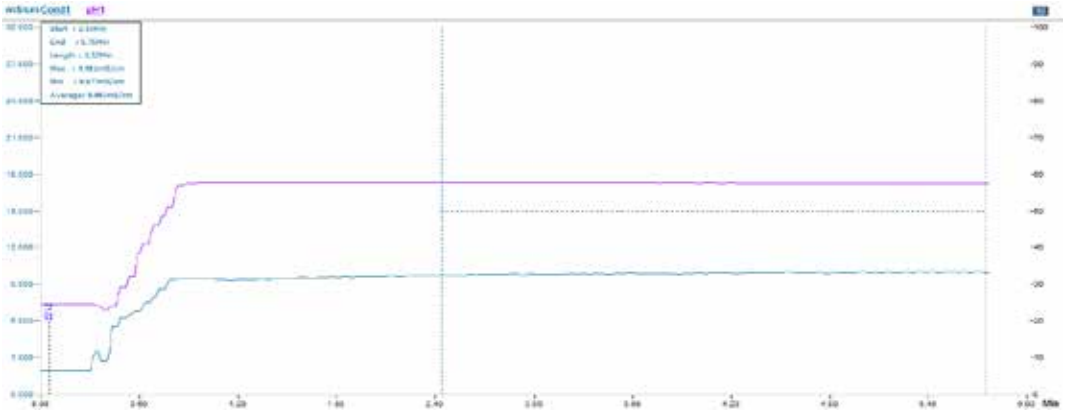
Flow Rate Adjustment

Flow rate control is a critical factor in the CBMS's buffer-filling strategy. The precise control of flow rates is pivotal in achieving the desired specifications for buffer solutions. The buffer-filling process responds to various liquid levels within relay tanks by adjusting flow rates accordingly, providing a safeguard against overfilling or depletion [5]. Such flow rate adjustment is essential for maintaining the effectiveness of multiple buffer filling throughout the preparation and distribution process.

Figure 6: CBMS buffer preparation performance example.

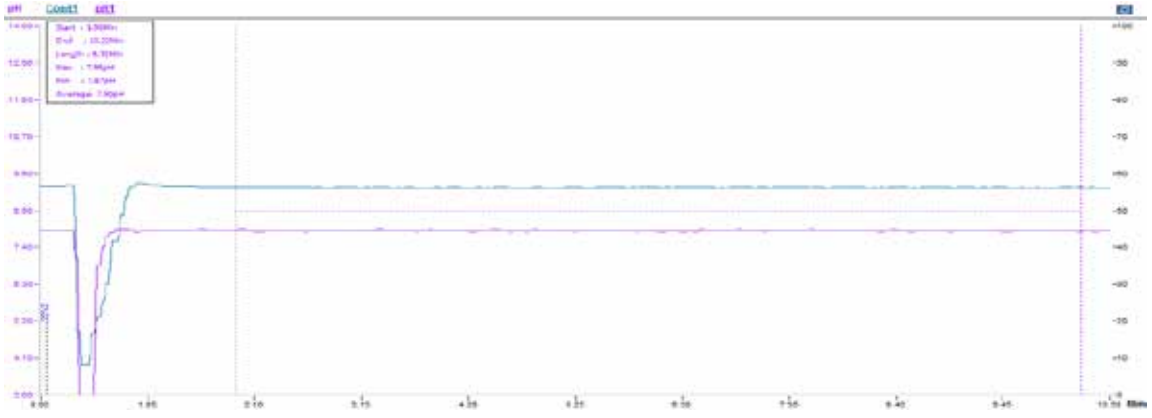
Formula 1 (25 mM Citric Acid, 0.05 M NaCl, pH 5.8±0.1, Conductivity 10±1)

Flow Rate	Target pH	Actual pH	Target Conductivity (mS/cm)	Actual Conductivity (mS/cm)
200 L/H	pH 5.8±0.1	Average pH: 5.76 Highest pH: 5.77 Lowest pH: 5.76	Conductivity: 10±1	Average: 9.881 Highest: 9.981 Lowest: 9.677



Formula 2 (20 mM PB, 0.54 M NaCl, pH 7.9±0.1, Conductivity 45±1)

Flow Rate	Target pH	Actual pH	Target Conductivity (mS/cm)	Actual Conductivity (mS/cm)
100 L/H	pH 7.9 ± 0.1	Average pH: 7.9 Highest pH: 7.95 Lowest pH: 7.87	Conductivity: 45 ± 1	Average: 44.977 Highest: 45.053 Lowest: 44.910



Buffer Switching and Priority

Buffer-filling strategy addresses scenarios where multiple requests for buffer solutions may arise simultaneously [5]. To manage these situations, the CBMS incorporates switching and priority logic that ensures that buffer-filling requests are handled in an organized and prioritized manner. When two or more requests are made, a base logic for arbitration determines the sequence in which buffer filling should occur, preventing bottlenecks and optimizing system performance.

Cleaning Between Buffer Switches

A sufficient hot WFI wash is performed in the inline mixing module for a short period of time immediately after switching the buffer. The cleanability is usually prevalidated. As the buffers made by the same mixing module belong to the same chemistry group, a rigorous cleaning involving surfactant, base, and acid are not required. In cases where a different group of buffers with different chemical natures are present, multiple inline mixing modules will have to be implemented.

The CBMS's buffer filling leverages tank liquid-level-based control, flow rate adjustment, and logical arbitration to maintain a steady and controlled supply of buffer solutions to relay tanks. This strategy underpins the efficient and reliable operation of the system, safeguarding the integrity of buffer solutions and ensuring they are readily available for downstream processes.

IMPLEMENTATION

The successful implementation of the CBMS across multiple projects has yielded substantial outcomes and benefits. In this section, we present an overview of the results achieved in practical applications of the CBMS in the biopharmaceutical industry.

Project Scope and Versatility

The CBMS has been effectively implemented in approximately 20 distinct production lines, serving a diverse range of clients in the biopharmaceutical industry. These projects encompassed various scales, involving both single-use bags and stainless steel tanks and accommodating the requirements of different processes and facilities. The adaptability of the CBMS to a multitude of projects underscores its versatility and broad applicability.

Buffer-Making Performance

In comparison to traditional ICPC systems, the CBMS offers enhanced performance. It mitigates pressure disturbances and chromatogram artifacts during buffer switches. End users find that the buffer solutions delivered by the CBMS are equivalent to those obtained from traditional tank farm vessels, and the CBMS was able to maintain product quality and consistency during operation (see Figure 6).

GAMP® Execution and Validation

GAMP project execution is usually required for delivering CBMS product to meet the stringent validation requirements of cGMP. GAMP execution ensures the functionality, compliance, reliability, and safety of the CBMS in regulated biopharmaceutical environments. By making the CBMS an OEM product through standardization on system design and process control strategy, validation support has been significantly simplified and product delivery lead time can be greatly improved.

On the other side, engineering systems similar to the CBMS would require a yearslong, lengthy custom engineering or automation project to implement. A CBMS as an OEM product represents a new option for pharmaceutical end users in a new plant design or an expansion project for an existing facility.

Plant Layout Alignment

Another important aspect of the CBMS's implementation is its adaptability to a variety of plant layouts. The capability of the OEM vendor to align the system with the specific spatial constraints and requirements of each client's facility is essential for CBMS implementation. This capability enables the CBMS to seamlessly integrate into diverse production environments.

Economic and Operational Benefits

Although exact numbers are still unavailable, the implementation of the CBMS has consistently yielded economic advantages for end users. The savings were considered tremendous [3]. Substantial reductions in capital investment expect to be in the range of 30% to 60% in comparison to traditional buffer tank farm systems [6]. Operating costs have been reduced due to the use of smaller vessels and smaller CIP processes [2]. General consensus on the savings seems to be in the range of 20% to 50% [3]. These economic advantages make the CBMS an attractive option for both greenfield projects and the expansion of existing facilities.

The implementation of CBMS has showcased its adaptability and seamless alignment with different plant layouts. It has delivered substantial economic benefits, automated manual operations, improved batch documentation, and added data integrity and accessibility. These outcomes underscore CBMS's viability as a robust solution for buffer management in the biopharmaceutical industry.

CONCLUSION

The CBMS stands as a transformative solution that offers effective buffer preparation in the biopharmaceutical industry. This comprehensive discussion highlights the system's innovative approach, its proven benefits, and ways around the technical challenges in its development and implementation.

The CBMS has evolved as a dynamic response to the conventional buffer tank farm approach. It adopts inline mixing technology and a series of relay tanks to offer the capacity to prepare buffers for an entire buffer preparation area. The CBMS decouples downstream processing and buffer preparation, resulting in smaller vessels and a substantially reduced cGMP footprint. This shift empowers the CBMS to deliver substantial savings in capital investment and operating costs for greenfield projects and the expansion of existing cGMP facilities.

The success of CBMS implementation is attributed to its standardized system design, process control strategy, and GAMP project execution. These elements enable the CBMS to operate seamlessly, delivering consistent and high-quality buffer solutions to downstream processing.

The CBMS's economic benefits, improved batch documentation, and enhanced performance have been demonstrated in various client projects, providing a compelling economic incentive for its adoption. The shift of CBMS toward a more automated and data-centric approach is also aligned with digital transformation and Industry 4.0 effort in the pharmaceutical industry.

The CBMS represents a leap forward in buffer preparation technology. It is poised to become an essential element in the quest for ongoing bioprocess intensification and operational excellence in the biopharmaceutical industry. Thus, it invites further exploration and consideration as the industry continues to evolve.

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BUILDING BETTER THERAPIES with Antibody Engineering

By Amit S. Choudhari, PhD, and Vikal Tripathy, PhD

Antibody engineering has transformed the development of therapeutic antibodies, enabling the creation of specific and effective treatments for a range of diseases. These antibody-based therapeutics are advancing in clinical development at a rapid rate and are being approved in record numbers. Currently, more than 100 monoclonal antibodies (mAbs) have been approved for the treatment of various disease conditions, including cancers, autoimmune diseases, and chronic inflammatory diseases. However, traditional antibody discovery processes have limitations. Computational approaches have helped researchers overcome those challenges and cleared the way for future discoveries of therapeutic antibodies.

BACKGROUND ON TRADITIONAL ANTIBODY DISCOVERY

Traditional antibody discovery processes like phage, yeast, and mammalian display technologies are time-consuming, laborious, and possess several limitations, such as identifying the specific antibody binding side (epitope) or obtaining antibodies with optimal properties. Computational approaches have played a critical role in this process, providing researchers with powerful tools to design and optimize antibodies with improved properties. These methods involve the use of advanced algorithms and computational models to predict and model the behavior of antibodies, allowing researchers to optimize key features of the antibody structure.

This article provides a description of therapeutic antibodies, how they are developed, and challenges in the development of antibody-based drugs, and discusses the future roadmap for discovery of therapeutic antibodies.

ANTIBODY: STRUCTURE, FUNCTIONS, AND DIVERSITY

Antibodies, also known as immunoglobulin, are protective/disease-fighter protein molecules produced by B cells (specialized immune cells) as a primary immune defense. When pathogens such as bacteria and viruses invade our body, antibodies attach to foreign substances (i.e., antigens) on its surface and help our body to get rid of them. Structurally, antibodies are made up of four polypeptide chains—two heavy (H) chains and two light (L) chains joined to form a Y-shaped molecule (see Figure 1A).

The entire Y-shaped unit can be divided into two main parts: the stem of the Y, known as the fragment crystallizable (Fc) region, and the forks of the Y, known as the fragment antigen-binding (Fab) region. The Fc region is composed of portions of H-chain and L-chain, which have constant amino acid sequences that interact with the receptors present on the cell surface to activate the immune system (i.e., effector function).

The Fab region is composed of the remaining portion of H- and L-chains that are divided into a constant and a variable region. Within the H-chain and the L-chain of the Fab variable region lies a frequently mutated special amino acid sequence region called hypervariable or complementarity-determining regions (CDRs) (see Figure 1B). There are six such CDRs. Three of these are present in the L-chain (CDR-L1, CDR-L2, and CDR-L3) and three in the H-chain (CDR-H1, CDR-H2, and CDR-H3). These CDRs are critical for recognizing specific configurations (i.e., epitopes, or antigenic determinants) on the surfaces of antigens and stimulating an immune response.

Moreover, antibody diversity is generated by the combination of variable heavy (VH) and variable light (VL) chains either through variable, diverse, and joining regions (V(D)J), recombination, or somatic hypermutation [1]. These two mechanisms together can produce massive antibody diversity ($10^{12–1015}$) by introducing

Figure 1: Antibody structure and underlining region/domain.

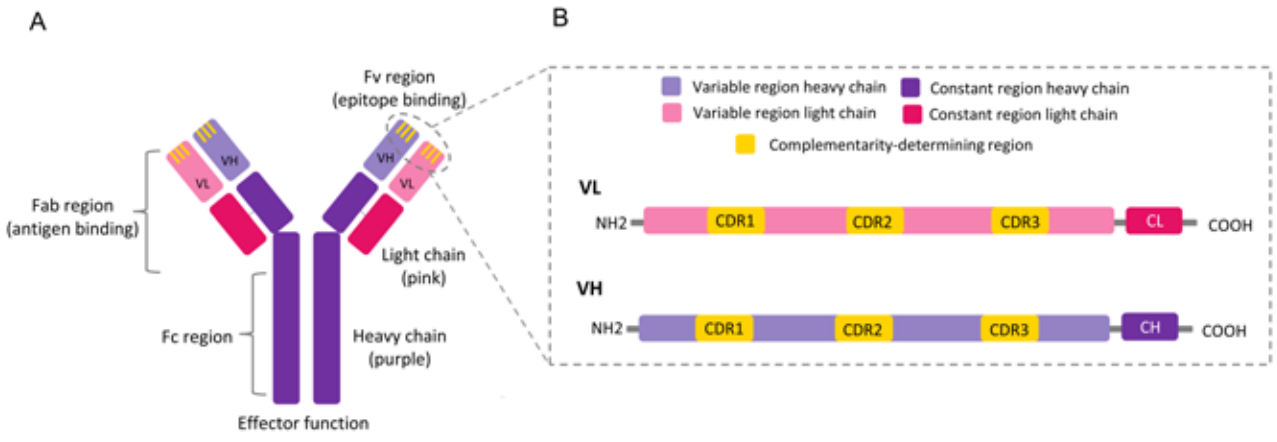
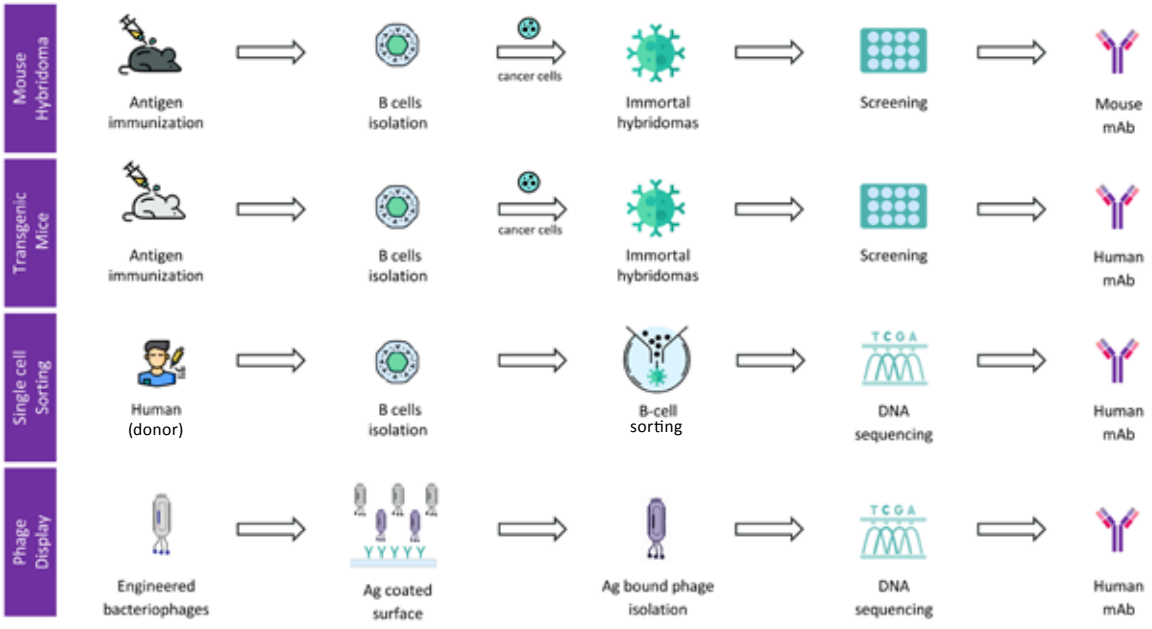


Figure 2: Approaches for the development of therapeutic antibodies.



mutations primarily in the CDR regions. Thus, it increases the probability of recognizing an arbitrary foreign antigen.

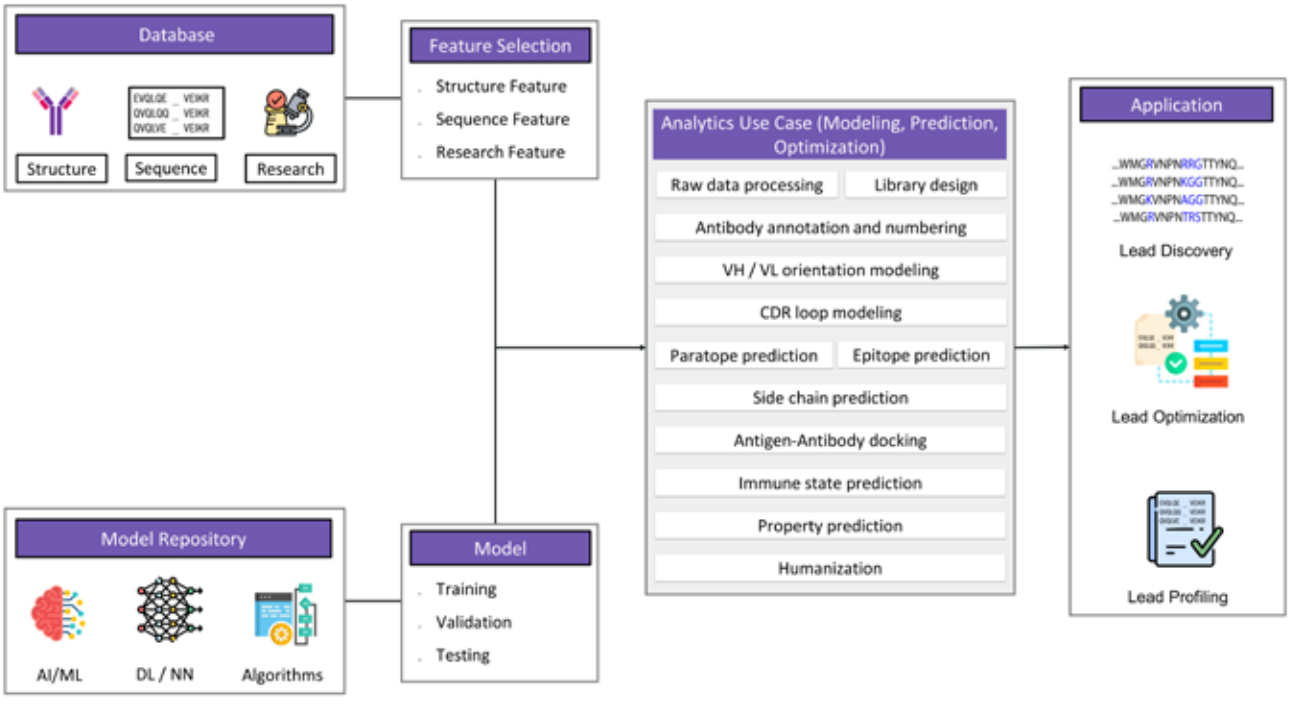
APPROACHES TO ANTIBODY DISCOVERY

Therapeutic antibodies against specific disease targets are developed in a laboratory by mimicking the biological process of the human body and immune system [2]. The process begins with the generation of hit molecules by immunizing the host (animals) with the antigen of interest. Some of the methods for hit generation are shown in Figure 2.

Approaches for the development of therapeutic antibodies include the following:

- Mouse hybridoma technique: This method begins by immunizing a mouse with the antigen (Ag) of interest followed by isolation of B cells producing antibodies specific to the antigen. These B cells are fused with cancer cells (myeloma) to produce immortal cells called hybridomas that persistently secrete antibodies.
- Transgenic mice method: In this method, the mice are genetically engineered to produce human antibodies. The mice are immunized with the target molecule and the B cells producing

Figure 3: Component and approaches for computational antibody discovery.



Computational approaches to designing and developing antibody sequence and structure are being increasingly used to complement traditional lab-based processes.

the desired antibodies are isolated and used to produce the antibodies.

- Single cell sorting method: In this technique, B cells are directly sorted from the human (donor) or an immunized animal and screened for the ability to produce antibodies that bind to the antigen molecule. Once a B cell producing a promising antibody is identified, its DNA is sequenced and used to produce the antibodies.
- Phage display method: Also known as surface display method, this technique involves introducing a library of genetically engineered bacteriophages (viruses that infect bacteria) into a sample containing the antigen molecule. The phage that binds to the target is then isolated and the DNA sequence that encodes the binding peptides is determined.

Each method has its own advantages and disadvantages. The method for developing antibodies is selected based on various factors, such as the target molecule, the desired specificity and affinity, and its intended clinical application. In the next phase of the discovery, the emphasis is on optimizing the properties of candidate molecules so that it succeeds in subsequent preclinical and clinical phases. This process is known as lead optimization.

The properties that can be optimized include binding affinity, specificity, selectivity, pharmacokinetics, aggregation propensity, functional activity, and safety. One way of lead optimization is to alter the sequences of the antigen-binding regions (CDR regions) of the antibody to enhance certain properties, such as binding selectivity and affinity.

In this process, VL and VH chains of CDR regions are analyzed, often by next-generation sequencing [3], followed by the creation of variants via mutagenesis or by using synthetic DNA. Through an iterative variant creation and subsequent screening process, lead molecules are selected to move forward in the workflow. These leads are used in in vivo studies to better understand the dynamic interactions with the biological system of interest. This then results in a therapeutic antibody candidate and ends the discovery phase of the drug development process.

COMPUTATIONAL APPROACHES TO ANTIBODY DISCOVERY

Computational approaches to designing and developing antibody sequence and structure are being increasingly used to complement

traditional lab-based processes. The application of computational biology, artificial intelligence (AI), machine learning (ML), and deep learning (DL) methods to antibody discovery has rapidly expanded in recent years to address various challenges in the field [4, 5]. This includes, but is not limited to, the development of antibody databases [6], molecular modeling and simulations [7], and the use of advanced analytics (see Figure 3).

Homology modeling, molecular docking, and molecular dynamics simulations are commonly used computational biology approaches to predict the 3D structure of an antibody or antigen, and predict antigen-antibody binding affinity and stability [8]. Apart from these approaches, various AI, ML, and DL methods have been implemented for prediction and optimization of antibodies. ML and DL algorithms can be trained on the large data sets of protein sequences, structures, and functions to identify patterns and predict outcomes, which is crucial for the development of effective antibodies. Some applications of DL models, such as convolutional neural networks and generative adversarial networks, predict antibody binders and generate synthetic antibodies [2] with desired properties and high binding affinity [9].

One recent breakthrough was the development of AlphaFold by the Google company DeepMind. AlphaFold is provided as an open access tool to the scientific community. It is a DL-based prediction tool that can accurately predict protein structure based on multiple sequence alignments [10].

Because the method relies on sequence alignments for accurate predictions, AlphaFold has limited usefulness in predicting the structure of "orphan" proteins, which have limited sequence information. This limitation is overcome by the development of large language models (LLMs). One example of an LLM is the protein language models, which are trained on large datasets of protein sequences and structures. Recently, Meta launched a breakthrough model called evolutionary scale modeling (ESM). The ESMFold protein language model harnesses the ESM-2 to learn sufficient information to enable accurate, atomic-level predictions of protein structure directly from the individual sequence of a protein [11].

ProGen and IgLM are other examples of language models that can generate novel antibody sequences when conditioned on specific inputs. ProGen is a pre-trained language model that can be fine-tuned to predict the binding affinity between antibodies and their targets [12], whereas IgLM is trained to generate synthetic libraries of variable length antibody sequences [13].

KEY CHALLENGES AND A WAY FORWARD

Despite the impressive progress in technologies applied to antibody engineering, developing antibodies with high specificity and binding affinity remain the challenges that require attention. In the future, it may be useful to include codon optimization to finalize antibody designs. Codon optimization is the process of modifying nucleotide sequence of genes based on various criteria without altering the amino acid sequence. Optimization of codon would result in an improvement in protein expression, as well as designing antibodies with high specificity, binding affinity, and biological activity.

Another important outstanding challenge is the de novo loop modeling of antibody CDRs—in particular, the CDR-H3. This is partly due to the large number of degrees of freedom that need to be sampled. Although there is an advance in DL models for protein modeling (AlphaFold2, OmegaFold, ESMFold, and Yang-Server) and antibody modeling (IgFold, and NanoNet), modeling of CDR3 is still a big challenge [14]. As both quantum computing and AI models advance, optimizing the CDR structure and predicting amino acid substitution would be possible.

The introduction of sophisticated research technologies such as next-generation sequencing (NGS) has significantly increased the speed and breadth of research processes for antibody discovery. NGS provides comprehensive sequence data, enabling the identification, optimization, and characterization of antibodies with desired properties. This has exponentially increased the data volume, which requires high-compute and high-storage solutions. As projects become collaborative in nature, it will become increasingly critical to safeguard the integrity of data security and continuity of operations.

The prospective solution for this would be to establish robust decentralized ecosystems based on the principles of trusted research environments (TREs) that enable data to be jointly analyzed without sharing all aspects of that data. Nevertheless, TREs would also provide a secure and controlled environment without compromising confidentiality [15]. This can allow researchers to work together more effectively, accelerate the pace of research, and ultimately lead to the discovery of new antibodies.

CONCLUSION

The use of computational approaches to design antibodies is increasing and complementing traditional lab-based processes. ML, through embedding and generative models trained on large datasets, represents a new paradigm shift in this field. Biopharmaceutical companies that can generate data at scale will have a significant advantage over others, leading to a focus on digital transformation efforts within the industry. This will include data storage, sharing, and searching, as well as deriving meaningful insights by linking various datasets. Ultimately, the successful translation of AI-enabled antibodies from bench to bedside in record time and at a reduced cost will be the most accurate measure of success.

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CELL CULTURE MEDIA MANUFACTURING CONTROLS for Bio-Manufacturing

By Ajay Babu Pazhayattil, PhD, Sarah Jennings, and Catherine Spengler

Advanced therapy medicinal products (ATMPs) and cell and gene therapies (C&GTs) represent a promising medical product class that employs gene therapy, cell therapy, or tissue engineering to address various diseases and injuries. One critical aspect of ATMP and C&GT manufacturing is using cell culture media. With thousands of ATMPs and C&GTs in clinical trial phases, the role of cell culture media has become even more significant to the biopharmaceutical industry.

ATMPs and CG&Ts are innovative therapies that can potentially provide transformative treatments for numerous conditions, including genetic disorders, neurodegenerative diseases, cancer, and cardiovascular diseases. To ensure product consistency and performance of lifesaving therapies, it is necessary to study critical cell culture media process parameters and their impact on the key culture media attributes.

There were 2,093 ongoing clinical trials globally at the end of June 2022 (phase 1: 776; phase 2: 1,117; phase 3: 200) suggestingthe upcoming slew of approvals and predictable demand in their commercialization. By region, North America leads with 808 active clinical trials, Asia Pacific has 640 trials, Europe has 329, and all other regions have the remainder [1]. However, the development and manufacture of ATMP and C&GT products pose unique challenges, including emerging regulatory frameworks and complex manufacturing processes.

Cell culture media is crucial for ATMP and CG&T manufacturing, ensuring optimal cell growth and function by providing essential nutrients, growth factors, and other components. The media quality and composition can directly impact the product's characteristics, including yield, purity, and potency.

Therapies that require ex vivo cell expansion rely on cell culture media as a critical raw material. For example, in the ex vivo expansion of human mesenchymal stem cells, well-defined serum-free formulations are desired to support efficient production while maintaining cell properties. Therefore, proper selection and optimization of cell culture media are vital. By using quality-controlled, process-optimized media formulations and customized media, consistency and reproducibility can be maintained. This ultimately benefits patients by providing safe and effective therapies. Even with the same specifications, different media formulations from different suppliers can lead to varied cellular responses, growth patterns, and experimental outcomes. The choice of a culture medium should be based on the specific requirements of the experiment and the characteristics of the cell line being used.

REGULATORY SCENARIO

Raw and ancillary materials, like cell culture media used in manufacturing GMPs, are not explicitly discussed. However, 21 CFR Part 210 (210.3(b)3) touches on components, which these products would most align to per their definition [2]. As such, there is an expectation that the media manufacturers will comply with general GMP sections. Media materials are indirectly regulated by ensuring adherence to standards outlined in the United States Pharmacopeia (USP), European Pharmacopoeia (EP), chemistry, manufacturing, and controls (CMC) guidelines, and voluntary consensus standards such as ISO.

In the US, cell culture media is classified as an ancillary material, whereas in the EU, it is considered a general raw material according to GMP guidelines. In certain cases, device guidelines, such as

Table 1: USP <1043> Ancillary Materials for Cell, Gene, and Tissue-Engineered Products [4].

Ancillary Materials Risk Tier	Typical Use in Cell, Gene, or Tissue-Engineered Product Manufacturing	Suggested Qualification or Risk Reduction Activities
2 Low-risk, well-characterized materials with intended use as ancillary materials, produced in compliance with GMPs	Cell culture medium additive (ex: tissue culture media)	Refer to USP <1043>
3 Moderate-risk materials not intended for use as ancillary materials (frequently produced for in vitro diagnostic use or reagent-grade materials)	Cell culture medium additives, induction agents, buffer components (ex: purified chemicals, reagent-grade)	No additional controls recommended
	Cell culture medium additive (ex: recombinant growth factors, cytokines, tissue culture media) Process biological fluid employed in tissue transport, cell processing, and purification (ex: process buffers)	Drug master file (DMF) cross reference, certificate of analysis (CoA), lot-to-lot effect on process performance, removal from the final product, stability assessment, functional assay, vendor audit, GMP manufacturing process, internal specs, lot-to-lot biocompatibility, cytotoxicity, adventitious agent testing
4 High-risk materials	Cell culture medium additive (ex: fetal bovine serum [FBS], animal-derived, including human, extracts)	Same as 3, plus verify traceability to country of origin, assure the country of origin is qualified as safe with respect to source-relevant animal diseases, including transmissible spongiform encephalopathy (TSE), adventitious agent testing for animal source-relevant viruses

21 CFR Part 820 [3], may apply. Hence, standard cell culture media manufacturers apply fit-for-purpose (see Figure 1) sterile and nonsterile GMP requirements. The USP <1043> Ancillary Materials for Cell, Gene, and Tissue-Engineered Products [4] compendia classifies ancillary materials (media), as shown in Table 1 [4].

OVERCOMING RISK TO FINAL PRODUCT

Contamination

Sterility assurance is critical because it can significantly impact the growth and behavior of cells and ultimately compromise the outcomes. Contamination by microorganisms such as bacteria, fungi, and viruses can result in reduced cell viability and proliferation. Precautions such as applying aseptic behaviors and techniques, maintaining a clean environment, implementing engineering or procedural controls, and regularly monitoring for signs of contamination (i.e., contamination control strategies [5]) are also essential during media manufacturing.

The potential to transmit adventitious agents exists with the culture media. Hence, a risk-based control strategy must be developed. To facilitate the reduction of viral risks, it is crucial to establish strong supplier controls and perform assessments specifically aimed at clearing or reducing viral risks. Proof of viral contamination controls are reviewed as part of the regulators' safety assessment of the finished ATMP. Therefore, it is essential to understand the impact of cell culture media components when determining the viral safety profile. Several clearance steps, such as purification and filtration, may be part of the manufacturing process. Hence, filter studies with viral spiking are part of process development.

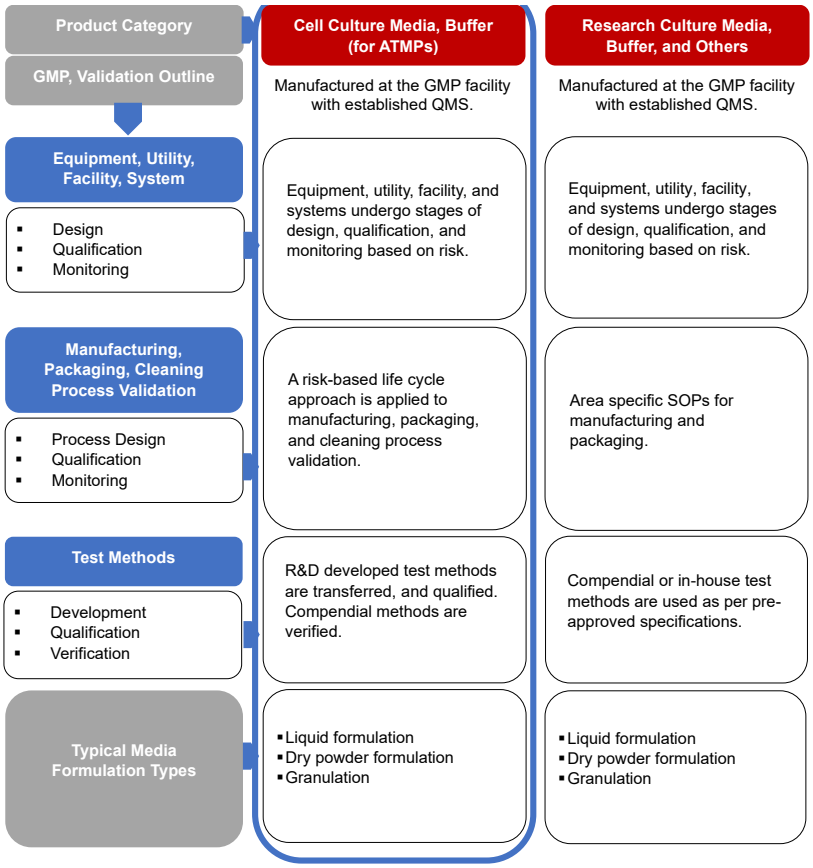
Typically, established controls involve the analysis of viral contaminants performed at different stages under various conditions. Further, adventitious agent testing is required per 9 CFR Part 113 [6], the EMA's "Guideline on the Use of Bovine Serum in the Manufacture of Human Biological Medicinal Products" [7], and other regulations.

Animal Origin Concerns

The International Conference on Harmonisation of Technical Requirements For Registration of Pharmaceuticals For Human Use (ICH) Q5A(R1) guideline describes the viral safety testing and evaluation of biotechnology products derived from characterized cell lines of human or animal origin (i.e., mammalian, avian, and insect). It outlines the data that should be submitted. Animal origin (AO) components may impact batch-to-batch variability, depending on the source and processing method, and pose reproducibility issues, resulting in a lack of product availability. There are also associated ethical concerns and difficulties in characterization due to the existence of many proteins and metabolites [8].

Once identified, these risks may be systematically addressed. However, based on the C&GT developer's risk mitigation strategy and criteria, animal origin-free (AOF) media can be an option. There needs to be transparency about the basis of an AOF claim. AOF refers to the absence of materials derived from animal sources, including human sources, in a product or manufacturing process. Hence, the processing, control, and qualification measures need to be defined by the supplier. Manufacturers should have a comprehensive process to support the AO contamination controls, including ensuring that materials are not secondarily exposed to AO.

Figure 1: A fit for purpose ATMP/C&GT media manufacturing strategy.



CUSTOMIZED FORMULATIONS FOR CELL CULTURE MEDIA

Choosing the right cell culture media for a specific cell type can be a daunting task, but it can be made easier with the help of media formulation experts from manufacturers who can provide customized formulations when necessary. It is important to consider the compatibility of culture media components with downstream process materials and assays, such as polymerase chain reaction (PCR), enzyme-linked immunosorbent assay (ELISA), or flow cytometry, as they can interfere with the results. For this reason, adjusting various attributes of the media—such as nutrient and growth factor concentrations, trace elements, and pH—may be necessary to achieve the desired outcomes.

Maintaining the culture media at precise pH and osmolality levels is crucial for optimal cell growth and function. Manufacturers implement in-process testing controls to ensure these critical quality attributes are maintained. Buffering agents and salt concentration adjustments are used to maintain pH and osmolality ranges when needed, as fluctuations can cause cell stress and impact outcomes. Nutrient depletion can also occur in culture media, reducing cell growth and function. Stability data is generated to support proper storage, establish expiration dates, and ensure adequate storage and monitoring.

MINIMIZING VARIABILITY IN MEDIA MANUFACTURING

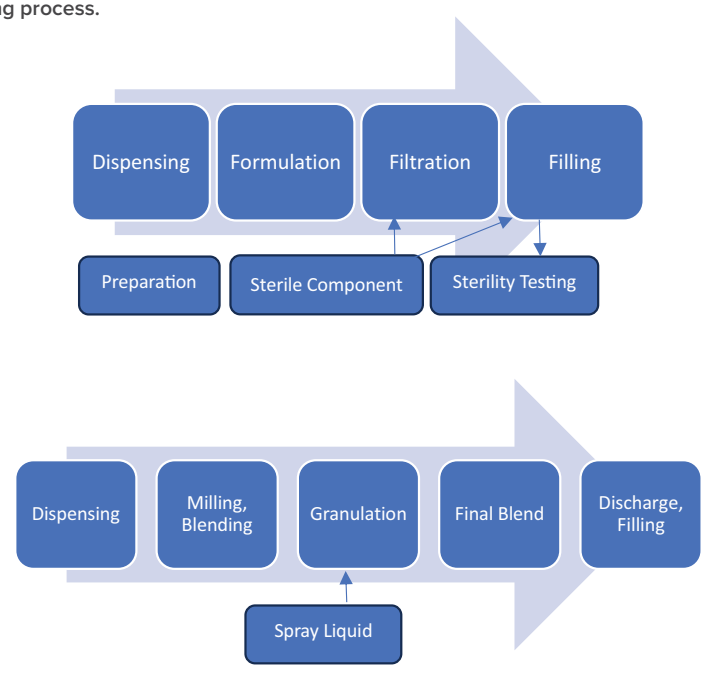
In manufacturing cell culture media, there can be variability in the composition and quality within and between batches, which can impact reproducibility. This variability can be caused by several factors, including the input of raw materials (material); manufacturing equipment, change parts, and product contact components (machine); process parameters (method); storage conditions (nature); test methods (measurement); and operator-to-operator differences (human).

To ensure consistent and high-quality cell culture media, it is essential to understand the sources of variability and develop a robust control strategy that minimizes both within-batch and batch-to-batch variations. The total variability can be expressed as the sum of individual component variations. This may be mathematically denoted as [9]:

$$S^2_{total} = S^2_{material} + S^2_{equipment} + S^2_{processes} + S^2_{test\ method} + \cdots$$

$$= S^2_{inter-batch} + S^2_{intra-batch}$$

Figure 2: Media manufacturing process.



LIQUID MEDIA PROCESSING PARAMETER CONTROLS

For liquid media manufacturing, a series of operations—including raw materials and water for injection dispensing, formulation, filtration, and filling—are executed with their established parameters and attributes to produce the desired quality of media product. To control the risk of cross-contamination and ensure effective cleaning, qualified inline cleaning (clean-in-place) and sanitization (steam-in-place) processes are to be employed where appropriate.

Product Sterility

During liquid filling, aseptic practices and gowning procedures are strictly followed, and cleanroom engineering controls such as classified areas and laminar airflow units are used. The product's sterility assurance level is controlled through the operations. Product sterility can fail if sterilized components (media formulation, container, and closure) are brought together under contaminated conditions. The aseptic processing operation is qualified using a microbiological growth medium, such as soybean casein digest medium. The initial and routine media-fill program considers the risk factors for contamination on a production line and accurately assesses the state of process control following the US FDA's "Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice" [10].

Process Parameters

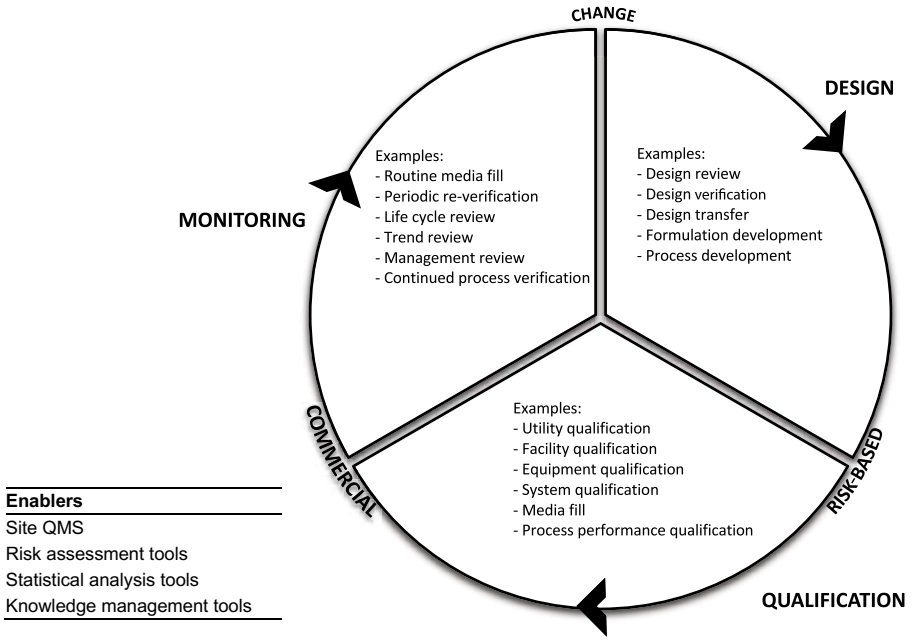
The variability in the cell culture media manufacturing process is a subject for research & development and manufacturing science, and technology study during process development and technology transfer to the manufacturing floor. In particular, the process parameters for a given batch size of media formulation are examined, including weight, seal integrity, charging, temperature, tank volume, fill pump percentage, order of addition, mix time, impeller speed, dwell time, and total production volume. The impact of these parameters on the media quality attributes and the extent of the impact is then evaluated for further optimization. Design of experiments may be performed where applicable.

Subsequently, qualified recipe-based systems/skid controls are developed to deliver consistent quality liquid media for the filtration stage. The formulation tank and filtration equipment require aseptic connections and qualified filters. Where necessary, it must be purged, wetted, and tested for filter integrity using bubble point, diffusive flow, or pressure hold test. Bioburden reduction, sterility, and contamination controls are achieved through sterilization of equipment/components, the use of sterile filters, controlled environments such as a cleanroom or isolator, validated cleaning and sanitization procedures, and continual environmental monitoring and testing for microbial contamination.

Sterilization

Container closure systems—such as bottles, drums, or bags—are commonly used for liquid media and are filled using either automated/semi-automated fillers or manual filling operations. All equipment and components that contact the product during the filling process must be sterilized to minimize the risk of contamination. Aseptic techniques should be employed in applicable segments of the manufacturing operations, such as component sterility assurance, filtration, or the filling process. The filling

Figure 3: Life cycle approach to media manufacturing.



manifolds must be wetted and purged where necessary. The auto-filler parameters may include fill volume, fill speed, time, weight, temperature, relative humidity, dosator pressure, or inert gas purging pressure.

Finishing Operations

Finishing operations are set up in a series after filling. Finishing parameters such as temperature, pressure, torque, speed, count, weight variation, induction seal power/temperature, and glue temperature are qualified. The filling assembly setup parameters for bags are also critical. To ensure product quality, a statistically sound sampling plan and sterile techniques must be used when sampling for sterility testing, routine in-process testing (e.g., appearance, conductivity, total organic carbon [TOC], pH, osmolarity), bioburden, environmental monitoring, and retention sampling. If intermediate stainless steel storage tanks or linear low-density polyethylene (LLDPE) tanks are used, hold times must be established to ensure the product is stored under appropriate conditions.

POWDER AND GRANULE MEDIA PROCESSING PARAMETER CONTROLS

Rise in Powder and Granule Media

In the biopharmaceutical industry, the use of powder or granule media has gained popularity due to its process flexibility and elimination of excessive liquid culture media storage, transportation, and handling issues. Dry media has become the predominant type supplied on a large scale, accounting for over 90% of media used [11].

The granule media format is a preferred choice among dry media formats due to its enhanced solubility profile, improved uniformity, and minimal variability achieved through granulation technologies. Granulation has allowed cell culture media manufacturers to offer a media format that can increase downstream ATMP and C&GT process efficiency, safety, and yield, surpassing the performance of traditional dry media formats. The operational consistency and reliability of the granule media format enable ATMP and C&GT developers to expedite product launches, ultimately benefiting patients.

Powder and Granule Media Process Parameters

Compared to the liquid media manufacturing process discussed previously, the powder or granule manufacturing processes have different processing parameters to be controlled, specifically for milling, blending, and granulation unit operations. The selection and design of the mill (e.g., ball mill, Fitz mill), blender (e.g., ribbon blender, slant cone bender), and granulator are important elements and depend on the media formulation specifics. The physiochemical attributes, including particle size distribution (PSD), can vary widely, leading to challenges in media formulation at scale due to varying flow properties and powder rheology. Therefore, a comprehensive full-scale process development characterization is necessary.

Milling equipment is employed for size reduction. For example, a ball mill uses steel grinding balls to grind materials by rotating a cylinder and causing the balls to fall back onto the material. A Fitz mill uses a rotor with knives that cut and shear the material into smaller particles within a feeding chamber.

Fluid bed granulator parameters

The fluid bed granulator parameters that must be fixed or controlled include air flow, inlet air temperature, inlet air dew point, product temperature, exhaust air temperature, shake duration, shake interval, atomization air pressure, spray rate, spray quantity, and drying temperature. The inlet air temperature and velocity must be carefully controlled to ensure that the granulation process occurs at the correct rate and that the granules do not become too large or too small.

The position of the spray nozzle and the optimized spray rate can ensure that the granules are formed evenly and that the trace materials are distributed uniformly throughout the granules. The PSD of the granules is assessed. Trial runs are conducted to avoid granules being too dense or too porous. Finally, the drying conditions are optimized to achieve the desired moisture content of the granules.

Blend process parameters

Blenders, such as slant cone blenders, can ensure uniform mixing of granules. The mixing variations that occur during the final blending process can be reduced through the application of control strategies that are based on well-characterized raw material properties, robust manufacturing processes, and precise measurement systems. The granules are loaded into the blenders and are blended by tumbling as the machine rotates at a fixed speed and time on a rotational axis. The blender's geometry is symmetric in design, with distinct hopper-shaped chambers. Sampling locations for process qualification must consider granule flow dynamics, such as those recommended in the statistically sound Grouped Area Variance Estimate (GAVE) method [12].

Blend studies can establish blending process parameters, including bin fill, order of addition, revolutions per minute, and time. Operating parameters are finalized during scale-up. Controls for filling operations and discharge operations, such as discharge rate and height, are required due to the potential for variability introduction. An advantage of granulation technology is that it can produce granule media containing trace elements.

MANUFACTURING PROCESS VALIDATION

Manufacturing technology, the manufacturing process steps (see Figure 2), and formulation type significantly influence how a media manufacturing process validation approach is developed. Therefore, adopting the life cycle approach to process validation is essential, because the approach is based on sound science and data. The activities fall into three general categories of design, qualification, and monitoring (see Figure 3).

CONCLUSION

The development and commercialization of the cell culture media manufacturing process requires a life cycle approach [13]. As such, it is important to study critical process parameters and their impact on the key culture media attributes, as well as implement a control strategy to ensure consistency and performance. The use and role of cell culture media in biopharmaceuticals are becoming significant, and the availability of media with consistent performance is essential for bringing lifesaving ATMP and C&GT products to market.

As this field continues to advance, it is crucial to remain vigilant of regulatory changes and implement robust processes that ensure the safety and efficacy of the final product. This requires collaboration between stakeholders, including regulatory bodies, researchers, and manufacturers, to establish best practices and standards that guarantee the quality and safety of cell culture media. Ultimately, these efforts will help to advance the biopharmaceutical industry further and improve healthcare outcomes for patients.

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QUALITY RISK MANAGEMENT for Biopharmaceuticals

By Michael Kuehne

In the dynamic and highly regulated world of biopharmaceutical manufacturing, maintaining and ensuring quality is a critical success factor. An effective quality risk management (QRM) system is a key component in the overall quality management infrastructure of biopharmaceutical organizations. It offers a structured, scientific, and risk-based approach to decision-making, addressing potential quality issues during manufacturing. High performing organizations effectively implement QRM into overall quality policies and procedures to enhance and streamline decision-making.

Implementing a robust QRM system is more than just a compliance requirement. It fundamentally contributes to the organization's commitment to patient safety, product quality, and data integrity. A robust QRM system consists of key characteristics with clearly defined processes that contribute to the system's success.

REVIEWING THE RISK COMPLIANCE DATA

The following graphical data shows the relative compliance risk for pharmaceutical manufacturing organizations based on US Food and Drug Administration (FDA) regulatory activity (see Figure 1). Monitoring regulatory trends based on actual FDA activity provides useful insight for evaluating internal quality management system performance and proactively identifying areas of opportunity to improve overall compliance. Six major pharmaceutical regulation subparts are charted with relative annual activity increasing significantly from 2016 to 2020. During that period, the Building and Facilities, Laboratory Controls, and Production and Process Controls subparts were the largest areas, receiving 483 observations during regulatory inspections.

Those areas present increased compliance risk that would benefit from a formal review, gap analysis, and remediation to improve overall quality system performance and serve as priorities for time and resources. Regulatory risk during the COVID-19 pandemic decreased dramatically as the FDA performed few, if any, on-site investigations. However, activity during 2022 represents renewed on-site investigations with associated regulatory risk.

Figure 2 provides an annual trend of the top cited pharmaceutical regulations from 483 observations during regulatory investigations. These regulations are from the subparts identified in Figure 1 and the largest contributors to pharmaceutical regulatory risk. Any efforts to evaluate biopharmaceutical risk should consider the specific requirements identified in these regulations and address gaps identified during formal review and gap analysis as part of a QRM plan.

A CASE STUDY

This case study concerns a major biopharmaceutical organization that specializes in producing monoclonal antibodies (mAbs) used in the treatment of various autoimmune diseases. As part of their commitment to quality and regulatory compliance, they have implemented a robust QRM system.

Challenge

The organization's production engineers identified a potential risk in their manufacturing process. The risk was related to variability in the cell culture phase, which could potentially lead to inconsistencies in the final product's efficacy and safety.

Risk Identification

The QRM team initiated the risk identification process using failure mode and effects analysis (FMEA) and brainstorming sessions

Figure 1: Data from total Title 21 CFR Part 211 key pharmaceutical subpart citations showing relative compliance risk for pharmaceutical manufacturing organizations.

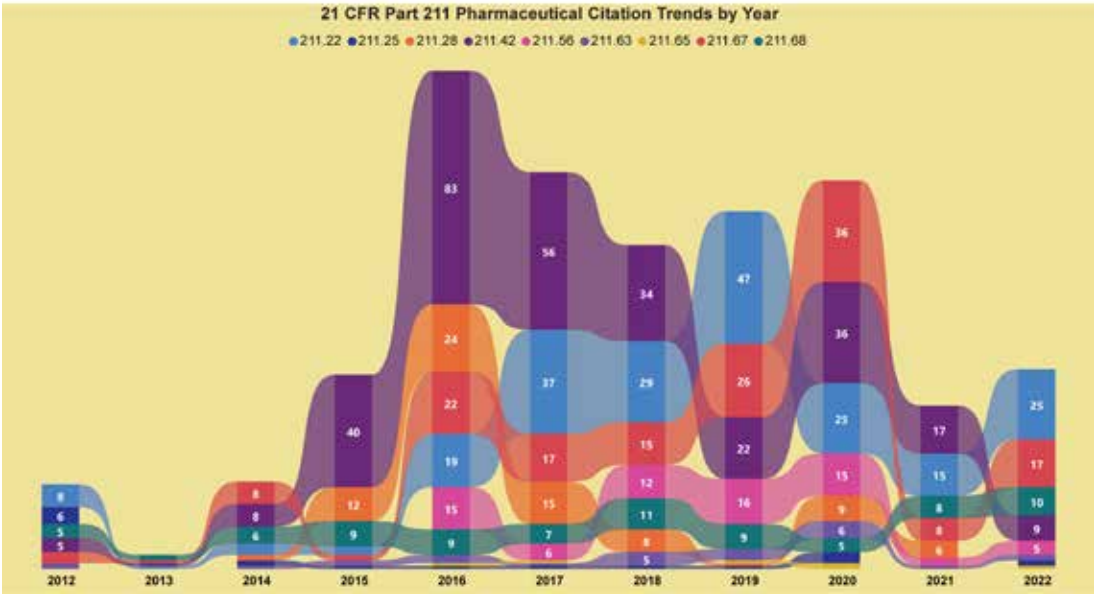
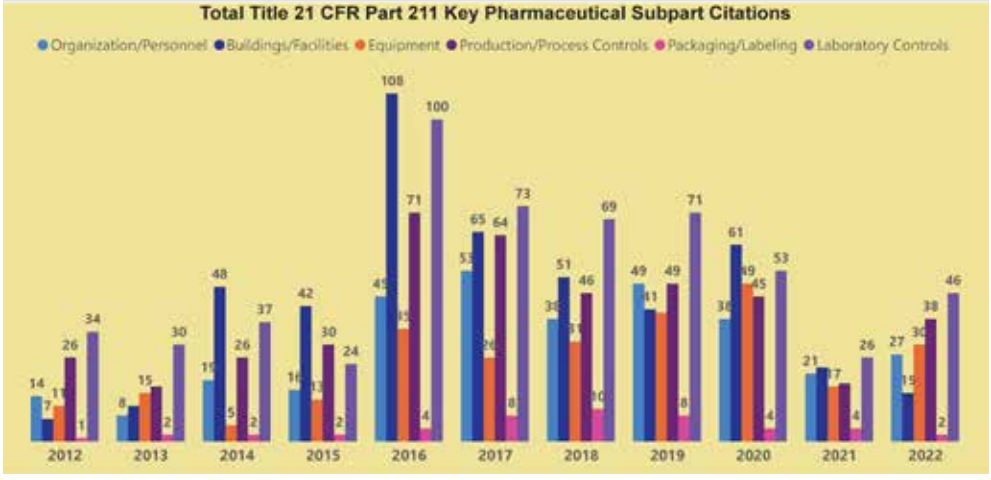


Figure 2: Title 21 CFR Part 211 pharmaceutical citation trends by year showing an annual trend of the top cited pharmaceutical regulations.



Pharmaceutical Subpart Name	Letter
Buildings and Facilities	C
Control of Components	E
Equipment	D
Holding and Distribution	H
Laboratory Controls	I
Organization and Personnel	B
Packaging and Labeling Control	G
Production and Process Controls	F
Records and Reports	J
Returned and Salvaged Drug Products	K

with cross-functional teams. They identified key risk factors, such as pH imbalances, temperature fluctuations, and contamination risks during the cell culture phase.

Risk Assessment

Using a risk matrix, the team assessed the potential impact and likelihood of each identified risk. They determined that temperature fluctuations posed the highest risk due to their high likelihood and potential to significantly impact product quality.

Risk Control

The organization decided to implement additional control measures to mitigate this risk:

- Enhanced monitoring: Installing advanced temperature monitoring systems with automatic alerts for deviations.
- Process improvement: Optimizing the cell culture process to be more robust against minor temperature changes.
- Employee training: Conducting extensive training for staff on the importance of maintaining optimal temperature conditions.

Risk Communication

The QRM team communicated the identified risks, their potential impact, and the planned control measures to all relevant stakeholders, including the manufacturing team, quality assurance department, and senior management.

Implementation

The proposed measures were implemented, and their effectiveness was closely monitored. This included regular review meetings and updates to the risk management plan.

Outcome

The new control measures led to a significant reduction in temperature-related variability in the cell culture process. As a result, the consistency and quality of the mAbs improved, leading to enhanced patient safety and regulatory compliance.

Lessons Learned

The proactive approach to identifying and managing a critical risk in their manufacturing process demonstrated the importance of a dynamic and integrated QRM system. The case also highlighted the need for continuous monitoring and improvement in risk management practices.

Case Study Conclusion

This case study exemplifies the application of a structured QRM process in the biopharmaceutical industry. It illustrates the importance of identifying, assessing, controlling, and communicating risks in a systematic manner to ensure the production of high-quality biopharmaceutical products.

CHARACTERISTICS OF A BIOPHARMACEUTICAL QRM SYSTEM

Identification of risk is a cross-functional effort that begins in the late development stages prior to technology transfer. In the early stages, research and development (R&D) is the main contributor in the risk identification process, which is facilitated by quality and manufacturing who are participants. As manufacturing develops detailed knowledge of the new process and technology, it provides a strong perspective on potential issues and risks that may exist in day-to-day manufacturing. At this time, all teams must compromise to ensure the final technology and process transfer meet the strategic goals of launching a new product.

Once the technology transfer is complete, manufacturing takes the lead in monitoring risk, along with quality. The manufacturing team also proposes any potential changes, which are reviewed by R&D, quality, and, possibly, commercial participants. Performance metrics are developed jointly between quality and manufacturing and used to periodically report to cross-functional leaders.

The main characteristics of a robust QRM system for biopharmaceutical manufacturers are identified in the following sections.

Risk Identification

The initial step in any QRM system is the identification of potential risks. It is necessary to understand what could potentially go wrong in the manufacturing process to manage and mitigate these risks effectively. Elevated performance in risk identification is demonstrated by organizations conducting risk identification with input from cross-functional subject matter experts.

This typically involves brainstorming sessions with relevant stakeholders, analysis of historical data and problem reports, and reviews of process documentation. Clear guidelines should be established for what constitutes a risk, and all identified risks should be documented and maintained in a risk register.

In addition to brainstorming sessions and historical data analysis, other tools such as FMEA, hazard identification, or process hazard analysis can be implemented for a systematic approach. Expert opinions and predictive models can also be used. A successful process should also involve reassessing the risk landscape periodically and after any significant changes. Changes requiring revalidation are a notable trigger to update risk profiles.

A robust biopharmaceutical QRM system recognizes that the process of risk identification is continuous and dynamic, adjusting to changes in procedures, equipment, materials, and the overall business environment. It also considers both internal and external sources of risk.

Risk Assessment

After identifying risks, it is crucial to evaluate them in terms of their potential impact on product quality and the probability of their occurrence. This allows the company to prioritize its risk management efforts.

Risk assessment usually involves qualitative or quantitative methods. Qualitative methods might include rating risks on a scale from low to high, whereas quantitative methods might involve statistical analysis or simulation. Risk assessment is about creating an informed understanding of the risk and considering the severity of the impact, the likelihood of occurrence, and the detectability of the risk. This aids in prioritizing resources and efforts for risk control.

The process should include risk ranking or scoring systems that can objectively evaluate and compare different risks. Detailed risk maps or matrices can be created to visualize the risk landscape. Risk assessments should be periodically reviewed and updated, especially when new information becomes available.

Risk Control

This step involves deciding on and implementing measures to mitigate the identified risks. Without this step, the risk management process would be incomplete. Risk control involves not only mitigating risks but also deciding whether to accept, transfer, or avoid certain risks. Risk control measures should be proportional to the significance of the risk.

Risk control could involve anything from making changes to the manufacturing process to training employees in new procedures. A key part of this step is documenting the control measures and monitoring their effectiveness over time. After devising risk

control measures, a pilot test can be conducted for complex or high-stake measures to ensure their effectiveness before full-scale implementation. The measures should also be reviewed and updated regularly, and particularly after any significant incidents.

Communication and Consultation

Effective communication ensures all relevant stakeholders are aware of the risks and the steps being taken to control them. This not only fosters a culture of risk awareness, but also ensures risk management efforts are coordinated across the organization. Effective communication promotes a shared understanding of risks, risk management practices, and individual roles and responsibilities in managing risk. It should involve all levels of the organization, as well as external stakeholders when appropriate.

This could involve regular meetings, reports, or automated notifications. The key is to ensure that the right information reaches the right people at the right time. The communication process should be a two-way street, allowing feedback from all stakeholders. In addition to meetings and reports, knowledge management systems or collaboration platforms could be used to facilitate communication. Clear protocols should be established for escalation of high-priority risks.

Continuous Monitoring and Review

The risk landscape can change over time, with new risks emerging and old ones disappearing or changing in severity. Continuous monitoring and review ensure that a QRM system stays relevant and effective. Incorporating accurate trend data based on regulatory activity provides an additional level of input elevating the effectiveness of risk management activities.

This can involve regular risk assessments, audits, and reviews of risk control measures. Any changes should be documented and communicated to relevant stakeholders. Monitoring and review processes should include the risks themselves and the effectiveness of the QRM system, changes in context, and the identification of emerging risks.

Risk Management Integration

Risk management should be an integral part of all organizational processes—not a separate activity. This ensures risk considerations are a part of all decisions, rather than being an afterthought. Integrating risk management with other business processes ensures risk management is proactive rather than reactive. It allows risks to be addressed before they can cause problems.

This could involve incorporating risk management into existing process documentation, training employees on risk management, or establishing a risk management committee. This could involve the use of integrated management systems or embedding risk management into standard operating procedures. Cross-functional teams or committees could be established to oversee the integration. Key performance indicators related to risk management should be established and monitored. Audits and reviews should be scheduled regularly and triggered by significant changes or incidents. Feedback from these activities should be used to drive continuous improvement.

Root Cause Analysis

Understanding the root cause of a problem allows for more effective risk management. It helps avoid merely treating the symptoms of a problem, which can lead to recurrence. The goal of root cause analysis is to prevent recurrence of problems by addressing their underlying causes, not just the symptoms. It allows for more efficient use of resources and improves process understanding.

Techniques such as the five whys and fishbone diagrams, among others, can be used to identify root causes. Once identified, these root causes should be addressed in the risk control measures. When conducting root cause analysis, it is important to ensure a blame-free environment where all ideas are considered. Tools such as Pareto charts could be used to prioritize root causes. Root cause prioritization may also reference regulatory trends based on current regulatory activity. Corrective and preventive actions should be devised to address the root causes.

Data-Driven Decision-Making

Decisions about risk management should be based on data, not on gut feelings or intuition. This leads to more objective and effective decisions. The use of data promotes objectivity, consistency, and efficiency in decision-making. It also allows for tracking and demonstrating the performance of the QRM system. An example of data-driven decision-making used by high-performing organizations uses available newsletters, visualizations, and trend tracking regulatory data to provide accurate insights to compliance risk.

This might involve collecting and analyzing data on process performance, product quality, and the effectiveness of risk control measures. Decision-making tools such as decision trees or Bayesian networks can also be used. An effective process should include not only collection and analysis of data, but also data management practices to ensure data integrity and usability. Advanced data analytics or artificial intelligence could be used for predictive risk modeling. Regulatory trends and current regulatory activity are also indicators providing insight into predictive risks of regulatory audits.

Quality Culture

A strong culture of quality fosters individual accountability, intrinsic motivation, and proactive behavior in managing risk and it ensures risk management is not the responsibility of just the quality department. Successful organizations building a strong culture of quality and compliance have notable focus and support from executive leadership. A successful quality culture can only succeed with outstanding support from organizational executives. The "tone at the top" significantly drives the performance and adherence of the organization to quality principles.

This could involve training, recognition programs, or changes to organizational structure. It is important to regularly assess the culture of quality and adjust as needed. Activities to foster a quality culture could include workshops, training sessions,

A robust biopharmaceutical QRM system recognizes that the process of risk identification is continuous and dynamic, adjusting to changes in procedures, equipment, materials, and the overall business environment.

recognition programs, and team-building activities. Regular culture assessments could be conducted through surveys or interviews and the findings used to inform culture improvement initiatives.

Flexibility and Adaptability

As the organization and its external environment change, the QRM system needs to be able to adapt. A rigid system that cannot handle change will quickly become ineffective. A flexible and adaptable QRM system allows the organization to respond effectively to changes and challenges, turning them into opportunities rather than threats. It helps ensure the system's resilience and long-term sustainability. Using data-driven metrics and tracking tools facilitates effective management of quality and compliance risk.

This can involve regular reviews of the QRM system and a process for making changes to it. Feedback from stakeholders should be actively sought and incorporated. Scenario analysis or stress testing could be used to evaluate and improve the system's adaptability. A change management process should be established to handle changes in a systematic and controlled manner. Integral to a change management process should be the incorporation of risk assessment and evaluation relevant to any proposed changes.

Compliance with Regulations

Biopharmaceutical companies operate in a heavily regulated environment. Compliance with regulations avoids legal problems and ensures products are safe and effective. It also promotes trust and credibility among stakeholders, and it provides a baseline for risk management practices.

Compliance can be ensured by keeping up to date with regulatory changes, incorporating these changes into the QRM system, and regularly auditing for compliance. Regular training should be provided to keep staff current on regulatory requirements. Regulatory intelligence activities could be conducted to anticipate and prepare for upcoming changes.

Compliance checks should be integrated into the risk assessment and review processes. Additionally, compliance reports and newsletters summarizing regulatory activity provide valuable insight into risks and trends associated with regulatory compliance for life sciences. Further expanding compliance data to broader time horizons increases insights into longer-term trends and the value of current trends in a historical perspective.

Traceability and Documentation

Documentation provides evidence of the QRM system's functioning. It also allows for traceability, which is crucial for root cause analysis and for demonstrating compliance with regulations. Proper documentation allows the team to preserve institutional knowledge, learn from past experiences, and demonstrate compliance. Traceability is crucial for investigating incidents, validating processes, and ensuring product quality.

Documentation should be maintained for all risk management activities, including risk identification, assessment, and control. It should be kept in a format that is easily accessible and understandable. Traceability can be maintained through unique identifiers for risks and control measures, and by linking related documents. A document management system could be used to manage and control documents. The system should support version control, approval processes, and easy retrieval of documents. Traceability could be maintained through traceability matrices or dedicated software systems.

CONCLUSION

An effective QRM system in biopharmaceutical manufacturing is multifaceted, involving the identification and assessment of potential risks, robust control mechanisms, effective communication strategies, and regular monitoring and review procedures. The QRM system should be flexible and adaptable, grounded in data-driven decision-making, and deeply integrated within the organization's culture and processes. The risk management process, which includes risk identification and mitigation, is a cross-functional effort requiring participation from R&D, quality, and manufacturing, with metrics for monitoring and reporting process effectiveness to cross-functional leaders.

Organizations performing at elevated levels consistently demonstrate an ability to incorporate risk criteria into daily operations using various tools to evaluate risk according to product and patient impact. Compliance with regulations and maintaining detailed traceability and documentation are also of paramount importance. Although implementing such a comprehensive system can be complex, the benefits of ensuring product quality and safety, and ultimately patient health, are profound. The successful deployment of QRM necessitates a continual commitment to each of these characteristics, fostering a culture of quality that permeates every aspect of the organization.

About the author

Michael Kuehne is a Principal at Comply FDA, where he leads the development and implementation of quality and compliance products and services for life science organizations designed to elevate capabilities to best-in-class performance and improve inspection readiness. Michael creates a collaborative quality management system assessment methodology using validated quality and compliance best practices to deliver strategic plans for sustained quality management system performance aligned with current Quality Management Maturity Model criteria. He is a patent author for innovation of clean room biological safety cabinets. He has held executive quality leadership roles in pharmaceutical and biologics organizations from Fortune 50 to startups and contract manufacturers.

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Frances Zipp Receives 2023 Professional Achievement Award

From left to right, ISPE Board of Directors Immediate Past Chair Michael L. Rutherford, Frances Zipp, and current ISPE Board Chair Scott W. Billman.

Frances (Fran) M. Zipp was awarded the ISPE Joseph X. Phillips Professional Achievement Award at the 2023 ISPE Annual Meeting and Expo. The award is named in honor of Joe Phillips, longtime supporter of ISPE and a leader in establishing the Society as an "integrator" of industry and regulators, both during his years of service with the FDA and later when he became International Regulatory Affairs Advisor to ISPE.

Fran is President and CEO of Lachman Consultant Services, Inc., which provides compliance, regulatory, and technical consulting services to global pharmaceutical and related industries, delivering strategic guidance and direction toward implementation of effective solutions to client needs across the biopharmaceutical network.

Fran has assisted and counseled senior-level management in a broad variety of areas involving corporate governance, compliance enhancement, 483 and Warning Letter responses and corrective actions, drug shortages, regulatory strategies, and compliance-policy-related matters. Fran has been part of the biopharmaceutical industry for over 40 years in both pharmaceutical manufacturing and consulting.

"As a longtime member of ISPE and former ISPE Board Chair, Fran's contributions to ISPE over the years have been remarkable and she's been directly responsible for multiple initiatives in ISPE," said Thomas Hartman, ISPE President and CEO. "She is one of the founding members of the ISPE Women in Pharma® international program. Fran also provided her leadership in the ISPE Drug Shortages Initiative and the ISPE Metrics Program."

"Fran inspired the ISPE International Board to invest in the workforce of the future," Hartman said, "and through the DAF-ACT enabled ISPE to play a key role in the COVID-19 industry response and positioned ISPE for opportunities of this type with the government in the future. She has been instrumental in the development of the Board Advisor program and ISPE Foundation. She has been generous with her time to ISPE programs over the years and these accomplishments demonstrate unprecedented ambassadorship."

In addition to these activities, Fran has been a regular presenter or moderator at many ISPE conference events, volunteered her company's time for GMP and data integrity training, has served as an expert panelist or facilitator on multiple regulatory driven events and webinars, and served as a reviewer for many ISPE guidance documents.

ISPE staff talked to Fran about her career and what ISPE means to her.

WHAT WAS YOUR FIRST JOB OUT OF COLLEGE?

I started out in a laboratory in a quality control department of Ciba pharmaceuticals. I only applied for the job and accepted the position because of the location of the firm—it was close to my favorite mall where I held a part-time job. My first line supervisor was an inspirational leader and he relayed to his team that we were an important element in availing drugs to patients. I was conducting the now extinct United States Pharmacopeia heavy metal testing on raw materials—not exactly glamourous or cutting edge—but we knew our role was important and we treated our tasks with the utmost integrity and respect.

I would drive home from work every day convinced I was making a difference and that I had the best job in the world. We would have weekly team meetings in the content uniformity lab and

our supervisor would explain how our work connected to patients. I was hooked. My minimum wage job was helping patients, it was the most important task I could do, and the pharma industry was giving me this amazing opportunity. I never forgot that and to this day, I am thankful every day that I had that experience.

As I look back after 40 years, I think it was my passion for learning as much as I could about this wonderful industry and the many opportunities I was offered, and also pushed to be offered, that allowed my career to span across departments, technologies, and geographies within the biopharmaceutical industry.

TELL US ABOUT YOUR CURRENT ROLE AND WHAT YOU DO.

Once again, I have to start with how thankful I am for the role in which I currently serve the industry and my team. As noted, I am the President and CEO of Lachman, and in this role, I have the opportunity to support and interact with an amazing team across the globe, all of whom share that same conviction I have carried with me since I was in my twenties: working within the pharma industry is a privilege and that industry makes a real difference.

Our team has, over 40 years, proactively partnered with the industry to help our clients achieve product and quality system excellence, enhance technologies, implement efficient and effective processes and systems, and understand regulatory challenges and opportunities. We never lose sight of why we do this: Our clients are serving patients. At some point in our lives, we all are patients or support loved ones who are. What could be more personal or important? Our value proposition sums it up: "We deliver high-value consulting, enabling clients to achieve product and quality system excellence for the patients that they serve."

WHAT DO YOU ENJOY MOST ABOUT YOUR WORK?

Every day I am humbled and inspired by the knowledge, drive, and commitment of our industry. I have learned so much from pharma colleagues, industry groups, regulators, and my team. I still end my workday, now not driving a short distance, but often running through an airport, thinking "I have the best job in the world." So, answering what I enjoy most is a tough question. I think what I am most proud of, as I enjoy every aspect of providing support, often in times of industry or client-specific challenges, is that I know my team of industry and regulatory professionals and subject matter experts shares my passion and commitment to excellence in all services we provide. We know we must be proactive, remain current on all aspects of our industry, give back to our industry by mentoring and participating in industry forums, and, most important, act with the urgency and integrity, which are the cornerstones of the pharma industry.

TELL US ABOUT A PROJECT YOU'RE PROUD OF OR ENJOYED WORKING ON.

One focus of our team that I personally feel energized by involves our work on educating on and helping implement practical solutions and controls in the areas of data integrity, data governance, and artificial intelligence–driven solutions in quality and manufacturing. There are so many opportunities for our industry, especially in controlled and efficient use of cutting-edge technologies, to transform the way our industry works—not only in manufacturing, development, and distribution, but in laboratory and quality assurance activities.

Robust and targeted regulatory compliant data, and the speed of decision-making based on this data, supports the timely delivery of quality products to patients. We all are aware of the shortage on a global basis of critical medicines. Helping firms that are clearly dedicated to addressing this crisis by partnering with them on advanced solutions in a sustainably complaint manner is, well, thrilling and a personal mandate.

WHAT DO YOU SEE NEXT FOR YOUR AREA IN THE PHARMACEUTICAL INDUSTRY?

With the rate of change in science and innovation in our industry, it is paramount that companies like ours [Lachman] are a guiding partner and leader for our clients. The world of pharmaceutical innovation is borderless, with more and more collaboration between regulators around the globe, and more access to technology that drives new treatments and therapies. Groups such as ISPE provide excellent forums for collaboration within our industry and continued participation is critical. Our focus, as an industry and industry partners, on being proud of what we do will continue to drive our success.

WHAT ADVICE WOULD YOU GIVE EMERGING LEADERS IN THE PHARMACEUTICAL INDUSTRY?

Be proud of what you do and approach your job with the highest level of integrity and commitment. Network, push yourself, never stop learning, be humble in the face of the accomplishments of our industry, and be grateful that you can contribute and make a difference. This difference not only helps others but will also guide you through your career.

WHAT HAVE YOU ENJOYED ABOUT BEING A MEMBER OF ISPE?

There is really not one program or project that I have enjoyed more than another. It is the people and resources I have encountered over my career. I always say, everything about work is personal, and ISPE is very personal to me. I grew up in ISPE and would not have had the opportunities I was afforded without the dedication of so many people, the great programs, education, and partnerships. I hope to continue to grow old (older?) with ISPE and continue learning. I welcome any opportunities to give back and I value all my interactions.

ABOUT THE ISPE INTERNATIONAL HONOR AWARDS

Award categories include the Max Seales Yonker Member of the Year, Richard B. Purdy Distinguished Achievement, Joseph X. Phillips Professional Achievement, Affiliate and Chapter Excellence, Committee of the Year, and Company of the Year. For more information and to nominate a colleague, Affiliate, Chapter, committee, or company visit ispe.org/membership/international-honor-awards

LAURA-ANN CHIN, PE

BIOTECHNOLOGY COMMUNITY OF PRACTICE CO-CHAIR

Laura-Ann Chin has more than 12 years of international and domestic contract and hands-on process engineering experience in the design and construction of current GMP facilities in the US, Europe, and Asia. She specializes in single-use solutions and modular technologies for scale-up, scale-out, and technology transfer in maximizing the performance of advanced therapy medicinal products, biotech, and bulk pharmaceutical facilities.

A leader in the engineering design process, Laura-Ann is currently the Director of Life Sciences at Barry-Wehmiller Design Group and her enthusiasm for the industry grows with every project she oversees. "My role is to essentially marry business development with the technical side of project execution. I thrive in an intellectually stimulating environment and am motivated when I get to solve engineering design challenges on a daily basis."

"As a process engineer at heart, I am constantly driven to ask the right questions to ensure each design is fully vetted. I like the fact that no single project is identical, things are always changing, and I get to work with many different clients to build world-class manufacturing facilities that improve the quality of human life and produce lifesaving therapies."

"I had the honor of leading the process engineering design for Merck's Keytruda pilot facility, which is a drug that has had a high success rate when coupled with chemotherapy to treat non-small cell lung cancer. To hear firsthand success stories from people with advanced-stage lung cancer that have been treated with Keytruda and have been able to have a second chance at life because of this drug, to be able to work with the very scientists that have been the drivers behind this lifesaving therapy, is an honor. As a cancer survivor, I know what it means to be given a second chance at life and I don't ever take that for granted. To be a part of the effort that leads to a final drug product that can cure and save lives is something I'm so proud of."

Laura-Ann extends her enthusiasm and energy to her volunteer work with ISPE. In addition to serving as co-chair of the Biotechnology Community of Practice (CoP) Steering Committee and being a member of the ISPE Biotechnology Conference International Program Committee, where she serves as an Education Track Leader, she is very involved with the Delaware Valley Chapter.

Since joining ISPE in 2015, she has served as the Chapter's Executive Vice President, Treasurer, Membership, and Emerging Leader chair. "One of the biggest benefits that I get from being on the CoP steering committee, as a Delaware Valley Chapter board member, or on a conference committee, is that it's an extension of my passion beyond the workplace. I get to tap into a global talent pool of like-minded and highly driven individuals who are just so intentional about improving the quality of human life."

"I have met some really awesome individuals through the CoP and Delaware Valley Chapter, ones that I look forward to seeing at conferences, or locally, ones that I trust and know I want to work with. It's an excellent community. You cannot build your network overnight. You build it over years of relationship building. That only comes through intentionally showing up at meetings or conferences—that's how you get to know people. I've been very fortunate to meet some really wonderful individuals who I have become lifelong friends with."

— Marcy Sanford, ISPE Publications Coordinator

GLENN LAWRENCE, PE, CPIP

CONTAINMENT COMMUNITY OF PRACTICE CHAIR

Glenn Lawrence's first position at Merck & Co. was as a shift engineer for a large factory in Rahway, New Jersey. It was a great learning ground for chemical processing and automation. Glenn was in operations when he was asked to join the engineering department, where he did plant design for active pharmaceutical ingredients and vaccines. He was then asked to take over the engineering department's process safety role, where he assisted Merck sites around the world in the design and installation of containment exposure engineering controls for potent compounds. At the same time, he joined the ISPE Containment Community of Practice (CoP) to increase his containment knowledge and expand his network of subject matter experts.

Glenn says that one of the most meaningful projects he worked on during his 37 years at Merck & Co. was during the AIDS epidemic. "At the height of the AIDS epidemic, Merck developed an antiviral therapy that prevented the HIV virus from replicating itself. Getting the drug to market became the number one objective for the company."

Glenn was selected to lead the process design for the manufacturing facility. "My team worked with the chemical research team during early clinical and technical trials to lay out how the plant would be designed, allowing the design teams to move quickly as soon as the clinical trials data showed that the drug was effective."

Merck & Co. held meetings with AIDS activists to assure them that the company was working as fast as it could to get the drug to market. Glenn says that the activists explained that every day the drug was delayed, was the equivalent of a Boeing 747 full of people crashing.

Merck & Co. started sourcing the drug out of their pilot plants for compassionate need, though the supply was not nearly enough to meet the need. Once construction of the manufacturing factories was complete, the team did not have enough people to complete the commissioning, qualification, and startup and validation in a timely manner due to the size and complexity of the facilities. To help resolve this issue, Merck & Co. management sent anyone at corporate headquarters who had an engineering degree or manufacturing experience to help with the startup of the facility. "It was a project that was very complicated, very high level, and one that changed and saved the lives of many AIDS patients. It was a mission rather than a project."

During his tenure at Merck, Glenn held a variety of critical roles and gained technical expertise in vaccine processing, therapeutic protein processing, chemical processing, sterile supply facilities, and clean utilities. He developed extensive knowledge in the design and execution of modular process equipment, single-use bioprocessing equipment, certified clean-in-place, sterilize-in-place, clean rooms, and process safety.

After retiring, Glenn joined a consulting firm and worked on projects for the Bill & Melinda Gates Foundation, the National Institutes of Health, and large and small pharmaceutical companies, including Merck & Co. Since leaving the consulting firm, he continues to volunteer with ISPE, serves on his university's Chemical Engineering External Advisory Committee, and is spending more time with his family and honing his saxophone playing skills.

A member of ISPE since 2009, in addition to serving as chair of the Containment CoP, Glenn was co-chair of the *ISPE Good Practice Guide: Containment for Potent Compounds* and a team member of the *ISPE Good Practice Guide: Good Engineering Practice (Second Edition)* and the *ISPE Baseline® Guide: Commissioning and Qualification (Second Edition)*. He is also active in the ISPE Delaware Valley Chapter.

— Marcy Sanford, ISPE Publications Coordinator

Key Findings from the 2023 C&Q Baseline® Guide Survey

By the Commissioning and Qualification Community of Practice Steering Committee

The *ISPE Baseline® Guide Volume 5: Commissioning and Qualification (Second Edition)* framework has gained significant attention, use, and adoption since the publication of the 2019 update. This article presents the key findings from the 2023 survey and shows the necessity for a new, more focused survey.

In 2023, a survey was sent to ISPE members to determine the adoption rate of the fundamentals described in the guide. Those survey results offer insights to the guide's implementation across various organizations. A new survey would accurately gauge the actual adoption rates and understanding of quality risk management (QRM) based commissioning and qualification (C&Q) implementation.

KEY FINDINGS FROM THE 2023 SURVEY

Awareness of the 2019 Update

The survey revealed that a substantial 85% of respondents were aware of the 2019 update to the guide. This indicates a high level of general awareness in the professional community about the latest developments in adoption of QRM-based C&Q.

Transition to Risk-Based Approaches

Approximately 68% of respondents indicated plans to transition from the traditional impact-assessment-based V-model to the risk-based approach. This shift signifies a growing recognition of the benefits of a more focused and flexible risk-oriented framework on which to apply project management and ensure quality assurance.

Implementation of QRM-Based C&Q

Most respondents are adopting QRM-based C&Q to align with current industry best practices. This trend is driven by corporate initiatives, speed to market, and regulatory expectation.

Knowledge Gaps in C&Q Baseline® Guide Fundamentals

Despite respondents' awareness of the C&Q guide, there's a general lack of understanding of the guide's fundamental principles in the application of QRM-based C&Q. Key gaps include continued use of the unsupported, non-risk-based V-model; how risk assessments are implemented to inform the manufacturing process control strategy; how risk is mitigated through the addition of controls; the role of quality in an integrated C&Q process; and the identification and documentation of critical process parameters (CPPs) in relation to product and process and individual systems.

Variable Definitions of Risk-Based Approaches

The definition of a risk-based approach varied among respondents. Many believe they are using a true risk-based approach when, in fact, they have merely modified past practices and guidance without fully integrating QRM principles. There is an apparent lack of understanding that the application of QRM is a prospective approach to apply quality by design to the design development process so that robust CPP control is optimized.

C&Q Costs Knowledge Gap

There's a notable lack of understanding regarding the costs of C&Q relative to total installed with equipment and systems verified as fit for intended purpose/qualified or total capital project costs, which include performance qualification/process validation (PQ/PV).

Underuse of Good Engineering Practices (GEPs)

The survey indicated a limited application of GEPs and a limited understanding of the concept of an engineering quality program needed to support the use of commissioning testing and documentation to support qualification. Fundamentally, GEPs deliver documented evidence such that installation and operation meet requirements.

Benefits of Implementing QRM-Based Integrated C&Q

For those who have implemented QRM-based integrated C&Q, several optimized methods have led to reductions in cost and time. These include overall process risk assessments, critical aspects (CAs) and critical design elements identified through system risk assessment (SRA), design review under GEPs providing design qualification as a deliverable, and focused quality reviews and approvals.

DELIVERABLE EXAMPLES

Did you know that there are a series of examples available as companion content with the C&Q Baseline® Guide? Use these to your advantage. Examples include user requirement specification (URS), SRA, design qualification, and acceptance and release covering single-use bioreactor, primary packaging (tablet blister), and secondary packaging (blisters).

2024 SURVEY

Given these findings, it is evident that although ISPE members are aware of the 2019 C&Q Baseline® Guide update, they have a significant gap in understanding and proper implementation. The current survey highlights several misconceptions and inconsistencies in the application of C&Q Baseline® Guide principles, especially regarding risk-based approaches and the integration of QRM in C&Q processes.

A new ISPE survey is accessible now via the QR code with the goal of more accurately reflecting industry understanding, adoption, and use of the C&Q Baseline® Guide. We very much appreciate your contribution to this survey, which will aid in our ability to provide additional content, training, and guidance to better equip industry to optimize C&Q and the overall project delivery process.

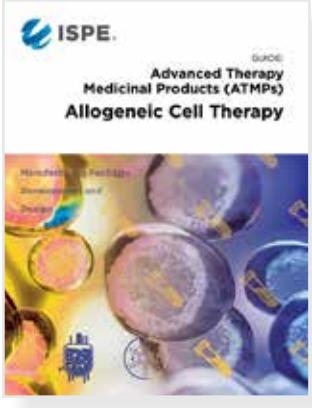
A new ISPE survey is accessible now via the QR code with the goal of more accurately reflecting industry understanding, adoption, and use of the C&Q Baseline® Guide.

Scan this QR code to take the survey.

New Guides Expand ATMP Knowledge

The *ISPE Guide: Advanced Therapy Medicinal Products – Allogeneic Cell Therapy* and the *ISPE Guide: Advanced Therapy Medicinal Products – Recombinant AAV Comparability and Lifecyle Management* were published earlier this year. These guides add to ISPE's library of knowledge in the growing and ever-evolving advanced therapy medicinal products (ATMPs) field.

ALLOGENEIC CELL THERAPY



ATMP therapies include cells, engineered tissues, or the manipulation of the patient's genome. Autologous cells are derived from a patient and returned to the same patient after in vitro manipulation. In allogeneic therapy, cells are collected from a donor. Then, after cell expansion and possible cell manipulation, the final cell therapy can be used to treat many patients.

The *ISPE Guide: ATMPs - Allogeneic Cell Therapy* was written and reviewed by a team of industry experts led by Komal Hatti, Director, Process Architect, IPS; Ian Moy, Senior Project Manager, Catalent Pharma Solutions; and Erik Steffensen, Managing Partner, Spot-on Pharma Consulting. This guide focuses primarily on allogeneic cell therapies, specifically manufacturing facility development and design.

"For allogeneic cell therapies, the cells are the product," said Steffensen. "This requires special considerations when designing the manufacturing process and the facility. In 2021, ISPE published the *ISPE Guide: ATMPs – Autologous Cell Therapy*. However, industry has been lacking guidance for allogeneic cell therapies where collected donor cells are modified and multiplied such that a manufactured batch can be used for many patients."

Allogeneic cell therapies have unique challenges due to the small manufacturing scale, limitations in scale-up, the need to manufacture multiple lots of products concurrently, and the need for flexibility to accommodate a varied and developing product portfolio. "This guide covers common challenges with allogeneic cell therapy facilities, design concepts specific to allogeneic cell therapy facilities, and GMP layout and architectural design development," said Moy.

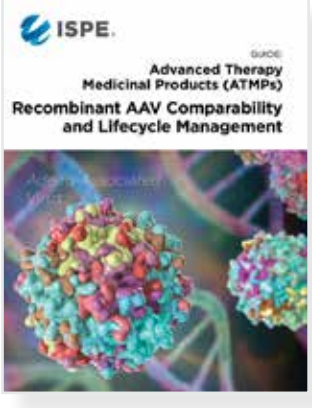
"This new guide builds on 30 years of manufacturing experience within recombinant proteins and antibodies while providing additional guidance for cell therapy specific issues," added Moy. "This guide provides valuable insight into best practices for the design, establishment, and operation of allogeneic cell therapy facilities."

Although this guide focuses on allogeneic cell therapies to the greatest extent possible, the authors recognize a significant amount of content is applicable to other types of ATMPs, particularly around regulatory compliance, technology transfer, utilities, HVAC, and supply chain.

Hatti said the authoring team paid special attention to these topics while researching and writing, "By increasing the knowledge base for manufacture of allogeneic cell therapies, this guide takes the industry closer to making cell therapies more affordable and thereby widens the patient base. The content and structure of the guide are organized to reflect similarities and highlight differences between autologous and allogeneic processes and facilities design."

RECOMBINANT AAV COMPARABILITY AND LIFECYLE MANAGEMENT

Comparability of an ATMP product is another area with little industry guidance. As gene therapy products race toward clinic and commercial launch, sponsor companies are faced with significant hurdles posed by evolving manufacturing platforms, process improvements across multiple stages of development, and a rapidly growing tool kit for the characterization of viral vectors. Taken together, this creates a complex landscape for demonstrating comparability driven by process changes.



Written and reviewed by industry experts led by George Todorov, Senior Process Technologist, IPS-Integrated Project Services LLC, and Lucile

Bessueille, Regional Head, Audit & Inspection, F. Hoffmann-La Roche AG, the *ISPE Guide: ATMPs – Recombinant AAV Comparability and Lifecyle Management* provides guidance in this ever-changing area.

"Drawing on a team of industry experts with global experience, the guide provides current understanding and best practices on recombinant adeno-associated virus (rAAV) comparability exercises, offering manufacturers a standardized approach for developing process and product comparability strategies. It provides considerations for evaluating rAAV vector products comparability pre- and post-change to the manufacturing process and proposes strategies to address the unique challenges posed by this new class of products," said Todorov.

Bessueille adds, "The information shared in this guide enables the reader to better manage rAAV comparability, and plan for the safe and effective delivery of revolutionary medicines throughout the product life cycle. It provides a playbook to help drug developers assess the need for comparability studies and design and execute studies to successfully demonstrate rAAV product comparability pre- and post-change."

After reading this guide, the reader will understand:

- How to address rAAV comparability challenges
- Recommendations when designing an analytical comparability strategy for rAAV vector products
- Current understanding and best practices on rAAV comparability exercises
- A standardized approach to develop process and product comparability strategies

In addition, the guide presents three realistic case studies for changes likely to be encountered during a rAAV product's life cycle. They cover various phases (preclinical, clinical, and commercial), detailing changes, how to assess them, what kind of development and characterization data should be generated, how the data informs the comparability protocol, and what additional considerations should be included in the comparability protocol.

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

Pharma 4.0™ Plug and Produce Working Group Publishes Concept Papers

By Marcy Sanford

One of the primary technical objectives of the ISPE Pharma 4.0™ Plug and Produce Working Group is to assist the Pharma 4.0™ digital transformation by enabling seamless integration and interoperability between all systems components and operational technology to advance the overall digital maturity toward predictive and adaptable operations.

To that end, the group recently published two new concept papers authored by a diverse group of subject matter experts in the field. Each paper builds on a concept presented in the *ISPE Baseline® Guide Volume 8: Pharma 4.0™* and presents a real-world test case scenario.

"The papers are the result of aligned Pharma 4.0™ architectural and connectivity concepts that were road tested in actual multi-vendor equipment implementations to demonstrate horizontal and vertical integration for plug and produce in the life science industry," said Pharma 4.0™ Community of Practice Co-Chair Wolfgang Winter, Director at Agilent Technologies Deutschland GmbH. "The 'road testing' happened in a combination of 'Plugfests' and proof-of-concept, or pilot installation, in collaboration with selected pharmaceutical manufacturing sites."

IT/OT ARCHITECTURES FOR PRESCRIPTIVE MAINTENANCE

The concept paper *Pharma 4.0 – Towards IT/OT Architectures for Prescriptive Maintenance* identifies the principles that an architecture should incorporate to move toward plug and produce capability. It is designed to help the reader understand the importance of those principles and apply them in the context of their unique starting position on their journey to realize Pharma 4.0™.

"We are not trying to define a new industry standard in this concept paper—instead, we present concepts that are informed and take in existing, relevant approaches, technologies, and standards where applicable," said Josef Trapl, co-author of the paper and Managing Director at Memo3 GmbH. "In the paper, the implementation of the predictive maintenance use case at a CMO [contract manufacturing organization], operating a 60 L pilot-scale reactor under GxP, demonstrated the feasibility of using smart sensor data for prescriptive condition-based monitoring of equipment that is outside of the typical system constraints in the old ISA-95 automation pyramid. The paper successfully leverages the NAMUR Open Architecture, but also reveals certain gaps in the existing approach. The team therefore explored the Industry 4.0 concept of modeling and transporting maintenance-relevant metadata through the use of the asset administration shell."

INFORMATION MODEL CONCEPT ON OPC UA FOR ALARMS AND AUDIT TRAILS

Plug and play in general describes a piece of equipment that is ready to use upon connecting to a computer without any configuration, like a home printer. Plug and produce has the same vision for manufacturing and aims to enable straightforward integration of new production equipment or a device to substitute or adapt assembly line parts.

Concepts like OPC Unified Architecture (UA) and Modular Type Package (MTP) are the groundwork for the standardization of interfaces and data formats for shop floor manufacturing equipment to enable plug and produce. However, current standards focus either on technical integration concepts or information structures.

Technical integration, information structure, and biopharmaceutical-specific elements and documentation need to be in place to fully realize plug and produce. The concept paper *Process Events for the Life Science Industry–Information Model Concept on OPC UA for Alarms and Audit Trails* proves that a standard model within OPC UA Alarms and Conditions (OPC UA Part 9) can be leveraged to realize plug and produce for exchanging pharmaceutical alarms and audit trails between OT manufacturing equipment and orchestration platforms or IT services like electronic batch record or historian.

"We are extremely excited to see this work come to fruition and are extremely proud of the team's accomplishments to make this happen," said Winter. "With these released, we are ready to tackle the next Plug and Produce concepts and POCs on our roadmap."

Other concept papers from the ISPE Pharma 4.0™ Plug and Produce Working Group include *Connectivity between Shopfloor & Manufacturing Operations Management Systems with OPC UA – A Tangible Step Toward Plug & Produce* and *A Simplified Integration of Qualified Laboratory Devices with the Asset Administration Shell as the Digital Twin.*

Access to concept and discussion papers is an ISPE member benefit. Papers can be downloaded at ispe.org/publications/papers

2024 ISPE BIOTECHNOLOGY CONFERENCE

2024 ISPE Biotechnology Conference Q&A

By Phillip R. Smith, PhD

The 2024 ISPE Biotechnology Conference will be held 17–18 June in Boston, Massachusetts, and virtually. Phillip R. Smith is the conference's Planning Chair. He shares what attendees can expect at the upcoming conference.

WHAT ARE THE TOP THREE REASONS YOU WOULD TELL SOMEONE THEY SHOULD ATTEND THIS CONFERENCE?

The ISPE Biotechnology Conference is known for its very strong technical program; the track topics and individual talks are highly relevant to today's biotech industry needs. The conference also provides a unique opportunity to network with industry leaders and peers and the exhibit hall is an excellent showcase of a broad variety of new and important technologies and service offerings that are applicable across the industry.

WHAT ARE YOU MOST LOOKING FORWARD TO?

I am really looking forward to the keynote addresses. With topics spanning healthcare access, global supply chain strategy, nanotechnology and mRNA, digital twins, and more, the keynotes promise to be exciting and relevant. I'm particularly excited for talks addressing hot topics in the industry such as digital technology transfer and advanced manufacturing technologies.

ANY ADVICE FOR SOMEONE TO MAKE THE MOST OUT OF THE CONFERENCE?

My advice is to read the program in advance, plan out the talks and exhibition booths you will attend, and come prepared with questions. This will enable you to extract the most value for you and your company while contributing to the conference.

WHY DO YOU THINK PROFESSIONAL DEVELOPMENT IS IMPORTANT?

We work in a fast-paced and rapidly evolving industry. Technologies are changing frequently, including new and advanced therapeutic modalities, manufacturing equipment and facilities, digital strategies, and quality and regulatory requirements. Focused professional development, such as that available at the 2024 ISPE Biotechnology Conference, enables one to stay abreast of these and other emerging trends. The conference is a key opportunity to develop in each of these areas, and, in addition, network with the industry's best.

WHY DID YOU ACCEPT THE INVITATION TO BE CONFERENCE CHAIR?

I accepted the invitation to be the conference chair for a few reasons. I believe in the potential of the conference to be a driving force in the industry to bring forward and share new ideas and technologies, and I am honored to be a part of that. Additionally, the conference provides an opportunity for Emerging Leaders to participate—they are the future of the biotech industry. I look forward to seeing their contributions. Finally, this conference brings together leaders, experts, and practitioners from biotech companies, academia, technology and service providers, and regulatory agencies. This productive dialogue is critical to the advancement of the biotech industry, and I am excited to see it happen in June in Boston!

WHY DO YOU ENJOY BEING A MEMBER OF ISPE?

The ISPE organization has an amazing array of opportunities for engineers across the biotech industry to leverage, from Communities of Practice to technical reports and guidelines and conferences and workshops. I value my past and present interactions with members of ISPE. They are among the best and brightest in the industry. I am honored to be a part of such an organization that is focused on guiding the biotech industry in bringing new and critically important medicines to patients in need while providing opportunities for professional development and fostering a collaborative environment.

About the author

Phillip R. Smith, PhD, is the Director of Process Technology in the GSK Biopharm R&D Clinical Manufacturing Pilot Plant in King of Prussia, PA. He leads a team of scientists who conduct technology transfer, facility fit, scale-up, and troubleshooting activities for drug substance manufacturing processes. Other responsibilities include authoring of regulatory submissions and industrialization of new processing technologies. Previous roles include late-phase process development, characterization, and control strategy development for downstream unit operations in GSK Biopharm R&D, and early-phase downstream process development and technology transfer at Bristol Myers Squibb. Phillip is also a leader in quality by design practice within GSK and a member of the Biopharm Sustainability team. He regularly presents at industry conferences and participates in various industry consortia. Phillip received his BS and MS in chemical engineering from Brigham Young University, and a PhD in chemical engineering from Stanford University. He joined ISPE in 2014.

2024 ISPE BIOTECHNOLOGY CONFERENCE

17 - 18 June 2024
Boston, MA, USA and Virtual

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2024 ISPE BIOTECHNOLOGY CONFERENCE

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ISPE

Join us as we delve into essential topics that lie at the intersection of innovation and regulation, including:

Artificial Intelligence (AI): Learn how AI is helping optimize biotech manufacturing processes, especially in innovative fields like ATMPs and gene therapy.

Facility Design: Examine trends and regulatory mandates in biopharmaceutical facility design to ensure adherence to industry standards.

Novel Technology Innovations: Explore cutting-edge advancements in biopharmaceutical manufacturing that meet rigorous regulatory requirements

Featured Speakers

Sharmista Chatterjee, PhD
Division Director CDER
FDA

Francesco Cicirello
Senior Director, Quality Compliance BioNTainer
BioNTech US Inc

Richard Denk
Senior Consultant Aseptic Processing & Containment
SKAN AG

Robert Langer, PhD
Institute Professor
Massachusetts Institute of Technology

Piper Trelstad, Ph.D
Head of Chemistry, Manufacturing & Controls
Bill & Melinda Gates Medical Research Institute

Rene-Pascal Fischer
Scientist & Software Architect
Fraunhofer IESE

Learn more and register at ISPE.org/Bio24

2024 ISPE Facilities of the Future Conference: Keynote Presentations

By Scott Fotheringham, PhD

The 2024 ISPE Facilities of the Future Conference opened on 29 January in San Francisco, California, with a series of six keynote presentations on innovations that are leading to advanced manufacturing facilities. Thomas Hartman, President and CEO of ISPE, introduced each of the keynote speakers.

KEYNOTE SPEAKERS

The first speaker, Karl Kogelmueller, Takeda Manufacturing Austria AG, described the ways Takeda is embarking on a digital transformation journey to meet its goals of creating an uninterrupted supply chain, taking care of its internal resources, and ensuring sustainability.

Carlos Santiago, of GlaxoSmithKline, outlined the design of his company's first integrated vaccines and research and development (R&D) building. Because almost three-quarters of the retrofit will be dedicated to lab space, the design was optimized for efficiency and includes offsite storage and service delivery.

Carla J. Lundi, Office of Quality Surveillance, FDA/CDER, described the work of her office in supporting quality in pharmaceutical manufacturing to counteract shortages of essential medicines. Key to this work is CDER's quality management maturity program.

Patricia Martin, Martin Equity, LLC, spoke about the value of the human resources that are essential to the workforce of the future. She spoke about worker dissatisfaction and aspects of a work situation that can be controlled to mitigate this by factors that are under the control of management.

Christian Randecker, Genentech, described the design of a new clinical supply center, which is flexible, uses innovative technologies, and can be replicated for clinical or commercial production.

Deborah Donovan, Moderna, shared her company's ambitious goal of achieving net zero emissions by 2030, mostly by reducing energy use onsite, relying on renewable energy production, and offsetting emissions with renewable energy certificates.

END-TO-END SUPPLY CHAIN DIGITAL TRANSFORMATION

Karl Kogelmueller, Head of Transformation Strategy, Takeda Manufacturing Austria AG

Kogelmueller outlined the ways Takeda, as a data-driven organization, intends to use digitalization and automation for cost management in its manufacturing operations and supply chain. He listed the external challenges impacting biopharmaceutical supply chains, focusing on increased economic, financial, and geopolitical risks as a result of the war in Ukraine. Kogelmueller then spoke of the four phases in a digital transformation: building insights with pilot projects, capturing value through scaling, achieving scale, and becoming a fully data-driven organization. Unfortunately, he noted, half of companies are stalled during the second phase.

Takeda has a strategy to link aspects of its digitalization journey to its business goals, which include an uninterrupted supply chain, investments in upskilling its people, and environmental stewardship. Everything is wrapped up in roadmaps the company can refer to along its journey, not only at individual sites but throughout the organization.

This is coordinated by an upgraded continuous improvement program that starts with an architect workstream. It designs blueprints for the future-ready areas in the sites. A builder workstream follows, in which engineers and manufacturing science staff determine what technologies to use. The other two builder workstreams focus on enterprise excellence and organizational learning, ensuring continuous improvements and organizational change management and learning. Kogelmueller stressed that continuous improvement is the baseline for transformational changes.

Despite its momentum, Takeda faces challenges. One of these is the enterprise-wide complexity of having large numbers of operating units in plasma biologics, molecules, and small molecules; multiple sites; and thousands of SKUs. To overcome this, it understands the need to systematically use its strategy and value creation, and combine both, to prioritize initiatives. Digital transformation requires a strong governance body—such as a top-level steering committee—capable of making tough decisions. By using all this, it can deal with that complexity and implement the transformation as planned. Such a transformation also requires

training employees in new competencies, developing new ways of engaging workers, and ensuring their well-being.

BUILDING A WORKPLACE OF THE FUTURE WITHIN A RESEARCH SITE

Carlos Santiago, Vice President, Head of Americas, GlaxoSmithKline (GSK)

Santiago described the creation of a workplace of the future for GSK's research scientists based on what the company had previously applied to its headquarters and some commercial facilities. This is a retrofit designed for a roughly 200,000-square-foot building in Cambridge, Massachusetts, to be used as the company's first integrated vaccines and infectious disease R&D center. Almost three-quarters of the building will be dedicated to lab space. To meet corporate sustainability goals, this retrofit will leverage heat recovery systems, use of sustainable materials, waste diversion, and water reduction.

To accomplish this, vaccines R&D will be moved from an existing facility—which will be decommissioned—into this building. The transition requires change management to avoid disrupting the existing pipeline by having two teams, integrated plans, and redundancy in some equipment and science.

EMPLOYEE WELL-BEING IS IMPERATIVE

Knowing talent is tough to attract and retain, GSK aims to foster an engaged workplace, using a design that focuses on worker well-being and health. The space is designed to meet WELL Gold standards, incorporating active design principles, integrating lab spaces with the natural surroundings, ensuring good air quality, and providing attractive amenities. Accessibility is ensured by overcoming physical barriers, adding assistive equipment, and including ergonomic workstations. Technology is used to simplify the work environment, such as a comprehensive app for wayfinding and other logistics.

The design encourages collaboration and is flexible to meet contingencies of geography and culture of this, or any, location. With the advent of more remote work, the design builds in allowance for partial attendance to optimize the size of the space. The design is flexible and, upon review, can be revamped over time to meet different conditions.

Offsite Provisioning Hub

Working with service partners, GSK will create an offsite provisioning hub to manage material storage and services that aren't required for just-in-time delivery. This optimizes the use of prime real estate, improving efficiency in the lab.

BEYOND CGMP: PROACTIVE QUALITY PRINCIPLES TODAY FOR FACILITIES OF TOMORROW

Carla J. Lundi, Senior Consumer Safety Officer, FDA/CDER, Office of Quality Surveillance (OQS)

Lundi talked about the work of the OQS to promote and support quality among pharmaceutical manufacturers. Currently,

A 2019 FDA report identified the root cause of drug shortages as the lack of quality management that focuses on continuous improvement and early detection of supply chain issues.

the OQS is most concerned with the global shortfall of critical drugs, particularly sterile injectables. The main reasons for new shortages are quality issues and manufacturing delays. She highlighted disruptions in the supply chain resulting in recalls and shortages, such as manufacturing reliability, active pharmaceutical ingredient (API) and key component availability, aging facilities, natural disaster and public health emergencies, economic upheaval, manufacturing site closures, and geopolitical issues. The top manufacturing compliance concerns contributing to shortages include microbial contamination, poor excipient quality, lack of data integrity, and inadequate controls.

FRAME Supports Viable Solutions

A possible solution to shortages is the use of advanced manufacturing technologies. CDER applies the FDA Framework for Regulatory Advanced Manufacturing Evaluation (FRAME) to support industry by issuing guidance on emerging technologies, clarifying regulatory and data requirements to support applications, and publishing discussion papers on artificial intelligence (AI) and machine learning. FRAME priority technologies are distributed manufacturing, end-to-end continuous manufacturing, point-of-care manufacturing, and AI. Guidance documents are designed to address regulatory concerns, including batch definition, process dynamics, change in production output, and continuous process verification.

The OQS currently focuses on opportunities for senior management oversight and manufacturing modernization, including automation, isolator and barrier technologies to improve the aseptic manufacturing of sterile injectables, and advanced quality management system approaches.

The FDA Quality Management Maturity (QMM) Program

A 2019 FDA report identified the root cause of drug shortages as the lack of quality management that focuses on continuous improvement and early detection of supply chain issues. CDER has defined QMM, which is a potential solution to drug shortages, as "the extent to which drug manufacturing establishments implement quality management practices that prioritize patients, drive continual improvement, and enhance the supply chain reliability through the strategic integration

of business decisions and manufacturing operations with quality practices and technological advancements" [1].

The goals of the QMM program are to:

- Foster a strong quality culture mindset
- Recognize establishments that advance and continually improve quality management
- Identify areas where quality management can be enhanced
- Minimize risks to product availability to ensure reliable market supply

A Federal Register notification published January 2024 announced that the FDA is soliciting drug manufacturing sites to voluntarily participate in a QMM program at CDER [1].

Lundi concluded by saying that quality assurance requires everyone's collaboration to protect the interests of patients through proactive management of supply chain complexities to ensure the availability of essential medicines.

WORKFORCE OF THE FUTURE: THE INFLUENCE AND IMPORTANCE OF PEOPLE

Patricia Martin, Partner, Martin Equity, LLC

Martin divided her presentation about the current state of workers and what they might need to evolve into the workforce of the future into concerns, conundrums, and control. She began by listing the most pressing employee concerns, which include the fear that automation is putting their jobs at risk, that they're ready to be retrained, and that few will have stable, long-term employment.

Martin shared survey results showing that, although only 11% of people work remotely, they report being the most satisfied with their jobs, particularly when they get to make the decision to work remotely. Results also showed that more than one-third of those working onsite or hybrid are dissatisfied with their jobs. Many don't have a choice to work remotely, including those in construction, labs, and manufacturing. This dissatisfaction could be due to several factors, but employers should consider what their workforce needs for their companies to deliver.

What Can They Control?

This level of job dissatisfaction matters to those in the pharmaceutical industry who are delivering the facilities that make essential medicines. Having a motivated and satisfied workforce can make or break a project and can directly impact the delivery of medicines to the people who need them most.

Martin used *The 7 Habits of Highly Effective People*, by Stephen Covey, to show what can be controlled to impact employee satisfaction. She talked about the need for people managers to focus on three things related to their workforce: concern, influence, and control. What are employee concerns? What influence does a manager have? What is under their control? She shared two tools to provide some control over the outcome.

The first is trust. Martin has found that trust depends on high credibility, reliability, and intimacy. Just as importantly, it relies on a low level of self-interest—a worker interested in the good of their team and their company is easier to trust. Trust is more difficult to establish for remote workers because they have fewer opportunities to interact in person.

The other tool she shared, called "getting the cow out of the ditch," was a humorous, three-step process for problem-solving. Martin uses this to resolve critical problems, such as the time when her former employer was faced with an inability to make an essential portfolio drug product. The process involves the following steps.

1. Get the cow out of the ditch, i.e., find an immediate solution
2. Then, figure out how the cow got there
3. Only then, determine how to keep the cow out of the ditch the next time

These tools work together. Trust is important because relationships with people are one-on-one, and a team can get out of a "ditch" if they give each other a hand.

FACILITY OF THE FUTURE DESIGN PHILOSOPHY TENSIONS FOR GENENTECH'S NEW CLINICAL SUPPLY CENTER

Christian Randecker, Senior Director of Operations Process Support and Process Engineering, Genentech

Randecker shared the design of Genentech's new clinical supply center, which ran its first current Good Manufacturing Practice (cGMP) batch in 2022. Genentech bucked its history of using stainless steel equipment for large-scale production. This allowed the transition in this facility to products for much smaller patient populations and more potent products with improved titers and yields. The mission was to build an agile, small-volume facility, leveraging new technologies, at unprecedented speed. The template design can be copied anywhere for commercial production.

Can Single Use Be Sustainable?

The facility relies fully on single-use technology (SUT), meaning nothing related to process or product is reused and, with no stainless steel, there is no need for clean-in-place, a parts washer, steam, or autoclaves. A life cycle assessment demonstrated that, although SUT generates considerably more solid waste, it has significant reductions in the use of energy and water, as well as aqueous waste, which tips the sustainability scale in its favor.

Flexible Design for Clinical and Commercial Production

The constraint of needing one design for both clinical and commercial production led to innovation. Utilities requirements were tweaked so clinical processes in one workcell could operate successfully at 50- to 2,000-liter capacities, with the option to reconfigure the layout without restrictions. By reconfiguring the layout, a consistent layout for commercial production was produced.

This design can be replicated identically in a new facility, including standard automation, equipment, consumables, procedures, and training. At the highest level is a single enterprise risk management (ERM) tool for taking in all process definition data,

then pushing it out to execution and control systems. This gives a common feel for operators in this or any copy facility and provides modular components, a flexible and adaptable system, and a more efficient and scalable network.

An Inspection-Ready Ballroom Design

Closed processing allowed an ISO 9 ballroom design, which maintains flexibility, optimizes material flow into and waste out of the facility, and improves sight lines. Compliance concerns, particularly about the lack of a wall between pre- and post-viral steps, were overcome by developing a layers-of-protection approach, with multiple layers of controls to prevent failures, followed by continuous improvement.

EXPANDING GLOBALLY WHILE ACHIEVING NET ZERO

Deborah Donovan, Senior Vice President of Environment, Health & Safety, Moderna Therapeutics

Donovan outlined Moderna's plan to meet its goal of net zero emissions by 2030 while expanding globally. Although its overall emissions have increased since 2021, mostly due to expansion of its existing facility, the global expansion—four manufacturing facilities under construction, two laboratories, corporate headquarters, and R&D headquarters—has contributed little to this increase due to sustainability initiatives incorporated into the new buildings.

Moderna's strategy encompasses sustainability by design, natural resource conservation, and decarbonization of the value chain. It has the benefit, as a platform company, of needing a limited number of materials and suppliers, most of which already have science-based targets and are committed to net zero themselves. The sustainability strategy depends on data to assess the current state, quantify carbon emissions, and monitor, manage, and control emissions to continuously improve.

All the company's scope 2 emissions (i.e., from purchased energy, including electricity) are offset by purchasing renewable energy certificates. Scope 3 emissions are more than 90% of Moderna's emissions, the largest of which is purchased goods and services, including from contract research and manufacturing organizations and clinical activities.

Over the next two years, Moderna will focus on energy efficiency projects at its existing site. This will then allow it to transition from natural-gas-fired equipment to heat pumps, having determined electricity needs and sized the necessary equipment. This gives the local utility company time to upgrade its equipment to meet the facility's future electricity demands.

Sustainability and LEED standards were incorporated into the design of the new buildings. There is one design for three of the facilities, all of which are electric. Its corporate headquarters is slated to be the most energy-efficient building in Cambridge, Massachusetts. Sustainability measures will be built in, including a focus on embodied carbon, design for resilience in case of a natural disaster, and aims for Fitwel and WELL certification, as well as LEED Platinum and LEED Zero once in operation. It will have heat pumps to provide both heating and cooling throughout the lab building, solar panels on the roof, harvested rainwater to supply the chiller plant, and electric vehicle charging. Electricity will be supplied by onsite and offsite renewables.

The roadmap to net zero includes starting up the new facilities, gathering baseline information, submitting a greenhouse gas roadmap for validation by the Science-Based Target initiative (SBTi), and continuing to enhance energy programs and greenhouse gas management programs.

> The 2025 ISPE Facilities of the Future Conference will be held in San Francisco, California, 27–28 January.

EXECUTIVE FORUM PANEL

Supported by ISPE's Women in Pharma®, this panel of six industry leaders was moderated by James Breen, ISPE Foundation Board Liaison and Vice President, Global Engineering and Technology at Johnson & Johnson Innovative Medicines. Martin, Lundi, and Donovan, who also gave keynote presentations at the conference, participated in the panel. The other speakers were Melody Spradlin, Vice President, Global Workplace Services, KLA; Katrina Moseley Journey, Vice President of Commercial, Luminopia Inc.; and Muriel Campbell, Senior Director of External API Manufacturing, Eli Lilly & Co.

In a wide-ranging and lively discussion that lasted more than an hour, the speakers provided a range of viewpoints based on their expertise in sustainability, engineering, regulations, marketing, and investing. They shared insights into the ways in which the transition to facilities of the future has impacted their careers and how they have responded to it, the ways others can prepare for an increasingly uncertain future, and how the industry can ensure sustainability is achieved. Here are a few of the many highlights from this discussion.

When Martin was asked how she thought people should prepare themselves for the coming changes, she joked that they should get a crystal ball. Then, seriously, she recommended gathering as wide a range of information as possible, and not limiting it to what is fed to us or what we already know.

Campbell, who was trained in Puerto Rico and raised her young family there, shared a pivotal moment in her career when she was recommended for an assignment in Indianapolis. It meant moving her three school-age daughters to a new place, but the move took her out of her comfort zone and expanded what she knew. She said it had been a big leap but is working out for the best for her family and her career.

Given the uptick of remote work, there is a concern about maintaining engagement for older workers who may prefer remote work and younger workers who may struggle networking when they aren't with their colleagues in person. Moseley Journey, who works for a healthcare tech company with a multigenerational workforce, said she makes a point of meeting with others to give them a connection to the company and help them get more comfortable expressing themselves. She believes it's incumbent upon the leadership team to reach out to younger or new staff to ask questions that are not about their core job such as, "What do you want to do with your life?" and "How are you thinking about the world around you?"

Many panelists wanted to answer what the biggest thing is that they've learned from being involved in ISPE. Spradlin credited ISPE as one of the reasons she was able to move ahead in her career. She referred to the network of women who were leaders across the country and who were involved in supporting everything from childcare when members had to attend meetings to career advice.

Wrapping up the forum, each panelist was asked to provide one word to define the facility of the future. The words chosen were resilient, connected, flexible, human, people-oriented, and resource—words that could easily be used to describe these panelists.

About the author

Scott Fotheringham, PhD, is a freelance medical and science writer who works with clients in the life sciences. Scott's interests span fields as diverse as pharmaceuticals, biotechnology, molecular genetics, food and beverage manufacturing, and medical cannabis. Scott has been a contributor to *Pharmaceutical Engineering®* since 2015.

Disclaimer

This article contains an unabridged, unofficial summary of regulators and industry panelists' presentations and discussion during a panel dialogue at an ISPE conference that has not been vetted by any agency or organization. The responses are an informal and brief synopsis of the panel's views and do not represent official guidance or policy of any agency or organization.

References

1. Federal Register. FDA. "Voluntary Quality Management Maturity Prototype Assessment Protocol Evaluation Program." 25 January 2024. https://www.federalregister.gov/documents/2024/01/25/2024-01423/voluntary-quality-management-maturity-prototype-assessment-protocol-evaluation-program

Meet the ISPE STAFF

Matt Lehmann

In each issue of *Pharmaceutical Engineering®*, we introduce a member of the ISPE staff who provides ISPE members with key information and services. Meet Matt Lehmann, Custom Training Manager, Professional Development.

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

Daily, my role typifies ISPE's tagline: connecting pharmaceutical knowledge, by being part of a team that helps pharma and biotech clients select a custom, privately delivered training course to attain their learning and development goals. Once a course is determined, I contact qualified instructors to see if they are available to deliver the training material on the requested dates.

I also support all aspects of onboarding new instructors and provide a Train-the-Trainer course when they become qualified. I was a training facilitator most of my 28 years in the pharma industry, so I have an affinity for trainers because of my love for helping people learn.

I often network on LinkedIn with potential clients and industry colleagues, informing them on what ISPE offers for professional development, conferences, publications, memberships, and programs.

What do you love about your job?

I love being part of the Professional Development team, supporting organizations to help them meet their training goals, and working alongside trainers who possess incredible knowledge and expertise and are willing to share it.

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

I enjoy spending time with my wife, being involved in church ministries, playing guitar, and traveling.

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INNOVATION

Eli Lilly Kinsale Limited

PROJECT
IE2b

LOCATION
Kinsale, Ireland

SOCIAL IMPACT

Chugai Pharma Manufacturing Co., Ltd.

PROJECT
UK4 Project

LOCATION
Tokyo, Japan

OPERATIONS – *Project Execution*

Pfizer Asia Pacific Manufacturing Ltd

PROJECT
Pfizer API Facility Extension

LOCATION
Tuas, Singapore

HONORABLE MENTION

United Therapeutics Corporation

PROJECT
Lightyear

LOCATION
Research Triangle Park, North Carolina, USA

OPERATIONS – *Facility Fit*

Takeda Austria GmbH

PROJECT
beePFS - Prefilled Syringe Filling

LOCATION
Linz, Austria

HONORABLE MENTION

Zydus Pharmaceuticals Ltd.

PROJECT
Oral Solid Dosage Manufacturing Facility

LOCATION
Gujarat, India

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