

Precision Manufacturing

Optimizing the Manufacturing Lifecycle for Transformative Medicines

PRECISION
for medicine

PROJECT FARMA
A PRECISION FOR MEDICINE COMPANY

BASELINE
CONTROLS



About Us

3200+

Team Members

40

Offices in NA, EU,
and APAC

100+

Tech Ops Partnerships

90%

Client Retention Rate

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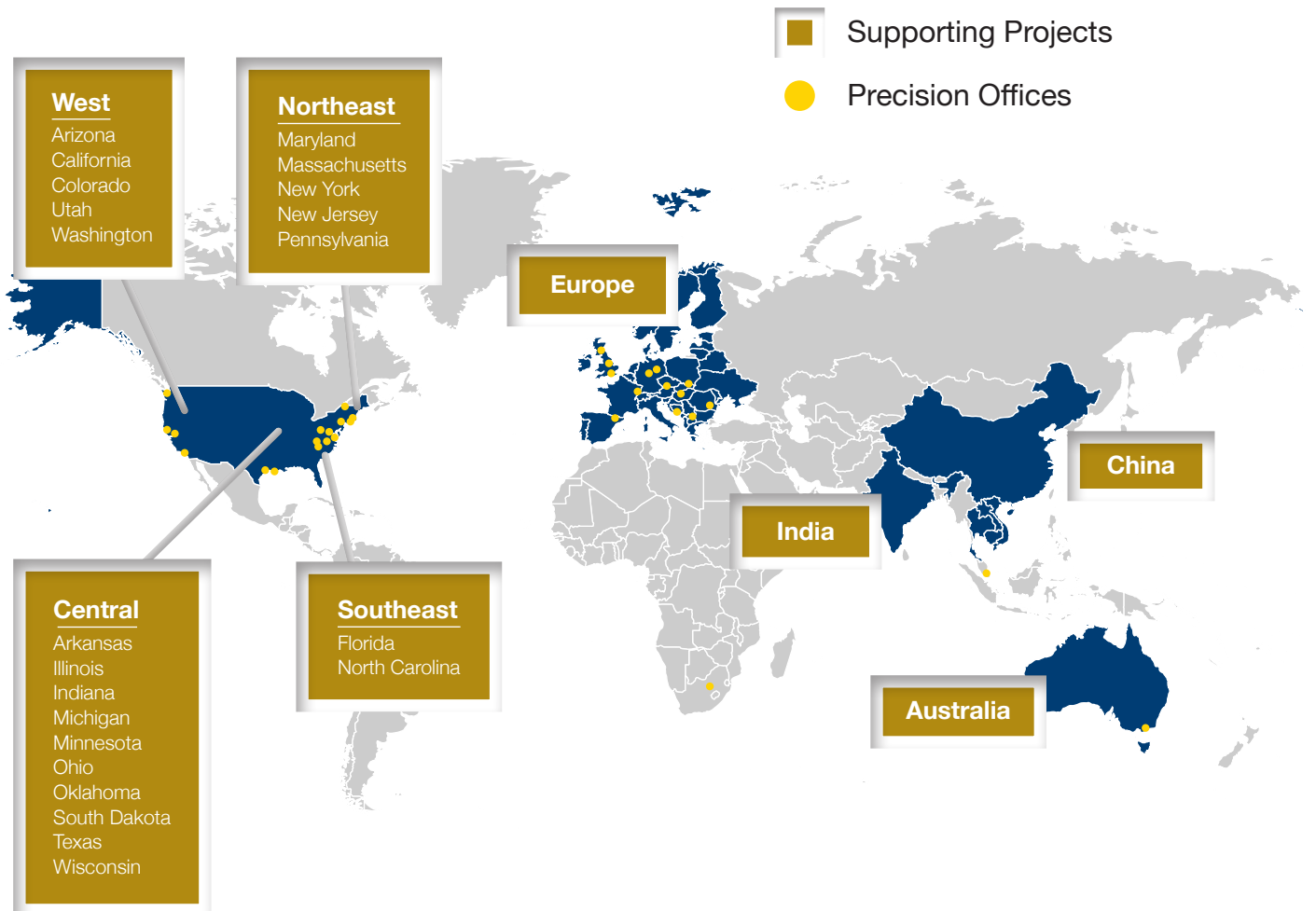
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Strategic Planning
for Your Facility's
Pre-Approval Inspection

We are a global leader in advancing technical operations from ideation through commercialization.

Our Services

- Due Diligence & Business Strategy
- Owner's Representative & Project Management
- Project Scheduling & Controls
- Capital Project, Facility Build & Tech Transfer
- Commissioning, Qualification & Validation
- Quality, Regulatory, & Compliance
- Automation & Controls
- Supply Chain
- Operational Readiness
- Facilities Management & Operations



Foreword

It is truly a rare and wonderful thing to know that your job makes an impact. Everyone who shows up to work at Project Farma, Baseline Controls and Precision for Medicine, has the honor of making a difference in patient lives. We have built a culture founded on a patient-focused mission. By placing patients at the forefront of everything we do, our team can easily rally around our cause and continue this important, lifesaving work.

We actively uphold our commitment to patients through partnerships with over 30 community, patient advocacy, and charitable organizations, contributing over 10,000 collective volunteer hours. Our commitment this year to the Melanoma Research Foundation, National MS Society, Salvation Army, Alliance for Regenerative Medicine, and being a charter member of the Alliance for mRNA Medicines underscores our dedication to advancing medicine and strengthening the healthcare ecosystem.

This commitment and mission became deeply personal when a team members' loved one faced a challenging diagnosis with an aggressive form of Mediastinal B-Cell non-Hodgkin's lymphoma. With limited treatment options, the patient, unfortunately, saw no significant improvement with traditional chemotherapy. In an incredible turn of events, our partnership with a leading cell therapy company with a T-Cell Therapy for B-Cell Lymphoma became a lifeline. After the treatment received FDA approval a year later, the patient received her first dose from the same manufacturing facilities our team helped build and commercialize. She experienced remarkable improvements in both mental and physical health just four months later. This success highlights the profound impact and transformative potential of companies dedicated to bringing life-saving therapies to market.

WE ARE
PATIENT
FOCUSED.



Within a year of the patient's diagnosis, a groundbreaking therapy secured approval, offering her a renewed chance at life. These real-life narratives serve as a constant reminder of our shared purpose, motivating us to persist in our work each day. The unpredictability of tragedy underscores the importance of our efforts, as it could be any of our loved ones benefiting from the treatments developed in the facilities and missions we contribute to. The convergence of factors, from innovative partnerships and stringent timelines to regulatory pathways and timely diagnosis, came together to grant this patient a vital second chance. Recognizing the collective impact, we understand that advancing the next generation of life-saving medicines requires the collaborative dedication of patient-focused teams.

For us, this story confirms the notion that time is of the essence and that swift action and momentum is everything when it comes to saving patient lives. Despite incredible technological advances propelling the growth of modern medicine, there remains considerable work ahead. In a dynamic field where best practices are continuously redefined and every advancement holds life-saving potential, it is our duty to share both our successes and the valuable lessons we've gleaned to optimize and improve the manufacturing lifecycle to reduce time to treatment.

This publication is a comprehensive overview of the manufacturing lifecycle and nuances of modern technical operations in transformative medicine. This compilation of articles, written by our immensely talented team, is designed to serve as a guide to those who are on the path of creating lifesaving solutions for patients. The experts delve into the heart of manufacturing considerations, offering key perspectives on the choices that shape the very foundations of today's cutting-edge facilities. The authors discuss the importance of project controls, early planning for operational readiness, steps to optimize validation, the imperative of strategic automation and more, ultimately paving the way for efficient and groundbreaking advancements in transformative medicine.

The road to innovation is filled with obstacles and unknowns and above all, a commitment to advancing patient care. One organization cannot carry this mission alone, we must continue to harness the power of knowledge sharing combined with patient-focused teams that are fiercely dedicated to advancing the next generation of life saving medicines. We extend our deepest gratitude to the authors who have generously shared their expertise and experiences. To the reader we hope this serves as an invaluable guide on your mission to transform and improve the lives of patients.

A Promising Future: The Biotech Sector's Outlook for 2024

John Khoury, *Executive Vice President*, Tony Khoury, *Executive Vice President*, & Anshul Mangal, *President*



In the wake of the pandemic, despite a perceived cooling of investor appetite since 2021, the biotech sector stands resilient with high investment numbers and groundbreaking innovations, setting the stage for an exceptionally bright outlook in 2024. The financial landscape, characterized by robust venture capital funding and impressive investment figures, reflects a profound commitment to advancing patient care and outcomes. As life science investors demonstrate strong confidence, and with substantial funding directed towards transformative platforms and key areas like machine learning and cell and gene therapies, the sector's potential for continued growth is immense. Amid historical regulatory milestones and staunch support from the FDA, investors are presented with a compelling opportunity to contribute to the sector's transformative advances and, ultimately, improve the lives of patients. Following the highs of record-breaking investment and the lows of the market correction, the biotech sector has weathered the challenges with unwavering resilience. The groundbreaking innovations and steadfast investor confidence collectively highlight an exciting and promising trajectory for 2024.

While public funding for biotechs remains stagnant, venture capitalists have steadfastly invested in transformative platforms poised to revolutionize the sector, consistently maintaining robust funding levels above those seen before the pandemic. In 2022, startups secured an impressive \$22 billion in funding across early- and late-stage rounds from venture capitalists, and the positive trend continued into 2023, with over \$12 billion raised through the third quarter. Notably, the US and Canada led in transaction value, totaling \$7.04 billion across 165 funding rounds, followed by the Asia-Pacific region with \$2.34 billion across 169 transactions. In May of 2023, the highest funding rounds unfolded, led by ElevateBio securing the top position with an impressive \$401 million in its Series D. During the same month, a team of Moderna veterans closely followed, achieving a noteworthy Series A raise for ReNAGade Therapeutics while marking a significant milestone, as this financing round stood as the largest in the private sector since September 2022.

VCs Enduring Support and a Promising Future for 2024

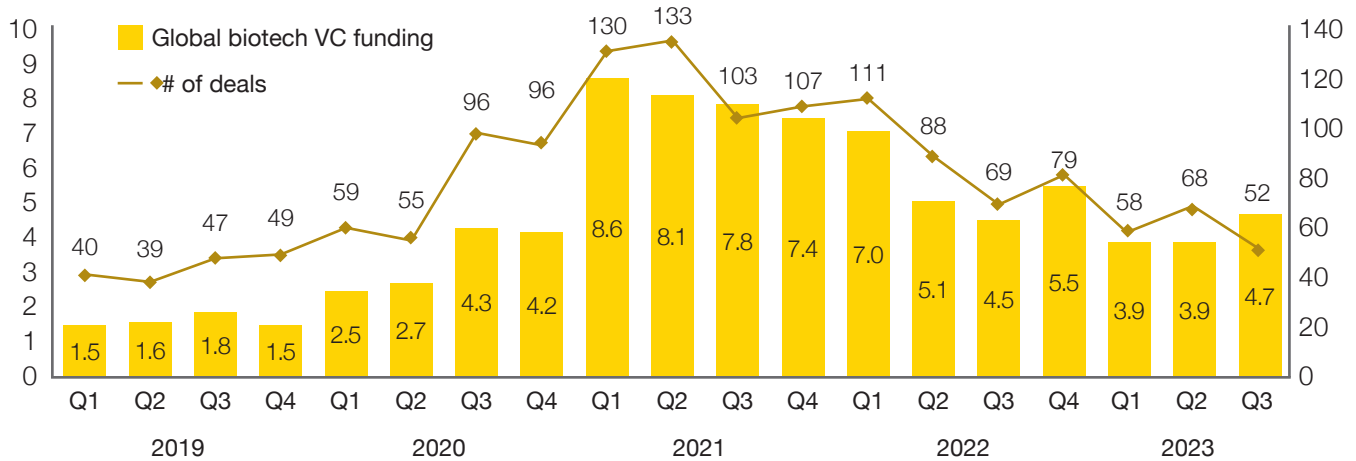
Despite the hesitancy still seen from the public markets throughout '22 and '23, the VC world continues to back biotechs. The first three quarters of 2023 showed VC funding has continued to level out but has remained above pre-pandemic levels. According to the 2023 Investment Funds Outlook Report issued by Barnes & Thornburg, investors will continue to pour as much capital into their life science funds as they did before the financial markets

turned bearish two years ago. A partner from Barnes & Thornburg stated that even though there's been some decline in VC investment activity, there's still a lot of optimism. "We think that activity and that excitement and optimism from investors really has to do with the innovation in the industry as well as just our experience through the pandemic, watching the value and importance of what different therapies can provide."

Nearly half of life science investors (47%) are demonstrating significant confidence in the sector, with 29% planning substantial investments averaging between \$6 million and \$10 million. Furthermore, a noteworthy 18% of investors express a robust commitment by intending to invest more than \$25 million on average. These figures underscore considerable financial optimism and strategic engagement within the life sciences, indicative of a high level of confidence in the sector's potential.

Biotech venture capital funding has declined from all-time highs but remains above prepandemic levels.

Biotech venture capital (VC) funding Series A onwards, 2019-Q3 2023, total investment, \$ billion; # of deals



Note: Chart includes deals > \$10 million from Series A to Series I in privately held companies during 2019-Q3 2023; excludes nontherapeutic biotechs such as contract and research services, industrial biotechnology, and food and agriculture.
 Source: McKinsey analysis based on Pitchbook, Inc. data, accessed Oct 2023; has not been reviewed by Pitchbook analysts

Investing in Biotech's Future: ML & CGTs Lead the Way

As the outlook for the biotech markets continues to trend in the right direction, investors have consistently identified several key areas of opportunities. Based on historical data as well as interviews and surveys with life science investors, companies with a strong R&D pipeline and those working on key platform technologies like Machine Learning and Cell and Gene Therapies are well poised to attract capital in the coming year. In 2022 platforms like those previously mentioned pulled in a staggering \$15.5B in funding, making up more than two-thirds of the total biotech VC investment landscape. These innovative platform technologies have drawn investors in as they stand to address a broader number of uses and indications over time.

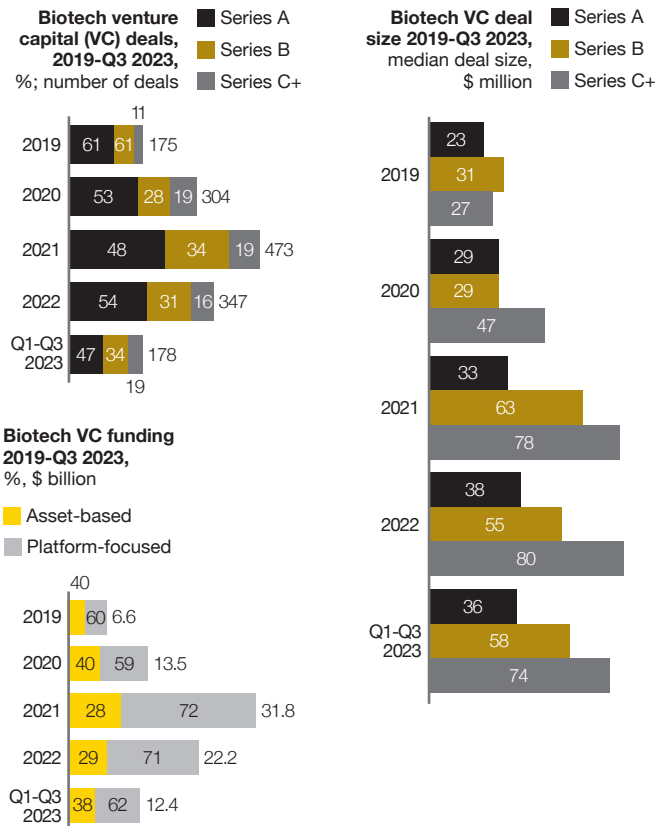
ML is Poised to Revolutionize the R&D Landscape

Between 2019 and 2022, VC investors injected over \$9 billion into start-ups focusing on machine learning (ML)-enabled drug discovery, signaling a transformative shift in the traditionally arduous R&D landscape for biopharma drugs. These ventures hold the promise of streamlining processes, potentially selecting molecules with higher success rates and facilitating purposeful molecular design for newly identified disease targets. While many companies are still in the preclinical stage, the growing interest in ML technology and its integration across the pharma value chain underscore its potential to revolutionize biopharmaceutical research, transcending its current status as a distinct category of biotechs.

An Emphasis on Innovation Pipelines

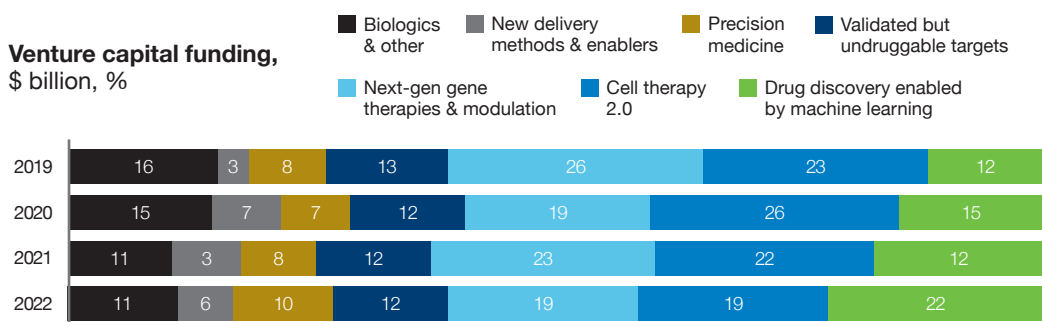
In light of recent data and survey findings, biotech companies emphasizing robust R&D initiatives, coupled with a solid clinical data and pipeline, are poised to achieve optimal success in garnering capital investment. Deloitte's 2024 Outlook for Life Sciences reinforces this perspective, highlighting the ongoing emphasis on innovation and enhanced R&D productivity as paramount priorities for biopharmaceutical executives. This stands as a reassuring indicator for investors, with a significant 30% of surveyed biopharma executives affirming their plans to prioritize R&D productivity, underscoring a persistent commitment to advancing progress within the sector.

The venture capital funding landscape remained strong in 2022, but a return to prepandemic norms may be under way.



Note: Figures may not sum to 100%, because of rounding. Chart includes deal > \$10 million from Series A to Series I in privately held companies during 2019-Q3 2023; excludes nontherapeutic biotechs such as contract and research services, industrial biotechnology, and food and agriculture.
Source: McKinsey analysis based on Pitchbook, Inc. as of Oct 2023; has not been reviewed by Pitchbook analysts

Biotechs focused on machine learning have been capturing an increasing share of venture capital funding.



Note: Figures may not sum to 100%, because of rounding. Chart includes deals > \$10 million from Series A to Series I in privately held companies during 2019-2022; filtered for "biotechnology" industry; excludes nontherapeutic biotechs such as contract and research services, industrial biotechnology, and food and agriculture.
Source: McKinsey analysis based on Pitchbook, Inc. data, accessed Oct 2023; has not been reviewed by Pitchbook analysts

Cell and Gene Therapies Anticipated Growth in 2024 and Beyond

In the face of an investment downturn, the cell and gene therapy industry saw multiple landmark milestones in 2023. Building on the current trends and successes, several reports have highlighted the cell and gene therapy industry as a key opportunity that will continue to draw strong investor interest. With over \$6.6B in investments in the first half 2023, the continued growth of this sector is marked by a number of factors including expanding indications, strong regulatory support, and a robust clinical pipeline.

Last year saw eight regulatory approvals, two of which were landmark firsts, in the EU and US. CRISPR Therapeutics and Vertex Pharmaceuticals received approval from the FDA for the first-ever gene editing CRISPR therapy to treat sickle cell disease and beta-thalassemia, while patients suffering from duchenne muscular dystrophy (DMD) have a new hope with the first gene therapy approval by Sarepta Therapeutics. With approximately 1,687 cell and gene therapy clinical trials around the world, the anticipated sector growth paints a compelling picture of transformative advances in this space.

As the sector continues its remarkable growth, the FDA is actively taking steps to match the pace and facilitate the development and commercialization of transformative medicines. In a recent initiative, the agency inaugurated The Office of Therapeutic Products (OTP) and declared its plans to recruit over 100 new reviewers, aiming to bolster the commercial pipeline. Peter Marks, MD, PhD, the Director of the Center for Biologics Evaluation and Research (CBER), has articulated a bold vision, aiming to approve 10-20 new cell and gene therapies annually by 2025. The FDA's dedicated efforts to support the commercial cell and gene therapy pipeline not only mitigate regulatory uncertainties but also instills confidence among investors, further solidifying the sector's promising trajectory. As the cell and gene therapy landscape continues to demonstrate resilience and transformative advancements, the positive momentum is expected to carry forward into 2024 and beyond.

Advancing Patient Care Through Transformative Innovations & Strategic Investments

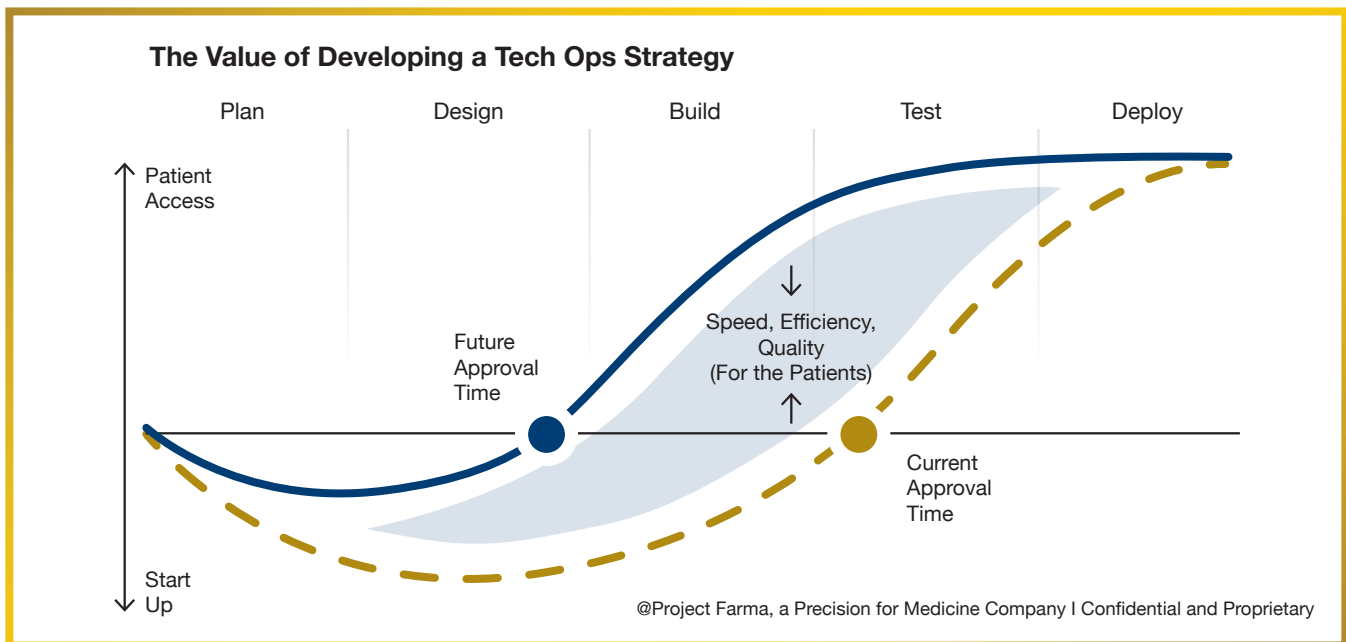
The financial optimism surrounding the biotech industry is not just a testament to monetary gains but a profound commitment to advancing patient care and outcomes. Despite a cautious public market, venture capitalists have consistently poured significant funds into the sector, and the continued appetite from life science investors continues to stay strong. The focus on areas like machine learning, cell and gene therapies, and robust R&D pipelines signifies a collective dedication to transformative innovations that will ultimately change the lives of many patients in ever-expanding indications. The cell and gene therapy industry, in particular, has seen remarkable success, marked by groundbreaking regulatory approvals, expanding patient populations, and a robust clinical pipeline, fostering confidence and support from both investors and regulatory agencies alike. The remarkable successes and support across the cell and gene therapy field underscore a shared mission to drive advancements in platform technologies while improving patient outcomes. As the industry thrives, propelled by both financial support and a deep-seated commitment to improving lives, the positive trajectory is set to continue, ushering in a new era of groundbreaking advancements for patients around the world.

Establishing the Right-Sized Technical Operations Strategy in an Uncertain Market

Danny Foody, *Director* & Phil Massey, *Sr. Director*



Determining the right technical operations strategy for a precision medicine or emerging biopharma company can feel like building a complex piece of machinery from scratch without instructions. It is intricate, multifaceted, and requires flexible design and approach. The components include establishing a physical footprint, development of quality management systems to mitigate chemistry, manufacturing, and controls (CMC) bottlenecks; navigating an evolving supply chain landscape; and recruiting top talent commensurate to internal and external throughput. Piecing these different mechanisms into a phased and executable plan requires a customized solution based on your company's process, a set of well-defined long term strategic goals and growth stage.



Key Drivers to Develop Your Tech Ops Strategy

Early-stage and emerging companies are rapidly populating the biopharmaceutical industry, making swiftly evolving therapeutic breakthroughs. The long road that begins with translating scientific discoveries, winds through CMC

scale-up, and ultimately leads to patients is highly competitive, with multiple chokepoints and increasingly elusive capital funding opportunities. A quantitative and qualitative technical operations (tech ops) strategy is crucial for companies to launch their journey with a sound roadmap while attracting investors.

In an evolving regulatory, technological, and supply-chain landscape, flexibility in tech ops planning and execution enables companies to mitigate and manage these challenges. Identifying knowns, unknowns, and assumptions is vital throughout the planning process. Next, concisely communicating these assumptions to appropriate stakeholders, such as board members or investors, better prepares companies for future changes. Creating a strategy is fundamental to matching company growth with industry progression.

Designing a Dynamic Plan

The traditional make vs. buy trade-off is easily recognizable. Making or internalizing manufacturing requires significant up-front capital but provides long-term benefits, including control over one's destiny and intellectual property (IP). Buying or externalizing manufacturing requires a lower initial financial commitment of expense funding, extending a company's cash runway. However, it forces them to rely on external partners and relinquish control.

Often, companies choose the best of both worlds by adopting a hybrid, phased approach. Clinical material for testing is typically needed right away or early on, forcing most companies to move forward with an external partner. A phased internalization strategy, which takes CMC operations from process and analytical development to small-scale production through late-stage and commercial manufacturing and quality control, positions companies to capitalize on their strengths — science and process. This method positions a company to maximize its initial investment, source material for preclinical and clinical milestones early, and internalize core operations while observing and reacting to regulatory and technological progressions. A dynamic approach also allows you to modify your operations as your company grows and you better understand your process, cost of goods, and the ever-evolving regulatory

landscape. Plus, remaining flexible allows you to mitigate supply chain disturbances.

By building a hybrid, phased approach, your company remains agile and can react quickly to market or technological developments.

Several creative approaches to extending cash runways for internal investment include negotiating and utilizing tenant improvement (TI) dollars, leasing space and equipment, and evaluating financial strategies with developers and landlords. Companies that implement these strategies are well-positioned to adapt as the industry changes. By building a hybrid, phased approach, your company remains agile and can react quickly to market or technological developments.

Aligning Pipeline Demand with Supply

Simplifying a biopharma company's technical operations entails aligning pipeline demand with supply. To calculate demand, input patient population, epidemiology, prevalence and incidence, standard of care, dosing, and

administration technique, should all be part of the equation. Then look at your process, including its description, duration, types of technologies, yields, and volumes, to forecast batch and material demand for patients and any associated analytical and quality control testing for Investigative New Drug (IND) submission, biologics license application preparation, and commercial manufacturing. Ultimately, the goal is to define annual demand through clinical and commercial milestones.

In parallel, establish a strategy for producing enough material to meet near- through long-term demand. Naturally, the near-term plan will be relatively static, relying on funding from external investors to produce immediate and mid-term material supply. Long-term planning with fewer financial commitments and phased internal capabilities positions the company to internalize its best asset, IP, while controlling its destiny and reducing reliance on external partners.

Collaborating with an external contract development and manufacturing organization (CDMO) is critical to establishing near-term supply. However, evaluate, select, and manage your partner CDMOs carefully to best mitigate the risks created by externalizing development and manufacturing. This includes investing in an external manufacturing program whose request for proposal achieves your project's scope and presents a clear understanding of your company's goals. Upon selection, invest in CDMO management support to ensure internal SOPs, policies, and quality agreements are established, successful tech transfer is performed, and continuous management and person-in-plant effectively deliver a successful partnership.

Phasing internal operations is highly specific to each company and process. Many advanced, precision medicine therapeutic processes include critical starting materials, from DNA plasmids or viral vectors as inputs to highly IP-controlled drug substance process steps and final formulation to bulk filling. Understanding an asset's molecular structure and compound drives greater emphasis on analytical and quality control testing, resulting in investing and planning of the analytical development / process development (AD/PD) footprint and talent. Creating internal, external, or hybrid operations requires investment in evaluating, selecting, and implementing quality management systems. Even externalizing operations requires compliantly managing and storing GMP data and the associated external policies and procedures.

Ultimately, modeling and understanding material demand and supply is the foundation for a successful tech ops plan. Aligning the supply can open the door to many different and complex strategies and options, requiring critical investments in time and resources to correctly determine a sound plan. A cardinal rule for biopharma companies is that without a reasonable understanding of your material demand and supply, you are flying blind.

Mitigating Supply Chain Bottlenecks

Few aspects in biopharma have seen more change in the past five years than supply chain. Intricacy levels and vulnerability areas drive the need to thoroughly understand your process and suppliers to mitigate risk while aiming to achieve flexibility. Supply chain planning includes plasmids, viral vectors, LNPs, and oligonucleotides. These media are often the first that come to mind. However, you need to factor in all materials used in manufacturing, including processing materials such as bioreactor bags, filtration columns, and vials. Going one step further, consider your capacity for freezing and storing manufacturing, patient material, warehousing process, and single-use materials as part of your supply chain.

Supply chain planning is equally as critical for internal and external operations. For example, although your manufacturing and testing may be external, if your partner cannot manufacture your drug substance due to peaking demand for single-use bioreactor bags, the entire production is put at risk. Preventatively storing bags and providing them to your external partner could mitigate that risk. That approach could drive internalizing aspects of the warehouse given the minimal cost yet critical impact on manufacturing.

Supply chain mitigation has become increasingly more critical and worthy of investment. These strategies are dependent on current industry trends and future forecasting of risk. Disruption can halt the entire process, so you and your vendors should implement backup plans in case one of their external partners is delayed. Managing your supply chain with a flexible and dynamic plan can help position a company to take more calculated risks with high confidence in material production and patient delivery.

Anticipating Changing Regulatory Guidance

IND preparation and submission is often the first significant milestone in a long drug development journey. With an evolving regulatory landscape in advanced therapies, we are seeing regulators actively define guidelines. At the same time, assets steadily progress through clinical milestones, creating a high risk when planning and submitting an asset's IND package.

Best practices commonly executed include early and often communication with the FDA. Initial contact with the request of FDA feedback on the clinical plan and process knowns should occur before running IND batch production to ensure that feedback can be incorporated. Other key areas to best position an asset for regulatory scrutiny include further understanding of process characterization and molecular and compound structuring. Also, further enhancement of analytical testing using next-generation sequencing (NGS) and compliance in data integrity assessment during preclinical testing.

Investment and planning in early-phase analytics and data acquisition are critical in preparing for evolving regulatory guidance. Developing these capabilities may include further external management, internalizing a small footprint to run NGS, and assuring compliance quality management systems are in place with procedures to capture and store data adequately. Establishing a good relationship with the FDA early on and encouraging open dialogue can improve your IND approval process and ongoing compliance.

Internalizing Manufacturing

- Requires significant up-front capital
- Provides long-term benefits including control of intellectual property

Hybrid Approach

- Positions company to maximize initial investment, source material early, and internalize core operations
- Allows for more modifications
- Promotes agility to react quickly to market or technological developments

Externalizing Manufacturing

- Requires lower initial financial commitment of expense funding
- Extends company's cash runway
- Forces company to rely on external partners and relinquish control

Early Planning for Operational Readiness

Chad Salisbury, *Sr. Vice President* & Michelle Sinsel, *Sr. Director*



Operational readiness in the pharmaceutical and biotech industries is a complex, cross-functional effort that brings together people, procedures, materials, equipment, and processes at a new cGMP manufacturing facility to make quality therapies for clinical and/or commercial use. While facility design, construction, and commissioning/qualification/validation rightly demand attention in such projects, operational readiness can be equally critical to this mission. Ideally, you should begin formulating your strategy in the design stage when putting the integrated schedule together with your construction partner, CQV partner(s), and your internal experts. Starting early allows the project leadership team to have a holistic view of each function's contributions to each project phase and measure the progress toward a fully operational facility via routine PM tools, analytics, and risk-based scenario analyses.

Planning for operational readiness factors into the entire facility delivery process. It creates a staged transition from design to cGMP production. Waiting until after the facility is well underway to begin the operational readiness planning process often results in lost opportunities and potentially significant delays. However, no single solution works for every company in every situation. The correct approach ensures that you have the right people and processes at the right time to manufacture your therapeutic in a high-quality, compliant, and operationally effective manner.

Strategic Staffing Means Timing Your Key Hires

The sooner you identify the need for key strategic positions, the better you will be prepared for future operations. It's tempting to wait until the facility delivery is well advanced before hiring operational staff, but that choice has drawbacks. First, when designing your facility and selecting equipment, you'll want input from people with relevant cGMP and technical experience to be involved in equipment design/selection, defining operational workflows, selecting suppliers, etc. People with experience operating and maintaining the equipment can realistically assess its day-to-day utilization, maintenance, process limitations, and quality considerations.

Second, when constructing, commissioning, and qualifying your equipment, these operational resources will be able to observe each element of the facility, execute testing on the equipment, train on equipment with vendors, and understand the equipment and systems integration. Experienced engineers and manufacturing operators who bring this expertise to the table help you identify and solve issues early before they become major problems later

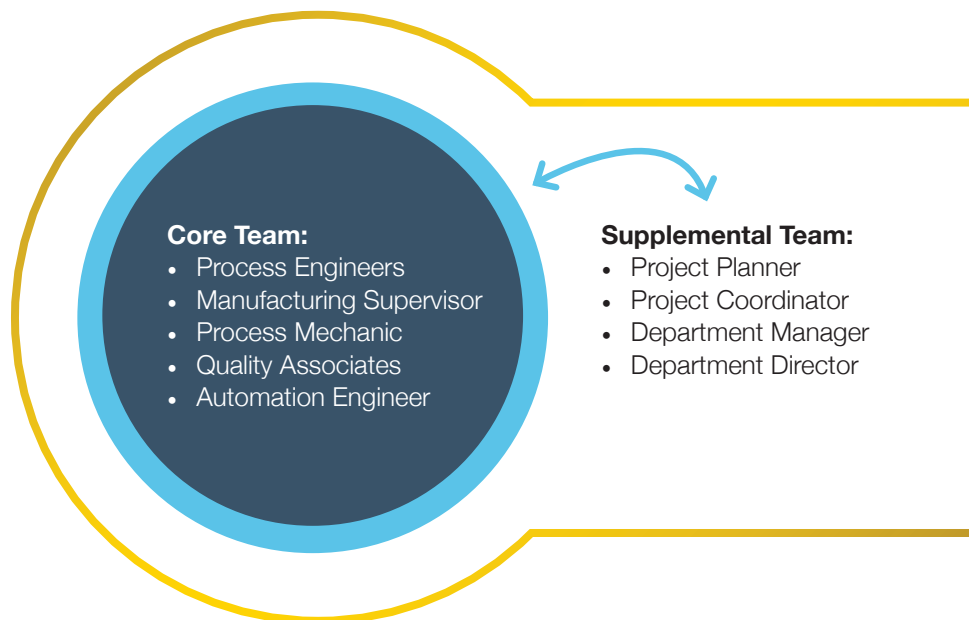
in the project timelines. Hiring these experts early in the process allows you to troubleshoot more effectively, make improvements prior to qualification, and develop a depth of internal knowledge that trains the future operational staff.

Consequently, staffing early comes with a price tag. If you employ staff too soon and they are on the payroll for a significant period before commercial manufacturing begins, then these non-revenue generating positions negatively impact your bottom line. The balance of hiring can be different for each company and the advantages and disadvantages should be thoroughly evaluated early in the project.

While financial considerations are often the key driver, an additional factor to consider is the cGMP labor market in your location. Suppose your facility is located in a pharmaceutical or biotech hub with a large, established talent pool to recruit from. In that case, hiring could be delayed somewhat because you can be confident that you'll find the right people. However, when investing in a greenfield facility in an area without an established pharma/biotech labor market extra hiring, training, and qualification time should be considered.

One common solution is to fill a few crucial positions as early as possible: process engineers, manufacturing supervisor, process mechanic, quality associates, and automation engineer, to name a few. This core group will learn the equipment, establish the core cGMP business processes, troubleshoot operations in advance, and train employees when you are ready to fully staff your facility. These key players must fit your company's culture, fill multiple roles throughout the project, and demonstrate curiosity and a willingness to learn to be a good fit for a startup operation.

Finally, hiring early can be advantageous to fostering the desired operating culture. Bringing these talented players to a diverse and excited team up front provides them with a target-rich environment for learning and more opportunities for growth than they may have in steady-state operational facilities.



Balancing Early Hiring and Return on Investment

When looking at the whole lifecycle of a project, it's important to balance capital and operating expenses. If the therapeutic is a high-profile, high-velocity product in a supply-constrained environment, time to market is key to creating significant ROI. In this case, it's often worthwhile for companies to lean into their operating budget in the short term because waiting to hire personnel until the facility is well underway can cost more in the long run. Delaying your drug by days or weeks in a highly competitive environment allows your competitors to capture market share.

It is imperative for companies to bear in mind that a new cGMP facility can have the best equipment, systems, and processes on the market, yet those capital investments aren't paying off without experienced operations and quality staff to make, test, and release quality cGMP batches. If your processes are not well defined and staff isn't knowledgeable or adequately trained and qualified, the entire manufacturing process can be delayed or risk not meeting regulatory criteria for licensure and ongoing cGMP compliance. Early hiring, when aligned with your project's timeline and objectives, can be a wise investment, setting the stage for a compliant and operationally effective facility.

Preparing for Technological Readiness

Another aspect of operational readiness is having your technology ready for manufacturing. Technological readiness is more than just buying the right equipment. It also involves understanding the entire step-by-step process that creates these therapies. Greenfield facilities are particularly challenging because they are often theoretically developing their processes while the facility is being designed and constructed.

The facility's and process's capabilities guide subsequent decisions, from what materials you need to order to the equipment's qualification ranges, written procedures, systems, and workflow. You can avoid future course corrections when you anticipate these during the design stage. For example, some companies plan their process while designing their building only to uncover process development data indicating they need to change direction.

Redesigning at that stage costs money and time. Also, someone with operational experience can look at an issue and translate it from a two-dimensional idea to a three-dimensional reality because they know how the design and construction of a space translate to real-life operations. That experienced person can point out design flaws before they require expensive corrections.

“

...having a core, cross-functional team of operations and quality resources early in the project brings a diverse perspective to identifying risks and providing solutions in the design and construction stage.

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It's impossible to anticipate every issue while preparing your facility. It is essential to have a core, cross-functional team of operations and quality resources early in the project bringing a diverse perspective to identifying risks and provide quick and sound solutions in the design and construction. This diverse team will build flexibility into the project strategy allowing companies to pivot when necessary.



In conclusion, early planning for operational readiness is a pivotal factor in the success of pharmaceutical and biotech manufacturing projects. It's a multifaceted endeavor that involves bringing together the right team at the right time to prepare for technological advancements and ensure a smooth transition from design to cGMP production. Waiting until later in the project can lead to missed opportunities and delays. This approach enables project leaders to have a comprehensive view of each function's role and progress, facilitating a fully operational facility.

Four Steps to Successful Project Planning and Controls

Adam Barlow, Sr. Vice President & Scott Reynolds, Sr. Director



The journey from drug discovery to manufacturing and marketing follows a complex path, where detours and roadblocks are all too common. Formulating a realistic timeline for biotech manufacturing requires detailed execution and high-level strategies based on order-of-magnitude assumptions, but unexpected setbacks can derail progress. For example, a company may want its product to be commercially ready within two years but if the critical path doesn't accurately reflect real-world factors affecting the end date, the deadline becomes unreachable, driving up costs and delays to the patient.

Critical path drivers can and will change in unpredictable ways. Project managers must be vigilant in remaining current with project risks and creating risk mitigation strategies to ensure each step in the plan is executed appropriately. Without flexibility and realistic expectations, a single misstep can cascade into a break point that moves the entire timeline. With a project as large and complex as drug manufacturing, directors and managers need a team of experts to ensure that their projects are completed on time.

Formulating a realistic timeline for biotech manufacturing requires detailed execution and high-level strategies based on order-of-magnitude assumptions, but unexpected setbacks can derail progress.

Four Steps to Successful Project Planning and Controls:

1 Create a Spider's Web of Deliverables

Companies expanding their manufacturing capabilities can scale up existing processes or invest in additional manufacturing facilities. On the surface, constructing a building seems relatively straightforward from a planning perspective. However, in biotech construction and manufacturing, numerous factors, such as infrastructure problems or late equipment deliveries, affect the construction schedule.

Planning the facility thus requires more than a simple start-to-end timeline. Instead, project managers form an integrated program schedule that resembles a spider's web with multiple workstreams built around interrelated critical paths. This "spider diagram" indicates the tasks that need to happen and how they are connected, creating a logical methodology for the project's completion. Managers can track their overall progress and see where the workstreams fall along each critical path.

When a workstream accomplishes its deliverables, the critical path shifts to the next one. For example, once the facility is constructed, it needs power, which allows it to support an IT infrastructure. Once the IT infrastructure is in place, the HVAC system can be automated for a regulated environment. Meanwhile, equipment must be selected, procured, installed, and tested, while raw materials must be specified, procured, and released for the development process. Each of these elements relates to the project's total scope, schedule, and cost, which rely on each other to determine a project's success. A dedicated project controls team can be the project manager's eyes and ears to ensure each piece falls into place.

2 Divide and Conquer Project Management

Separating project controls from project management is a divide-and-conquer approach that allows each side to excel. Project controls teams focus on gathering and consolidating crucial information while management liaises with stakeholders for critical decision-making. First, the project controls team monitors individual tasks and workstreams. They look for patterns to identify trends, such as if certain groups consistently miss deadlines. For example, if only 60% of deliverables are completed on time, the entire project will be delayed. Identifying and flagging delays early on saves time later.

Next, the team takes this data to the project manager, alerting them to problems before they spiral. In many cases, re-sequencing the work can fix the issue. Alternatively, they can adjust the level of deliverables' importance to allow the faulty group to focus on the most essential items. Re-examining priorities as needed prevents a single deliverable from upsetting the entire timeline.

3 Float on the Workstream

Managing a continuously shifting web of tasks requires a project controls team to monitor the manufacturing operations, engineering, quality, and regulatory departments' deliverables in their respective workstreams. To do this effectively, the project controls team constantly monitors changes in the integrated plan while collaborating with the project manager to determine how much float each deliverable carries, i.e., flexibility in completion schedules.

While some items carry zero float and cannot be moved from their position on the timeline, others can be shifted without creating delays. Teams continually monitor and adjust tasks as needed when outside factors, such as supply chain holdups or other unavoidable delays, threaten the completion date. By modifying deadlines as needed for items with float, the project remains on time. Likewise, some tasks can be completed ahead of schedule to save time on the back end. For instance, regulatory documentation can be drafted while facilities are still under construction to avoid unnecessary postponements after the building, equipment, and process are ready.

Depending on a project's scope, the number of activities needed for its completion can vary from a few hundred to tens of thousands. Successfully managing these actions requires checks and balances to identify the steps needed for each item in the critical path. It also requires hands-on relationships and routine communication that rely on trust and accountability. Sending an email to check an item's status is much less effective than visiting sites and team members and talking them through their process.

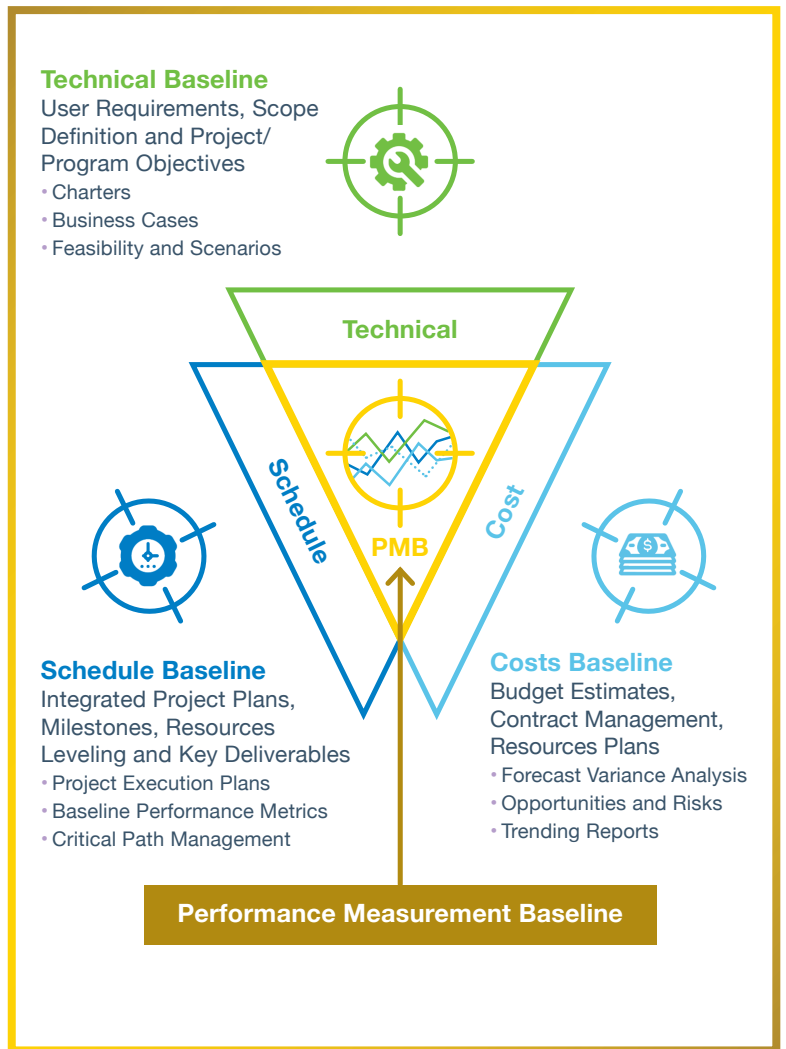
4 Form a Project Controls Workstream

In the complex landscape of pharmaceutical and biotech manufacturing, forming project controls workstreams is a critical component of successful project planning and execution. These workstreams are like the navigators of the project, ensuring that all elements align with the overarching goals. To establish effective project controls workstreams, it's imperative to assemble a team of experts in diverse fields, ranging from regulatory compliance and quality assurance to supply chain management and financial oversight. Each workstream should be led by experienced professionals who understand the nuances of their specific area, and they must work in harmony to create a well-coordinated project framework.

The first step is defining the scope and objectives of each workstream, ensuring that it aligns with the broader project goals. Once this structure is in place, it becomes easier to set up milestones and key performance indicators (KPIs) for each workstream. These KPIs serve as checkpoints and measures of success, allowing project managers to gauge progress and address any issues promptly.

Communication and collaboration are the lifeblood of project controls workstreams. Regular meetings, status updates, and cross-functional collaboration are essential for maintaining alignment and addressing potential challenges.

Additionally, an effective project controls workstream should be adaptable, ready to adjust course when unexpected developments arise. By implementing such well-structured workstreams, pharmaceutical and biotech companies can not only enhance the efficiency of their manufacturing projects but also proactively manage risks, reduce bottlenecks, and ensure timely delivery of vital medications to patients in need.



In conclusion, successful project planning and controls in the intricate world of biotech manufacturing demand a comprehensive approach. As we've explored, setting a realistic timeline, and understanding the dynamic nature of critical path drivers are essential. It's crucial to adapt to unforeseen changes, manage risks, and employ strategies that ensure the project stays on course. Dividing the project into manageable workstreams, closely monitoring progress, and forming dedicated project controls teams are the practical steps that lead to success. By embracing these four critical steps, biotech companies can navigate the challenging path from drug discovery to manufacturing and marketing with greater efficiency, keeping projects on track, costs in check, and ultimately delivering benefits to patients in a timely manner.

Single-Use, Stainless Steel, or Both? Key Points to Consider for Today's Manufacturing Facility

Greg Gara, *Sr. Vice President* & Christian Hermanas, *Sr. Manager*



Designing cutting-edge, novel therapeutics demands high levels of innovation, upfront planning, and in-depth scientific knowledge. Mass-producing these medicines, however, requires an entirely different skill set. Companies must decide whether to rely on single-use materials, stainless steel equipment, or a flexible solution that includes both elements while balancing capital and operating costs. Meanwhile, ongoing supply chain disruptions, capital funding issues, and staffing challenges continue to disrupt the industry. Understanding current trends in manufacturing is the first step in determining the right solution for your company.

Single-Use Technology

Pros:

- Easy deployment
- Increased flexibility
- Low risk of contamination
- Faster turnover produces greater yield
- Reduced capital expenditure

Cons:

- Not always scalable
- Requires ongoing forecast
- QbD must consider extractables and leachables
- Workforce skills gap
- Damage can cause further risks

Hybrid Approach

Pros:

- Augmenting stainless steel with disposable material reduce cleaning time
- Stainless steel can be customized and maintained in-house and supplemented with disposable material to become more cost-effective
- Approach can be applied to upstream or downstream
- Balances sustainability with cost effectiveness

Cons:

- Comes with disadvantages of both single-use and stainless steel equipment

Stainless Steel

Pros:

- Trusted, verified, well established
- Advanced measurement and control
- Available in large capacities
- Increased operator comfortability

Cons:

- Inflexible infrastructure
- High utility and operating cost
- Routine cleaning & maintenance
- Contamination can still occur
- Increased capital expenditure

Single-Use Solutions

Newer companies often rely on single-use materials to expedite production timelines and avoid the upfront capital expenses of using stainless steel. Manufacturing can start once the facility is ready rather than waiting for custom-built equipment with long lead times. Disposable materials make preparing media and buffer solutions quick and relatively easy, plus simplify scale-up. Another benefit is that companies using single-use technology can change or adjust methodologies faster with less impact on their manufacturing process.

Although disposable products have the lowest startup costs of the three, they carry high operating expenses vs. investing in stainless steel equipment. A risk to using single-use materials is they are more vulnerable to supply chain constraints and damage during shipping. The utilization of these systems also brings enhanced quality requirements, beginning with supplier qualification through closed processing and contamination control requirements, especially for facilities subject to EU Annex 1 updated requirements. Disposable equipment is also less customizable and may require proprietary software for operation, complicating integration. To mitigate these issues, single-use technology should be automated whenever possible to decrease staff workload. In a contracted labor market, reducing workload gives companies a competitive advantage.

Investing in Stainless Steel Equipment

Stainless steel equipment requires a significant upfront capital investment but comes with lower operating costs than disposable technology. It's also easier to repair in-house. However, getting a stainless steel system up and running takes much longer than using prefabricated, disposable solutions. Stainless steel systems require regular cleaning and steaming prior to use, plus routine maintenance, usually resulting in production downtime. When calculating

operating costs, companies must consider the extra water, steam, and power usage required to make this asset fully operational. Steaming in place and running multiple wash cycles as part of the manufacturing process adds time, consumes significant resources, and increases the facility's environmental, health, and safety requirements compared to a single-use disposable facility.

Also, stainless steel equipment has a limited lifespan and may become outdated if not properly maintained. Companies who have invested in this equipment in the past may choose to employ single-use or a mix of both

options moving forward to replace devices that have broken down and become obsolete. Current trends are moving towards more disposable solutions, either entirely or as a hybrid approach that combines stainless steel equipment with single-use components.

Current trends are moving towards more disposable solutions, either entirely or as a hybrid approach that combines stainless steel equipment with single-use components.

The Hybrid Approach

Large, established biotech companies usually have stainless steel equipment in place. However, augmenting these with disposable materials, such as flexible tubing for transfer lines, may be advantageous because they reduce cleaning time and can be quickly changed. Many companies considering transitioning from stainless steel to single-use materials find that a hybrid solution maximizes the best of both worlds.

Companies can choose stainless steel for the equipment they want to customize and maintain in-house and disposable products where they are more cost-effective. This approach can be applied to a company's upstream or downstream manufacturing space, maximizing their investment. Another option would be to use stainless steel equipment for upstream processes and single-use material for downstream because of the differences in volume and complexity. For example, solutions prep is easy to employ single-use materials because it offers a simple, closed system. Also, disposable products don't require cleaning and maintenance, reducing downtime.

However, this solution also has the disadvantages of single-use and stainless steel options. It carries the ongoing operating costs associated with using disposable products and the cleaning and regular maintenance required for stainless steel equipment. Companies can balance capital and operating expenses when they optimize both solutions through strategic planning and commitment.

Planning for Sustainability

Disposable solutions seem less sustainable than stainless steel equipment because their very nature requires them to be thrown away after each use. Companies may hesitate to purchase materials that ultimately end up in landfills. The clean-in-place (CIP) requirements for stainless steel equipment generate liquid waste that requires wastewater treatment facilities, whereas single-use disposable technology eliminates this waste stream. Sustainability is a larger, more complex issue than just landfill use and wastewater treatment. Companies with sustainability goals must consider multiple factors in their manufacturing process.

A sustainability goal might be net zero energy consumption or water conservation. Increasingly, companies generate their power supply through solar panels, geothermal energy, or other renewable sources. Rinsing stainless steel bioreactors with recycled water before deep cleaning is another way to conserve resources. Also, companies can prioritize renewable materials and energy-saving designs when building new facilities. Plastic waste can be decontaminated, ground up, and recycled into a new product. Companies that value sustainability are finding creative options to abate their environmental impact and meet their goals.

Conclusion

Mass-producing novel therapeutics is an intricate process without one-size-fits-all solutions. Deciding between single-use materials, stainless steel equipment, or a flexible solution is a complex decision-making process that depends on capital and operating costs as well as a myriad of other factors. When you understand industry trends that drive manufacturing, you can create the right solution for your company's needs.

A Step-By-Step Approach to Implementing Quality Infrastructure

Meghna Sengupta, Sr. Consultant & Austin Potthoff, Manager



New drug approval doesn't happen without quality data. When data is misplaced or inaccessible, it can delay or increase risks to the drug development process. However, many pharmaceutical and biotech companies continue to operate with data management infrastructures that aren't designed for the current expectations of our industry or still use paper records to store vital information. Regulatory authorities no longer see paper-based systems as sufficient because electronic systems are more traceable, accurate, and reliable while

providing a digital environment that increases the utilization, application, and power of the data generated during the drug development and manufacturing processes. Also, they don't necessarily cost more since startup expenses for an electronic quality management system (eQMS) can be counterbalanced by reducing staff hours otherwise dedicated to creating handwritten records.

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The solution is a phased approach that allows companies to gradually shift to a better, more efficient system without compromising study timelines.

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Investing in quality infrastructure helps ensure data integrity and regulatory compliance. But how can companies upgrade their systems without shutting down their studies? The solution is a phased approach that allows companies to gradually shift to a better, more efficient system without compromising study timelines.

Is It Time to Implement an eQMS?

Companies should evaluate their quality infrastructure at critical pressure points, including:

- Regulatory health authority requirements
- Product lifecycle requirements (Preclinical, Phase I/II clinical, Phase III/Commercial)
- Organizational growth
- Product portfolio and product demand
- Internal and external audits

Regulatory agencies require companies to use a quality management system (QMS) when they begin Phase 3 clinical trials. However, the benefits of implementing certain elements of an eQMS as early as preclinical or early-stage clinical trials can be tremendous if the business can afford the time and startup costs requirements. Maintaining clinical phase-appropriate quality standards and flexibility in the QMS is important to manage quality, compliance, and risk. However, as your company grows and embarks on commercial manufacturing, the data you need to manage increases exponentially, from a few standard operating procedures (SOPs) to complex risk management documentation, validation documentation, and batch records, to name just a few. Simple solutions not built for the industry, like generic file-sharing programs or paper files, become too cumbersome when scaled up. The more information accumulates, the more chances it could become misplaced or mislabeled without a well-designed, dedicated system.

If your drug has been approved and you don't have additional products enrolled in clinical trials, you may choose to begin this process when you are expanding personnel or manufacturing throughput. Bringing in more resources and people is essential for growth but adds complexity. For example, without a transparent, user-friendly system, new employees might struggle to access the necessary documentation or information in a timely manner. Ensuring quality infrastructure speeds up training and onboarding timelines while guaranteeing that all data is secured in a compliant system.

Internal and external audits and regulatory inspections are routinely conducted, and both assess and challenge the performance of an organization's QMS. They are necessary for product approval and routine commercial manufacturing. If the company's information isn't well managed before these audits, it might fail to meet regulatory requirements. Delays to new product releases due to audit or inspection findings can be extremely costly to new and established pharmaceutical manufacturers. Reducing the chance of these delays can often justify the up-front capital needed to administer a new eQMS.

Change is hard, and it's easy to think that adopting a new system isn't worth the investment or time required. In the pharmaceutical industry, time is of the essence because delays translate to delays in lifesaving therapies for patients. Companies need a system that provides control and easy access to records. There are better options available that offer help and support to make the work of managing a pharmaceutical company simpler, not harder.

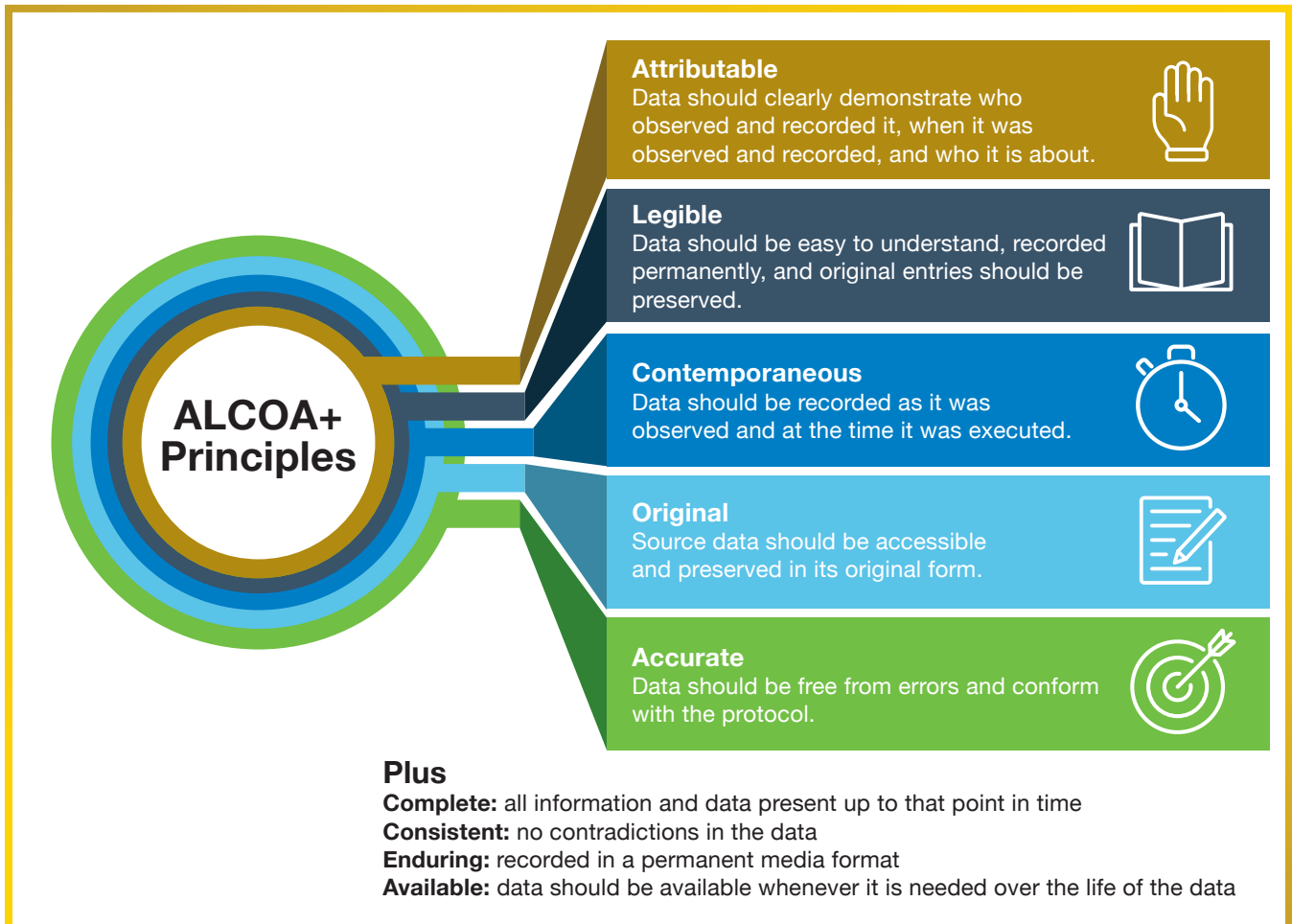
Steps Needed to Determine Whether a Change is Needed:



1 Evaluate Current & Future Needs

First, you should assess the capabilities and limitations of your current system concerning your current and upcoming requirements. Even if your company is at a product lifecycle stage where you're not required to have a QMS, we recommend evaluating the system you currently use to track data and look for ways to improve it. By inventorying and categorizing your current system, you will better understand what you need in a new one. Also, remember that having paper-based systems as a backup for business continuity in case of a system outage due to a cyberattack or technical failure is good risk mitigation. Next, weigh your future needs and plans for growth. Changing systems is an investment in future studies and not just a way to keep up with current ones.

Additionally, consider if your current system addresses the requirements in the FDA's Code of Federal Regulations 21, Part 11, such as the ALCOA+ principles defined below. An off-the-shelf eQMS will be compliant with FDA, European, Japanese, and other global regulatory authorities' policies, so carefully weigh improving your current system vs. transitioning to an established system.



The final and often most substantial consideration when evaluating your future needs is the time required to deploy a new system. How long it takes to go from evaluation to operation of a full eQMS depends on several business factors. For example, decide how much data you need to transition into your new system. If you are ahead of the game and want to implement your eQMS during preclinical or before clinical Phase 3, then you likely won't need to factor in much— if any— time to move data. On the other hand, if you are an established business with years' worth of quality records, you can plan on 1- 3 months of additional time for strategizing and transitioning your critical data. In either case, plan to invest time into ensuring your master data input to your new QMS is integral, complete, and suitable for the new system. Incomplete, errant master data will inhibit the effectiveness and efficiency of your QMS implementation.

2 Engage Key Stakeholders

Another way to phase your transition gradually is to hold off on rolling out the new system to the entire company at once. Buy-in starts at the top, and companies need support from their most influential leaders to reduce reluctance to change. Company leaders serve as ambassadors, explaining to others why the new system will ultimately benefit the company and alleviate their workload.

Also, when implementing the eQMS, begin with the most relevant individuals, such as the end users who will be employing it the most: quality assurance, quality control, document control, facilities, and engineering, to name a few. Find the employees with the most significant input in documentation infrastructure and equip them first to teach others. This train-the-trainer approach increases acceptance as you gradually transition to the new system. Don't underestimate the criticality of effective change management for the organization to ensure that the organization embraces, supports, and sustains the initial deployment and subsequent operations.

3 Vendor Evaluations

After conducting your evaluation and procuring buy-in from your organization's leadership, it's time to shop for a new system based on your existing and potential needs.

Consider how much capacity and how much detail the system should have. Some vendors provide all-encompassing solutions with a heavy price tag but may provide more options than you need. Also, decide which QMS aspects you require. Does your current system provide training/learning management, document management, computerized maintenance management, and laboratory information management? Does it include standard quality event management of corrective and preventative actions, deviations, non-conformances, risk management, change control, supplier quality management, and audit management? Depending on how you answer the above questions, you may already have solutions for most QMS functions, and you can choose a vendor specializing in the specific areas your current system lacks.

4 Implementation

Finally, reach out to trusted vendors with a track record of success and break down their pros and cons. Vendor cost, capability, implementation time frame, and customer support availability are key factors to present to decision-makers when finalizing your provider choice. Your initial deployment should meet your short-term needs, while the system should be able to grow with your business in an aligned manner. If the QMS is only suitable for your immediate situation and doesn't position you for growth, you should consider this before making a final decision.

A new system can be custom-built for your organization's precise needs, or you may choose an out-of-the-box configuration to save time and money. Be forewarned that vendors vary in how much they expect to actively participate in the implementation process. Some want to perform the inventory and setup, while others only expect to build the system and step back while your company executes it. Establishing an implementation plan and project risk register up front is fundamental to avoiding misunderstandings later. This is especially valuable if you plan to transfer existing data into your new eQMS. Some vendors simply require access to the data and will handle transition and formatting for an additional fee, while others require you to do this work yourself.

Once a new system is in place, it should first serve as upgraded document storage for quick reference with minimal training. For example, instead of using desktop folders to store information, users can adopt a design with a search function that makes it easier to access material. As users become accustomed to this new library, they can add new documents for approval and grow it into a complete QMS. A dedicated system will include more sophisticated features than document storage, allowing users to employ its most basic storage functions first and grow into the rest. A good provider will grow with you and allow you to phase in your system capability based on your requirements.

Full implementation timelines vary, and a phased approach will take longer than quick adoption. You'll want to work closely with your chosen vendor to align goals and timelines to plan which elements of the system you will be utilizing and when. Managing the vendor relationship can be tricky, and having an experienced third party providing additional support and expertise is helpful. Typically, you should expect the time from evaluation to operation of an eQMS to take anywhere from 6 to 18 months, depending on the complexity of your chosen solution.

Working with an Expert

The pharmaceutical industry is growing rapidly, and finding the perfect system for your company's needs means navigating a complex world of vendors and solutions. Working with an impartial consultant who brings expertise to the table saves you valuable time and resources. They take time to understand your company's unique needs and goals and recommend vendors that are the best fit, saving you time and money and providing peace of mind.

Five Steps to Making Your Validation Master Plan Work for You

Kayla Fouch, Sr. Manager, Parla Hoelter, Manager
& Adam Pfeiffer, Vice President



Biotech companies planning a new facility build or expansion often choose to create a validation master plan (VMP) to define the strategic approach for achieving and maintaining a qualified facility. This document defines the scope of the validation efforts for the project including the key components necessary for the entire commissioning, qualification, and validation (CQV) lifecycle and how they relate to project specifics. Many companies will go through the motions of generating a high level or generic VMP to check a box based on what they might have seen in the past and then completely disregard the document until an issue arises or a misalignment is discovered. A properly optimized and implemented VMP should be an aid that is a proactive document, streamlining processes and keeping facilities up to date on evolving regulatory requirements.

Optimizing for Long-Term Efficiency

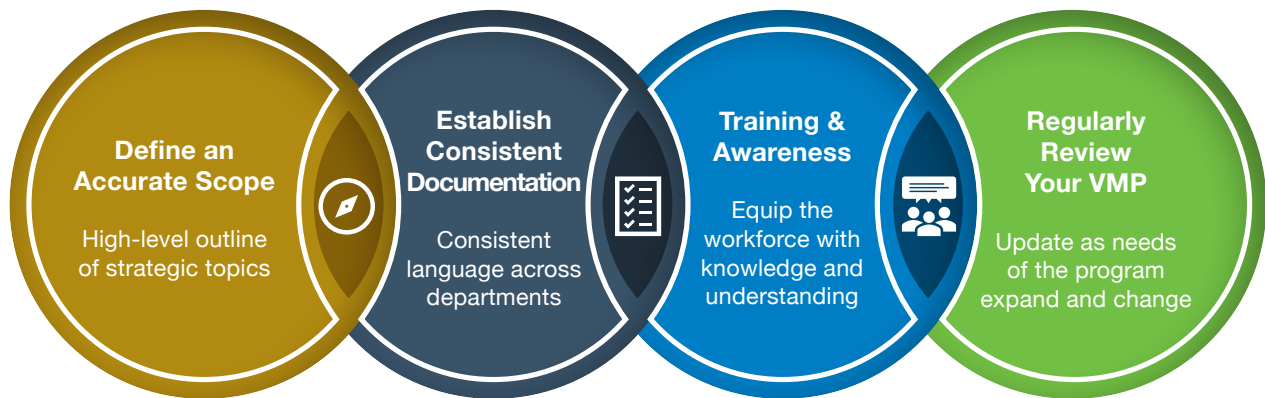
Though a validation master plan isn't explicitly required, it provides a useful framework for creating the documentation required by the FDA. Because it's not technically required, some companies consider a VMP unnecessary. However, these companies often find themselves in the middle of validation implementation without a solid master plan, complicating their validation processes and leading to costly remediation activities later. There is some initial friction in the process of creating a VMP as it forces stakeholders to have difficult conversations and make project critical decisions up front. However, solidifying these decisions at the beginning minimizes the schedule, regulatory, and budgetary impact of changing validation strategies in the middle of the project. Having guidance on correctly creating and implementing a VMP helps companies manage those deliberations to form a living document that improves their manufacturing processes rather than impedes them.

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For many early-stage companies, the value of establishing a VMP alongside other significant guidance documents may be overshadowed by more immediate concerns related to achieving speed-to-market. However, the primary utility of a VMP lies in its long-term efficiencies. By creating a framework upon which to build subsequent validation project plans (VPPs), companies position themselves to realize significant returns on time and resourcing as well as a reduction in remedial activities. Having a CQV program without a VMP is like coaching professional sports without a playbook.



It may be tempting to think that creating an overarching strategy is slower than making validation plans on a project-by-project basis. Creating one limited plan at a time can provide short term schedule savings; however, over the course of the entire project lifespan it is often the case that the series of small plans do not align in scope or approach. This can result in gaps and misalignments which are difficult to explain away during audits. Regulatory bodies such as the FDA strongly prefer unified systems rather than a patchwork of processes, as any quality or validation policy documents should be applied consistently across the entire operation. Creating a VMP upfront makes it easier to develop project specific VPPs as needed because it provides an overarching framework on which more detailed plans can be built. In effect, a strong VMP details out how the policies outlined in the site's quality program shall be implemented across all project efforts.

Step 1: Define an Accurate Scope

The first step in creating an effective VMP is to clearly define its scope. A VMP is a high-level document designed to help project managers make more detailed VPPs, validation documentation, and SOPs. It can outline strategic topics such as departmental responsibilities, relevant reference documentation, system scopes, and required activities. An effective VMP often doesn't need to get into the fine details of the project plan to allow for some flexibility to adapt to obstacles encountered during project implementation. Since a VMP can be a parent document for many associated VPP documents, it is critical to ensure that the VMP provides enough structure to ensure different project teams follow a consistent validation program without making the VMP so specific that it cannot apply to every project at the site.

If the VMP is too detailed, it becomes inflexible or rapidly obsolete. Keeping the VMP at a high level maintains enough wiggle room for departments to meet their qualifications while following industry best practices. One example of how VMPs guide detailed SOPs is in creating validation schedules. The VMP establishes first, second, and third-level timetables for validation and structural documents. These determine the general trend of the validation process, but within that framework, there is flexibility to refer to department-specific SOPs, which are easier to adapt to project-specific needs when necessary.

Step 2: Establish Consistent Documentation

VMPs determine what documentation is required from each department for validation efforts and define the terminology used to provide consistency in validation deliverables. Without these guidelines, companies may find that different departments use diverse terminology for the same systems, which can create confusion and raise red flags for regulatory agencies. In contrast, if a project manager makes a project plan based on a robust VMP, they can ensure they have planned for all the required documentation for their systems and that the individual pieces fit with the company's implementation of their policies and procedures. Any commissioning and qualification documents, VPPs, or SOPs derived for specific processes must align with the plans detailed in the VMP. This allows for project deliverables to be consistent between projects, and results in a more unified site validation package.

Step 3: Training & Awareness

Training and awareness are pivotal in ensuring the success of a company's VMP. First and foremost, they equip the workforce with the knowledge and understanding required to effectively implement the VMP's strategies and procedures. Well-informed employees are better prepared to carry out validation tasks accurately, reducing the likelihood of errors that can lead to costly remediation activities. Moreover, training and awareness promote consistency throughout the organization, ensuring that everyone follows the same validation standards and best practices. This consistency is particularly crucial in regulated industries where deviations can have significant consequences. Additionally, by fostering a culture of awareness and education, companies can adapt to evolving regulatory requirements and industry standards, thus maintaining compliance and staying competitive. In essence, training and awareness serve as the cornerstone in translating the VMP's intentions into successful, well-executed validation activities.



In essence, training and awareness serve as the cornerstone in translating the VMP's intentions into successful, well-executed validation activities.



Step 4: Regularly Review Your VMP

A VMP should be established with the understanding that it is a living document and should be updated as the needs of the program expand and change. Reasons to update a VMP include implementing audit feedback, responding to new guidance from regulators, changing the quality program, updating roles and responsibilities, or modifying capital expenditure programs.

To truly optimize your VMP, companies must periodically review it to ensure it aligns with current validation needs and industry standards. Unfortunately, some companies create VMPs early on but never fully refer to them to receive the benefits of the document. It's easy for project managers to silo themselves and focus on the needs of their departments or projects without referencing to the principal VMP for direction. If the site has multiple projects which have been designed without the principles laid out in the VMP in mind, crucial tasks can fall through the cracks. A VMP which does not fit the specifics of a project can and should be updated to illustrate to any regulatory bodies

that any edge cases or planned deviations from the original implementation outlined in the VMP were intentional and approved. Otherwise, it can give the impression that validation activities are proceeding in a manner that is not in a state of control.

Companies also need to reference their VMP regularly during times of growth. As a company adds new employees to its roster, the need for clear, consistent best practices becomes even more apparent. Often employees experienced in work in a GMP environment will have exposure to a validation implementation that is different than the VMP. In the absence of exposure to the VMP and awareness of the rules, these employees will implement processes that are familiar to them, which may or may not align with the site's quality program. The VMP serves as a resource, providing an objective standard that ensures best practices stay consistent even as the company grows.

A VMP should also be used when leveraging validation services provided by vendors, such as computerized system turnover packages. Without oversight, vendors may bring their own VMPs into the system that clash with the company's VMP, creating a lack of compliance. Crucial factors like data integrity are left out and must be tested later in addendum documentation. Sometimes, when there are competing VMPs, employees end up double validating the systems to hit every standard, resulting in an increase in work and spend. A flexible and well used VMP can be updated to allow for additional strategies such as wrapper protocols, which can reduce the resourcing required to align documents that are not congruent with site validation policies.

As a living document, the VMP can be changed when appropriate to reflect the changing needs of the company or industry standards, including capacity for risk. For example, a company's capability to accept risk frequently scales down as operations scale up and the quality program matures. A sound VMP includes an overall assessment of how the manufacturing process may affect product quality and helps identify potential risks.

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Conducting routine risk assessments is imperative to ensuring product quality. The risk assessments should be conducted at regularly scheduled intervals and any time the manufacturing process changes. First, they clarify what elements need validation and create appropriate methodologies. Next, they determine a logical order for proceeding with the validation. By streamlining these processes, the VMP keeps facilities in compliance without unduly increasing production timelines.

How Can I Create a VMP for Existing Processes?

If your company is already manufacturing products without a VMP in place, it's not too late to create one. To retroactively formulate a VMP, consider what worked in the past and what didn't, to identify what you'd like to change and what gaps need to be filled. Next, compare your past validation methods to your ideal plans to determine the impact of changing your procedures. Sometimes, you'll want to grandfather in past procedures to avoid unnecessary

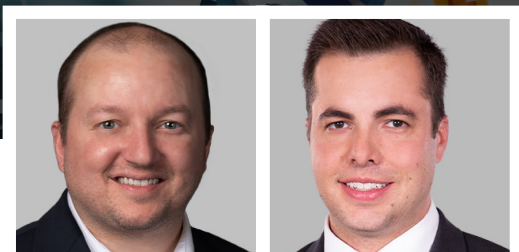
workload. You can also identify areas where work is duplicated, or if certain managers have been assigned unnecessary tasks. Creating a new VMP for an existing policy can help you improve your processes and align them with industry standards.

Long-Term Success in Validation

Ultimately, an effective validation master plan improves efficiency, compliance, and overall effectiveness in validation processes leading to a smoother path to approval. In creating and maintaining a VMP for existing processes, a multi-faceted approach is essential. The key steps of optimizing the VMP for long-term efficiency, starting with defining an accurate scope, followed by establishing consistent documentation, prioritizing training and awareness, and regularly reviewing the VMP, form a comprehensive strategy. By defining the scope, organizations set the foundation for a VMP tailored to their specific needs. Consistent documentation ensures clarity and adherence to best practices. Training and awareness elevate the expertise of the workforce, and regular reviews keep the VMP aligned with evolving requirements. This approach not only streamlines validation processes but also fosters a culture of excellence and adaptability, enabling companies to achieve both short-term and long-term success in validation endeavors.

Empowering Biotech Innovations Through Automation: A Guide to Strategy Development & Implementation

Cory Proctor, *Sr. Director* & Nicholas Weinreich, *Sr. Manager*



In the rapidly evolving landscape of biotech companies, the integration of automation and digitalization into the drug production pipeline is becoming the new standard as more organizations realize the benefits of these solutions. However, with the multitude of automation solutions available, it becomes increasingly challenging to develop strategies that align with each company's unique requirements. This article aims to provide a comprehensive method for designing and implementing automation strategies tailored to the unique needs of each company.

Automation Systems

When defining an automation strategy, it is critical to identify the specific areas where automation solutions can be implemented to optimize control, monitoring, data management, and reporting processes. By examining these areas and potential solutions, manufacturers can effectively leverage automation to streamline operations, enhance data integrity, and improve overall efficiency.

Process Utility Control & Monitoring

Determine how each process and utility system will be controlled and monitored then define where related data will be collected.

Batch Reporting

Leverage a streamlined Manufacturing Execution Software to collect and consolidate data while ensuring comprehensive compliant batch reporting.

Environmental/CTC Control & Monitoring

Designing and establishing an effective data collection and tracking mechanism for critical utilities is paramount, as these environments have a direct impact on product quality and safety.

Batch Records

Electronic or paper-based batch records used to compile and manage data ensure traceability, accuracy, efficiency, and compliance while adherence to regulatory standards.

Analytical Systems

Automation in analytical systems ensures seamless data transfer, reduces manual errors, and enhances the integrity of analytical results.

Evaluating Solutions

Consider factors like overall automation readiness by determining technological capabilities, process maturity, and operational readiness for automation implementation.

By addressing these key areas, manufacturers can identify opportunities for automation implementation, improve process control, enhance data integrity, and optimize operational efficiency. Leveraging automation technologies and collaborating with experienced partners enable companies to develop robust automation strategies that align with their unique needs, ensuring regulatory compliance and competitive advantage in the evolving biotech industry.

Leveraging automation technologies and collaborating with experienced partners enable companies to develop robust automation strategies...

Considerations for Defining an Automation Strategy

Automation has become an integral part of manufacturing, enabling companies to enhance efficiency, accuracy, and compliance in their processes. However, developing an effective automation strategy requires careful consideration of the company’s current phase as well as the specific requirements of their products. In today’s competitive landscape, companies are increasingly turning to automation solutions to optimize their manufacturing processes. Phase-appropriate investments and an understanding of speed to market, cost-cutting, process definition, and validation play crucial roles in shaping a company’s automation strategy.

<p>Compliance Standards & Automation Systems</p> <p>21 CFR Part 11 compliance serves as the foundation for an effective automation strategy. It also provides the essential framework for data integrity and specifies hardware and software requirements.</p>	<p>User Security</p> <p>Leveraging robust user authentication to control data access can help ensure compliance. Maintaining separation between GMP and non-GMP systems allows for more granular control and simplifies change management.</p>	<p>Critical Data Monitoring, Collection, & Reporting</p> <p>Leveraging robust user authentication to control data access can help ensure compliance. Maintaining separation between GMP and non-GMP systems allows for more granular control and simplifies change management.</p>	<p>Critical Backups</p> <p>Protective measures like regular backups at both the equipment level and automated systems for critical raw data are essential to preserving data integrity and supporting recovery processes.</p>	<p>Align Investment with Company’s Current Phase</p> <p>Factors like process understanding, speed to market, process definition, and validation efforts shape the automation strategy and must be well defined prior to implementation and should be enhanced through automation.</p>	<p>Consider Cost of Automation on Validation Activities</p> <p>The complexity of manufacturing design directly impacts validation efforts and costs, requiring meticulous planning and collaboration between automation engineers and process experts for successful implementation.</p>
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A well-designed automation strategy, driven by a deep understanding of Part 11 requirements, not only helps developers streamline their processes but also enhances quality, traceability, and overall efficiency. By partnering with automation experts well-versed in the nuances of manufacturing, companies can navigate the complexities of Part 11 compliance and create a future-ready automation strategy that aligns with their unique needs and regulatory obligations.

Embracing the Therapeutic Revolution: Developing a Flexible Automation Strategy

The biotech industry is experiencing a therapeutic revolution, marked by rapidly evolving market conditions and technological advancements. This dynamic landscape poses unique challenges for manufacturers, requiring them to adapt their automation strategies to keep pace with innovation. It is therefore critical to develop a flexible approach that can seamlessly integrate emerging technologies while minimizing the impact of system changes and validation efforts.

By considering modularity, scalability, and interoperability in the design phase, manufacturers can ensure that their automation solutions are adaptable and future-proof.

A flexible automation strategy should be able to accommodate future technological upgrades and seamlessly integrate new systems and equipment. By considering modularity, scalability, and interoperability in the design phase, manufacturers can ensure that their automation solutions are adaptable and future-proof. To take full advantage of new technologies, it is essential to minimize change impact to existing or planned engineering and validation efforts.

Employing standardization and harmonization principles in automation design helps minimize the impact of changes. Industry best practices help manufacturers ensure compatibility and interoperability between different systems and processes. Which, in turn, simplifies the integration of new technologies and facilitates efficient engineering and validation activities. This approach not only enables manufacturers to stay competitive but also enhances agility, efficiency, and product quality.

Balancing Current Automation Needs with Future Circumstance

It is crucial to consider both the current circumstances of the company and its future goals of the facility. The automation strategy should provide a solid foundation that accommodates the existing manufacturing processes while also being adaptable to future expansions, changes, or advancements.

The first step is assessing the ideal level of automation for the manufacturing process. This involves evaluating various factors such as process complexity, product volume, regulatory requirements, and operational efficiency. Several automation options exist, including islands of automation, centralized batch reporting, and electronic batch records, each offering unique advantages and challenges.

Assessing Future Facility Needs and Purpose

In addition to assessing the ideal level of automation, it is essential to consider the future purpose of the facility when defining the strategy. This includes evaluating factors such as the potential for a single process or multiple/changing processes, additional laboratories, or future expansions.

For a facility focusing on a single process, the automation strategy should be designed to optimize and streamline that specific process. It should incorporate automation solutions tailored to the unique requirements of that process, ensuring efficiency, quality, and regulatory compliance. In contrast, facilities with multiple or changing processes require a more flexible automation strategy. Such strategies should accommodate the diverse needs of different processes, allowing for seamless transitions, equipment reconfigurations, and data integration. A modular automation approach can facilitate the integration and scalability of new processes, accommodating future expansions or changes.

To create an initial automation strategy that encompasses the company's current circumstances and future goals, the following steps should be taken:

- 1** Conduct a thorough assessment of the existing manufacturing processes, considering process complexity, volume, and regulatory requirements.
- 2** Based on the assessment, determine the ideal level of automation, choosing from islands of automation, centralized batch reporting, electronic batch records, or a combination thereof.
- 3** Evaluate the future purpose of the facility, including potential changes, expansions, or new processes, and ensure the automation strategy can accommodate these future developments.
- 4** Consider a modular and scalable automation design that allows for flexibility, adaptability, and integration of new technologies or processes as the company grows.
- 5** Collaborate with automation experts, leveraging their knowledge and experience to develop an automation strategy that aligns with the company's current circumstances and future goals.

By taking the above steps companies can lay a solid foundation for automation implementation that ensures the strategy optimizes current manufacturing processes while remaining flexible and adaptable to the future.

Comparing Islands of Automation vs. a Centrally Controlled Facility

When implementing an automation strategy, companies are faced with the decision of choosing between islands of automation and a centrally controlled facility. Each approach offers unique advantages and considerations. A comprehensive understanding of their ideal use, benefits, and drawbacks can lend to an informed decision when defining their automation strategy.

Islands of Automation

Islands of automation involve leveraging original equipment manufacturer (OEM) automation solutions for control, monitoring, and reporting allowing for targeted optimization and control. Under this strategy, each system operates independently, with its own controls, recipes, and reports.

PROS

- **Right-sized investment:** Islands of automation allow for initial investment that matches the company's scale, with the flexibility to expand as needed in the future.
- **Minimal impact from equipment changes:** As individual systems are separate, changes to one piece of equipment have minimal impact on the overall process.
- **Efficiency gains:** Leveraging OEM equipment controls result in cost, engineering, and validation efficiencies, saving time and resources.

CONS

- **Variety of solutions:** Implementing islands of automation throughout the facility often requires dealing with a variety of solutions, which can increase complexity and maintenance efforts.
- **Reliance on multiple vendors:** With separate systems, relying on multiple vendors for equipment support can introduce coordination challenges and potential delays in case of issues.
- **Equipment updates:** Updates and modifications need to be made on each individual piece of equipment, which can be time-consuming and may require additional resources.
- **Integration limitations:** Not all equipment may be capable of integrating seamlessly for user security, backups, reporting, central batch control, or electronic batch records, leading to potential data silos and manual workarounds.
- **Transition challenges:** Shifting from an islands-of-automation setup to a standardized platform can encounter friction and complexities, requiring careful planning and execution.

Centrally Controlled Facility

A centrally controlled facility relies on a central control system or process control system for comprehensive control, monitoring, and reporting of the entire manufacturing process.

PROS

- **Consistent manufacturing process:** A centrally controlled facility ensures a standardized and consistent manufacturing process across all stages. This reduces human interaction and minimizes the potential for human errors, leading to improved product quality and regulatory compliance.
- **Efficient batch release process:** The implementation of a centralized system enables a streamlined batch release process, allowing for review by exception. By automating data collection, analysis, and reporting, the facility can focus on exceptional cases, saving time and resources.
- **Easy equipment updates:** A centralized control system simplifies equipment updates and modifications. Changes to controls and recipes can be easily implemented and propagated throughout the system, ensuring swift adaptability to evolving requirements.

CONS

- **Impact of equipment changes:** Changes to the equipment in a centrally controlled facility have a high impact on the overall manufacturing process. System modifications or replacements may require extensive engineering and validation efforts, potentially disrupting operations and causing delays.
- **High initial investment:** Establishing a centrally controlled facility involves significant upfront investments in equipment, engineering, and validation. The costs associated with deploying and integrating a centralized system can be substantial, especially for medium to large-scale processes.
- **Need for well-defined processes:** A centrally controlled facility relies heavily on well-defined manufacturing processes. Without clear and robust procedures in place, implementation issues may arise, jeopardizing the effectiveness and efficiency of the automation system.

Combining Strategies for a Hybrid Approach

Companies may also combine different strategies to create a hybrid approach tailored to their specific needs. Understanding how a hybrid approach could be integrated can optimize their automation investments and achieve synergy in their manufacturing processes.

PROS

- **Customized optimization:** Hybrid strategies allow manufacturers to tailor their automation solution to meet their specific needs. By combining different strategies, companies can optimize their processes, adapt to unique requirements, and achieve a higher level of customization.
- **Synergy of capabilities:** By integrating diverse automation systems, hybrid strategies bring together the capabilities of different solutions, resulting in enhanced functionality and efficiency. This synergy enables seamless data integration, improved process control, and streamlined reporting.
- **Cost-effective implementation:** Hybrid strategies can offer a cost-effective approach to automation implementation. Leveraging existing OEM equipment and combining it with a centralized control system reduces the need for extensive equipment replacements or upgrades, optimizing investment costs.

The importance of effective planning, collaboration with automation experts, and comprehensive system integration cannot be overstated when implementing hybrid strategies. Companies should prioritize thorough documentation, testing, and validation processes to ensure the seamless operation of the combined automation solution.

Manufacturing Nuances for Transformative Medicine

Joseph Neroni, Sr. Director, Sarah Stoll, Sr. Director, & Landon DeCosta, Sr. Director



Companies can choose between several innovative methods for creating their leading-edge therapeutics in the biopharma industry, but each approach brings unique challenges as well as opportunities. Creating radioligands (RLTs), mRNA therapies, cell therapies, and gene therapies requires extremely complex procedures, specialized equipment, and top-notch expertise.

Across these modalities, attracting experienced talent and continuing to train a dedicated workforce is critical. In addition to drawing the right talent, drug developers must consider the location of their facility, shipping, and supply chain logistics to deliver their drug to the patient. Companies must also consider how scaling up and out can either help or hinder their time to deliver incredibly complex treatments to patients. Understanding the nuanced differences and industry trends in producing each of these modalities helps companies strategize the best approach for their product and ultimately bring life-saving treatments to patients in need quicker.



Radioligands: Promising Therapeutics, Complicated Logistics

In oncology research, radioligand therapies (RLTs) provide an innovative solution to the problem of how to attack cancer cells without damaging healthy cells. Although it is a lifesaving therapy, RLTs are difficult to produce and distribute.

The last several years have seen an explosion of research and clinical trials testing new radiopharmaceuticals. Due to their novelty, one of the most obvious challenges plaguing RLTs is the shortage of skilled workers with deep knowledge or experience on how to produce them. Radioligand therapy companies can bridge the talent gap by partnering with academic institutions and research centers, offering internships, and fostering collaborations to attract and train professionals with expertise in nuclear medicine, radiopharmaceuticals, and related fields. They can also invest in ongoing education and development programs for existing employees to enhance their skills and knowledge in this specialized field. Radiotherapy companies can address the challenge of time in shipping to patients by optimizing logistics and strategically locating their manufacturing facilities. Having facilities in metropolitan locations can expedite shipping due to better access to transportation networks. This proximity reduces transit times, ensuring timely delivery of radiotherapy equipment and materials. Additionally, a metropolitan location can provide access to a skilled workforce and resources, further streamlining production and distribution processes. Efficient logistics and strategic facility placement contribute to overcoming time-related challenges in the delivery of radiotherapy services especially for the “last mile:” getting the drugs to patients. Companies planning to invest in RLT drugs should consider these factors and strategize their logistics early to avoid “last mile” holdups.



Understanding the nuanced differences and industry trends in producing each of these modalities helps companies . . . bring life-saving treatments to patients in need quicker.



mRNA Drugs: Timing is Everything

Like radioligand therapies, mRNA therapeutics are both highly promising and logistically complex. In the past few years, mRNA therapies and vaccines have gained notoriety for their potential to deliver genetic information and transiently deliver proteins to treat genetic diseases, tumors, and viral infections. However, sales and operational planning (S&OP) and demand management are intricate processes impacted by post-pandemic vaccine uptake and demographic impacts on the demand for booster vaccinations.

The need for multiple treatments may pose challenges in maintaining a durable therapeutic response. While researchers are exploring ways to enhance the longevity of the therapeutic effects through modified mRNA sequence or repeated dosing, manufacturers of mRNA therapies can stay adaptable for patient demand by establishing flexible production processes that can quickly respond to changes in dosage requirements. Manufacturers can also emphasize collaboration between researchers and patient advocacy organizations to accelerate the development of mRNA therapies that promise efficacy and longevity, reducing the need for frequent boosters.

Ultimately, the landscape of mRNA therapeutics is marked by both promise and complexity. The potential to address various medical challenges, from genetic diseases to viral infections, is evident. Yet, the intricacies of S&OP and demand management, especially with the need for multiple treatments, add a layer of complexity. Emphasizing collaboration with researchers and patient advocacy organizations further paves the way for the development of mRNA therapies that not only ensure efficacy but also reduce the necessity for frequent boosters, ultimately enhancing their impact on patient health.

Cell Therapies: Bespoke Treatments Need Custom Solutions

Cell therapies offer patients custom-made treatments for otherwise incurable diseases and conditions, but developing these therapies can be complicated under even the best circumstances, as supply chain, cost, and foundational science obstacles continue to impact the industry. Nonetheless, the promise these therapeutics hold continues to spur research and investment, driven by forward-thinking approaches and new technologies designed to optimize these applications for cost and time.

To produce cell therapies, companies may opt to use autologous (stem cells from the patient receiving the treatment) or allogeneic (stem cells from a healthy donor). Because both methods of producing cell therapies are equally important to saving patient lives, companies face additional manufacturing nuances when determining the mode of donor cell retrieval.

Autologous and allogeneic cell therapies encounter common fundamental challenges. While the personalized nature of cell therapies is crucial for treating complex diseases and severely ill patients, it poses obstacles to manufacturing scale-up. Companies can employ various strategies to maximize patient cells in cell therapies and overcome manufacturing scale-up challenges.

- 1. Improved patient identification:** Streamline the process of identifying suitable patients by developing more accurate diagnostic and patient selection criteria, allowing for a larger pool of potential candidates.
- 2. Automation and standardization:** Invest in automation and standardized protocols to enhance the efficiency of cell processing and reduce the risk of errors during manufacturing, which can help scale up production.
- 3. Scalable manufacturing platforms:** Develop adaptable and scalable manufacturing platforms that can handle varying patient cell quantities without sacrificing quality or personalized aspects of the therapy.
- 4. Process optimization:** Continuously refine and optimize manufacturing processes to minimize waste, reduce costs, and improve the yield of viable cell therapies.
- 5. Supply chain optimization:** Ensure efficient and secure supply chains for sourcing patient cells and delivering the final therapies to treatment centers, which is crucial for scaling up.

By implementing these strategies, companies can strike a balance between personalization and scalability, making it possible to maximize the use of patient cells in cell therapies.

Gene Therapies: From Bench Research to Commercial Manufacturing

Creating gene therapies is an intricate process that does not easily translate from bench research to commercial distribution. Unfortunately, the fundamental scale-up processes that manufacturers employ for other drugs don't apply to gene therapies, i.e., the yield does not necessarily increase in proportion to the amount of raw material used.

The difficulties in producing gene therapies on a commercial scale affect demand, footprint, cost, and throughput. One solution is to partner with an academic or R&D team early in the development process to create a feasible manufacturing procedure and implement CMC-specific equipment. Working with expert researchers helps companies create a methodology that smoothly transitions from bench research to commercial production. Meanwhile, technology is rapidly catching up with the science behind gene therapies, creating opportunities for scaling up rather than scaling out.

Final Thoughts

Ultimately, successfully navigating the intricate landscape of manufacturing transformative medicines demands a multifaceted approach. The complexities of logistics driven by the need for precision in speed must be met with innovative manufacturing solutions that can swiftly adapt to evolving patient needs. Furthermore, the active involvement of patients and shaping their treatment journey while raising awareness of the transformative potential of these medicines is crucial. Biopharma companies must continually reevaluate their manufacturing processes as technology evolves to keep up with industry best practices and remain competitive in an aggressive arena. It is equally important to keep pace with the evolving regulatory and quality standards to ensure risk-based approaches to manufacturing adhere to evolving cGMPs. Working with an experienced partner to help understand the nuances in the industry and the unique complications inherent to these popular, innovative modalities is the first step in determining an efficient and cost-effective approach to revolutionize treatment.

Strategic Planning for Your Facility's Pre-Approval Inspection

Nate Traugber, Sr. Director & Jim Watson, Vice President



The path from drug discovery to full commercialization contains many steppingstones, including meeting FDA Pre-Approval Inspection (PAI) facility user requirements prior to commercial manufacturing. However, many emerging pharmaceutical and biotech companies begin their facility plan later in their journey than they should, leading to delays and unplanned costs. Early strategic planning creates a road map of success that companies can follow to ensure their facilities are inspection ready.

What Triggers a PAI?

The FDA performs a PAI to assess potential product, process, and facility risks. If the FDA initiates a PAI, they assemble a team of chemistry, microbiology, process/facility, and formulation experts to review the company's manufacturing processes.

Product Risks

- New molecular entity
- First application filed by applicant
- First Abbreviated New Drug Application (ANDA) filed for an approved drug
- Reference Listed Drug (RLD) has complaints, adverse drug event, stability issues
- Patient population or for serious condition
- Breakthrough therapy, shortage situation

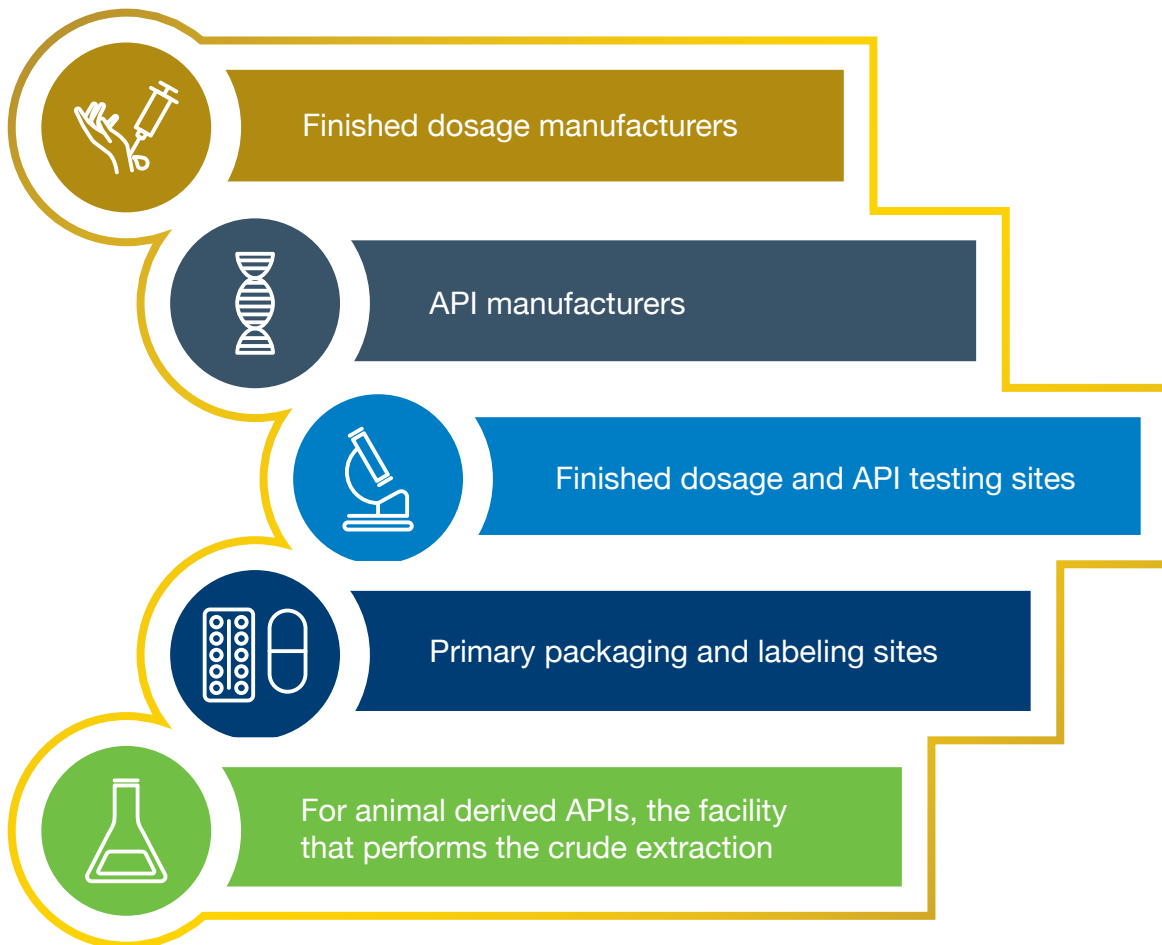
Process Risks

- Narrow therapeutic range (95%-105%)
- API derivation is high risk (derived from animal tissue)
- PAT, NIR, QbD
- Developmental data is incomplete
- Batch records non-specific
- Complicated process
- Substantially different process than previously covered at facility

Facility Risks

- cGMP issues relevant to application product
- Recent Field Alert Report (FAR) relevant to application product
- Recent recalls relevant to application product
- Numerous applications filed at once

PAIs are conducted to assure the FDA that the facility can manufacture the proposed drug and that the data submitted are accurate and complete. They are product-specific and highly data-focused. Prior to a PAI, the facility may also undergo a facility evaluation. Facility evaluations are conducted for:



What Does the FDA Evaluate?

A PAI is conducted to contribute to the FDA's assurance that a manufacturer named in a drug application can manufacture the drug and that submitted data are accurate and complete.

- 1. Readiness for Commercial Manufacturing:** Determines that the manufacturing facility has a quality system that is designed to achieve control over the facility and commercial manufacturing operations.
- 2. Conformance to Application:** Verifies the formulation, manufacturing or processing methods and analytical methods are consistent with descriptions of the application for clinical batches, commercial scale batch, and Active Pharmaceutical Ingredient(s).
- 3. Data Integrity Audit:** Audits raw data, hardcopy or electronic, to authenticate the data submitted in the application. Verifies that all relevant data were submitted such that product reviewers can rely on the submitted data as complete and accurate.

Preparing for the PAI

Being underprepared for a PAI can result in many significant delays in commercial manufacturing. Any concern or discrepancy found by the FDA during the PAI may lead to subsequent inspection, hurt company reputation, and ultimately lead to the drug not being approved. There are specific stems a company can take to be fully prepared for the PAI.

Readiness for Commercial Manufacturing	Conformance to Application	Data Integrity
1 Evaluate your overall cGMP compliance and focus on change control, deviations, and trends	1 Enlist a team to verify that the formulation, manufacturing, processing and analytical methods are consistent with descriptions contained in the application	1 Audit all raw data for factual integrity, contextual integrity, completeness, authenticity and accuracy
2 Evaluate the specific PAI product and process including sampling plans and testing components	2 Audit records, equipment, procedures, and batch records against the proposed and actual production processes that are used for the manufacture of the batches	2 Review the FDA's application integrity policy
3 Review batch records and evaluate the quality system specifically for batch release, discrepancy management and investigation completeness	3 Prepare stability chambers for verification of configuration, orientation, recording charts, alarm logs, temp and humidity conditions	3 Create corrective and preventative action plans (CAPA) and prepare appropriate justification for potential adverse findings or failing test

Plan to Mitigate Risks by Objective

In order to ensure a successful PAI, companies should deploy a proactive compliance approach for their Pre-Approval Inspection. To further prepare, companies are encouraged to conduct a mock PAI wherein a dedicated project manager or third party investigates every issue the FDA would cover during a real PAI. Should any issues around cGMP, quality systems, equipment, processing methods, documentation or data arise, companies should seek expert support to address them to yield the highest chance of a successful PAI.

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