Partnering for Bio/Pharma Success

**Development**
Service Opportunities and Gaps
The Right Fit for Biologic Drugs

**Manufacturing**
Commercializing CGTs
Process Development Options
To Build or Not to Build
Formulating for Fill/Finish

**Operations**
Supply Chain Flexibility

**Quality/Regulations**
Audit Preparedness

**Outsourcing**
Answering the Pandemic Call
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Outsourced services within the bio/pharma industry are growing robustly driven by a variety of factors, such as a greater emphasis on niche patient-populations and rare diseases, a rise in the number of smaller bio/pharma companies, increased market fragmentation, and more demand for patient-centric solutions. According to market research, the contract development and manufacturing organization (CDMO) outsourcing market has the potential to increase by $44.17 billion between 2020 and 2024 (1).

An aspect of drug development that can be facilitated through the use of an outsourcing partner is the development of an effective drug delivery solution. “A good outsourcing partner can provide drug companies with expert guidance into the most effective drug delivery technologies to enable them to successfully commercialise their product,” confirms Arul Balasundaram, formulation manager at Recipharm’s Queensborough facility (United Kingdom). “Such a partner can find the ideal balance between ease of formulation, method development, and subsequent manufacture.”

Delivering success through expertise
“In the development of a drug delivery system, there are several benefits that outsourcing offers that can help drug developers gain a competitive advantage,” says Behzad Mahdavi, vice-president open innovation biologics, cell & gene therapy, Catalent. “[Generally], pharma and biotech subject-matter experts are mostly limited to evaluating one method of delivery because of limited time or other resources, or simply because of a narrowness or focused expertise in their own organizations.”

To improve the potential for success in development, having knowledge and the ability to assess multiple enabling technologies in parallel to target different barriers or formulations to reach the target is imperative, Mahdavi continues. “A development partner with multiple technology capabilities can help bring different perspectives and therefore offer advantages over single technology solution providers,” he notes.

For Ralph Landau, head of Development, Drug Product, Cambrex, a good CDMO should be able to offer a wealth of drug delivery expertise. “A CDMO can offer deep support in developing the right formulations, including delivery systems, by balancing previous experiences with innovative problem-solving to decrease complexity and enhance quality,” he says. “The
right CDMO works with customers as a partner to transparently fill manpower and knowledge gaps. Regardless of the size or maturity of the company, an outsourced partner offers a multitude of benefits that help to bring safe, effective drug products to the market faster. Additionally, advantages can be gained in partnering with an expert for specialist dosage forms, such as topical products for skin, eye, airways, or mucosal membranes, asserts Lynn Allen, vice-president Business Development, MedPharm. “To facilitate optimum formulation development, unique experience and knowledge are required, something that most development companies lack in-house,” she emphasizes. “This is especially the case for specialist topical products as the requirements for delivery are quite different from oral and intravenous routes of administration.”

Meeting patient needs

“Drug delivery is advancing to meet patient needs,” reveals Satish Shetty, director of Product Development, Cambrex. “Instead of a general population approach, there are now defined pediatric and geriatric patient groups via regulatory agencies in the US and Europe. Advances are being made in drug delivery systems to circumvent common conventional dosage limitations, including poor solubility and bioavailability, blood-brain barrier permeation, GI tract degradation, dose-dumping, and so on.”

“Drug delivery solutions that are easy to use and require less frequent administration play a major role to achieve better patient compliance,” adds Maaike Everts, technical marketing leader for parenteral drug delivery, Evonik. An example of a delivery solution that can improve patient compliance is a long-acting injectable, such as bioabsorbable microparticles and implant based on lactide/glycolide polymers, which reduce the frequency of administration, she explains. “These formulations can deliver peptide and small molecule drugs for weeks or months following a single administration, replacing daily injections and daily oral dosing,” Everts says.

Other examples of delivery solutions that can be employed to boost patient compliance and optimize drug performance, include microparticle, nanoparticle, implant, and in-situ forming technologies, Everts continues. “Typically, the goal is to address some combination of formulation challenges that can optimize the release profile, reduce frequency or dose volume, increase bioavailability, avoid toxic side effects, or facilitate more efficacious plasma levels,” she states.

“A lot of attention is being placed on reduced dosing frequency, by modifying potency and release profiles, which increases compliance for all patient populations,” concurs Shetty. “This includes a focus on minimizing the fluctuation of drug concentration and maintenance of blood levels within a desired range.”

Patient compliance is a significant issue in pediatric populations, asserts Andrew Parker, director Open Innovation, Small Molecules, Oral and Specialty Drug Delivery, Catalent. “When developing a pediatric indication of an existing adult formulation, different delivery solutions/formats must be developed to resolve this issue,” he says. “The use of mini-tablets has generated increased interest in recent years because of their ability to be used as sprinkles (as considered by FDA if the mini-tablet is less than 2.5 mm in size), and so can be dosed with food stuffs such as yogurts or porridge. Mini-tablets also provide an attractive solution as potentially being able to easily translate the existing adult format without significant further formulation development.”

Landau highlights the fact that drug developers are taking more time to review other solid dosage forms to determine how the shape and size might impact compliance. “Mini-tablet forms (tablets ≤2 mm in diameter) are helping to increase the acceptability of pediatric drugs and guidance has been drafted by FDA for other solid dosage size and shape requirements,” he adds. “Studies have been carried out to investigate different patient swallowing ability profiles by age, as well as general patient preferences.”

Additionally, Landau notes that there is growth in patient administration of drug therapies for different disease states, such as rheumatoid arthritis, psoriasis, diabetes, chronic pain management, long-term management of asthma, and mental health issues. “With the patient in control of staying on track with treatments, there have been a variety of hurdles to compliance,” he says. “Mechanical complexity, physical dexterity and needle phobias are some of the most common challenges that cause patients to get off track with dosing, which negatively impacts treatments.”

Despite the market dominance of oral solid dosage there are some drugs that cannot be delivered in a conventional way due to instability, and to meet rising patient expectations, pharmaceutical companies are required to make more user-friendly forms for these products too, Allen specifies. “Many patients prefer to use dosage forms that positively impact their health whilst integrating seamlessly into their lifestyles,” she explains. “This is especially important with topical formulations as the cosmetic and aesthetic properties are a critical aspect as patient compliance is often driven by the ease of use and the application experience. Using an outsourcing partner that understands the end-user’s opinion and preferences are crucial from the start to ensure these factors are incorporated into the product profile from the outset of development.”

Critical to success

Employing a drug development specialist outsourcing partner can provide a sponsor company with access to experts with a proven track record in selecting the optimum delivery solution based on the needs of the drug substance in question, asserts Balasundaram. “A good partner will also be able to draw from experience to assess risk at every stage of the process, can advise on overcoming inherent development hurdles and provide the timeliest and most cost-effective solution for projects,” he summarizes. “In doing so, [a good partner] can help enhance the efficiency of the development process and minimize time-to-market making selection absolutely critical to success.”

Reference

Finding a right-fit partner for biologics drug development has become increasingly important, especially as hundreds of new biotherapeutics—cell therapies, gene therapies, bispecific antibodies, antibody drug conjugates (ADCs), vaccines, etc.—move through a burgeoning biologics pipeline. But what criteria, skills, experience make for a good manufacturing partner? Just as important, what is the evaluation process by which potential partners are screened?

**Drug developer seeking partner**

To start with, what are biologic drug developers looking for in a contract development and manufacturing organization (CDMO) or a contract manufacturing organization (CMO), or other service provider? Jean-Christophe Hyvert, chief commercial officer at Lonza, notes that Lonza, for example, is positioned to work with many biotech companies of various sizes. He points out that emerging and small biotech companies make up approximately 80% of the total drug development pipeline today and are a key segment for CDMO companies. About 50% of Lonza’s partners, for example, are represented by emerging, small biotech companies and virtual companies.

“This particular biopharma segment is looking for a CDMO that can address their specific needs; not only free capacity but also critically importantly: experience with fulfilling regulatory requirements, procurement power, legal frameworks, and speed, without added risk. These small companies also require a well-established partnership offering and flexible funding milestones that add value at every development stage,” Hyvert states.

For biologic drug developers partnering with a CDMO or CMO, it is critical that the CDMO/CMO provide services that meet developers’ needs as well as have the capacity to manufacture the desired pipeline, says a company official at Samsung Biologics. With rising biologics demand, the Samsung official says, the company is seeing drug developers’ in-house capability hitting a limit, ultimately resulting in them outsourcing services to meet these demands.
When choosing the right outsourcing partner, biologic drug developers look for well-trained employees, well-maintained facilities, and trustworthy communication with quality and data integrity, the Samsung official says.

A look at vaccine fill/finish

Amid the ongoing work to bring new biotherapeutics to market is the added challenge of bringing new vaccines to market to combat the global COVID-19 pandemic. “The global pandemic has created supply constraints and long lead times for many products used in the biopharma sector; everything from gloves and other PPE [personal protective equipment] to resins and single-use disposals as well as primary packaging components have been impacted,” says Randy J. Maddux, chief operating officer, iBio.

Maddux points out that the pandemic also emphasized the gaps that exist in available fill/finish capacity. “And, as a result, we’ve seen a number of players make investments to bring more capacity on-line. That said, indications so far are that the biopharma sector has done a good job in planning for aseptic fill/finish of the new vaccines and reallocating and reprioritizing capacity where needed to meet current demand,” he says. He also cautions that the situation could easily change as the rate of vaccine administration ramps up and/or further disruptions in the supply of fill/finish components occur.

“For us, there was no big difference before and after the pandemic in regards to the technological aspect of the fill/finish process,” interjects the Samsung Biologics official. The most challenging aspect came from the supply of primary packaging materials, the official notes. Even before the pandemic, the utilization rate of CDMO companies continued to increase to meet ongoing biologics demand and supply balancing, but the COVID-19 pandemic added unanticipated demand in a very short period of time.

Hanns-Christian Mahler, head drug product services, Lonza, adds that sterile fill/finish facilities are also not available in abundance, and the capacity of existing sterile facilities is often quite well utilized. One should also not forget that there are also many other medicines to be supplied, not only COVID-19 vaccines, he emphasizes. “Hence, there is, from my perspective, still a significant need to have more sterile manufacturing capacity globally.”

Technical expertise

Mahler observes that there are many factors to consider for long-term manufacturing supply agreements for a biotherapeutic project. The first key question that a biologic drug developer and prospective manufacturing partner may need to ask is whether the available sterile facility is suitable from a technical perspective:

- Does the facility have the relevant quality certifications?
- Is there sufficient capacity available, or can it be made available in due course to meet the supply-demand?
- In addition, are there sufficient experts available, or can they be hired in due course?

“Apart from these factors, regulatory expertise is becoming of crucial importance, especially in the context of the novel and/or accelerated pathways. As the diverse biopharma landscape changes, the methods we use for developing and manufacturing drugs, increasing control, and streamlining operations through automation become necessary in the future of manufacturing,” adds Hyvert.

Furthermore, service providers need to constantly monitor industry trends and be in tune with clients’ needs, developing technologies, and digitalized solutions, says the Samsung Biologics official. “Process intensification technologies, such as N-1 perfusion and non-stop centrifugation, are reflective of latest industry trends, and implementing these would make a CDMO an attractive partner,” the official states.

Industry advice

In terms of industry advice that can help maintain a long-term partnership between contract manufacturing service providers and drug developers, data integrity and transparency should be the top priority, says the Samsung Biologics official. “It is critical that a service provider maintain close communication with clients to achieve this. For example, Samsung Biologics provides real-time remote client access to our quality document viewing and approval system, allowing for faster release of product batches, and agile response in case any issues occur,” the official states.

Maddux concurs that frequent, open communication and a spirit of collaboration and teamwork are keys to any successful long-term partnership. “This takes the form of establishing trust between key stakeholders, often to the point where there is a personal relationship of mutual respect. Establishing a well-written MSA [master services agreement] that contemplates likely challenges and things that may go awry is important, but it is virtually impossible to cover every situation. The ability to work together in the gray areas between the black and white as written into the contract is the ‘gold standard’ for successful long-term partnerships,” he states.

New challenges have brought on accelerated approval pathways such as fast track and priority review, adds Hyvert. “We are witnessing an increased pressure to quickly deliver therapies for the patients who need them the most, which puts pressure on process development and manufacturing capacity. The COVID-19 pandemic has increased the emphasis on speed to market, disrupting supply chains, the supply of raw materials, and access to quality capacity, which causes delays in clinical trials,” he says.

“Forming a strong partnership is definitely the key to creating a transparent and open relationship based on trust and flexibility to solve customer issues, such as changes in capacity and timelines as well as technical challenges,” Hyvert adds.
Cell and gene therapies (C&GTs) have made huge advances in a few short decades. By February 2020, five therapies were on the market and FDA had approved nine more, while 362 treatments were in the US pipeline, up 25% from the previous year, according to the Pharmaceutical Research and Manufacturers of America’s latest survey (1). In September 2020, the first patient was dosed with autologous chimeric antigen receptor (CAR-T) lymphoma treatment using an automated closed system. “Despite complex and mainly manual processes, we can produce these therapies. Now we must work on making processes reproducible,” says Joerg Ahlgrimm, president and chief operating officer at The Discovery Labs, who was previously head of global C&GT operations at Lonza Pharma & Biotech.

Significant progress has already been made, he notes. “The fact that we can routinely upscale a viral vector to 200–500 L standard represents a huge accomplishment. Years ago, we could not even have imagined reaching this point. And now, we are approaching 2000-L batch sizes,” he adds. The Discovery Labs is building a Center for Breakthrough Medicines to accommodate 80 to 120 C&GT customer development programs at any point in time. For now, the goals are clear, Ahlgrimm says: stable cell lines, better scalability, smaller footprints, and better automation. He sees autologous therapies dominating with adeno-associated virus (AAV) and lentivirus vectors the dominant vehicles for manufacturing.

Both autologous and allogeneic therapies face steep hurdles to commercialization. Where allogeneic therapies are a bit more similar to traditional biopharmaceuticals, autologous therapies change the manufacturing paradigm completely, adding the extra steps of cell collection from patients and transport to and from patients to manufacturing, necessitating a just-in-time approach that is new to the industry. “On the autologous side, most processes are still extremely...
The past few years have seen closer partnership between developers and CDMOs and technology vendors, including smaller, specialized equipment companies, some of which are new to this corner of the industry. CDMOs provide a showcase and reference and show how their technologies can be used. “Upstream, many of our suites feature automated equipment, including new bioreactor technologies,” says Moran. One new presence upstream has been Distek, which has introduced bench-scale bioreactors designed to make scale-up or scale-down more efficient, she says.

Downstream, Moran notes, the focus is on recovering the maximum amount of full vector particles by optimizing chromatography resins, materials, and charges. Discovery is also planning to have capabilities in ultracentrifugation, which can lead to a more manufacturable process, Moran says. Refractive index is being evaluated as a way to improve extraction of the material. “It’s a bit less manual and can improve recovery,” she explains. In formulation, she notes, Discovery’s scientists are not only focusing on final formulation parameters, but also on improving buffers. “By optimizing the best salt concentration, we can make our own buffers rather than buying them.”

January 2021 brought a major vendor-CDMO collaboration, when Cyntara and Lonza completed work on a new 17,000 m² modular KuBio plant based in Guangzhou, China. The facility, which includes both process development and manufacturing capacity and employs single-use technology, can be used for AAV production as well as for more traditional monoclonal antibody production, and has been designed to optimize quick scaleup or scaleout. Partners say the project took two years, from site selection to completion.

Hurdles in data and supply-chain management
Additional challenges for cell and gene therapy developers include the need to coordinate manufacturing activities to optimize scheduling, and the flexibility to accommodate changes in protocols that can be expected in brand-new manufacturing processes. The manufacturing setup for autologous therapies is different from anything that has existed in the past, says Alberto Santagostino, senior vice president and head of cell and gene therapy manufacturing at Lonza Pharma & Biotech, who spoke about these issues in a BioPharm International webcast (2). “It is important to integrate data management, chain of compliance, and chain of custody, by tracking every single unit operation, every activity, every piece of equipment, and every operator back to every batch, and connecting that data to the external supply chain,” he said.

Automated and closed processes are becoming critical, especially for autologous therapies, preventing contamination as well as operator error.

The company has partnered with the software specialist, Vineti, to integrate Lonza’s manufacturing execution systems and electronic batch recordkeeping software with Vineti’s supply chain orchestration platform, using application programming interfaces to feed chain of identity and chain of custody data to Lonza’s manufacturing floor. From a supply-chain standpoint, autologous treatments pose inherent risk since both supply and distribution are traced to a single source. “Anything as simple as needing to change a time or day for cell collection when a patient is ill can interrupt cycle times and deliveries,” says Mark Sawicki, CEO of Cryoport Services, a logistics specialist that is working with Lonza and Vineti. However, allogene-
Autologous processes dominate, but allogeneic is gaining more visibility in cell therapies.

Hewitt says similar projects are being considered in other parts of the world, including the United States and European Union over the next 12 to 18 months. He sees the project proving that onsite, decentralized manufacturing at the point of care will be possible. "It won't be the only way to do things in the future, but will be an option for some facilities," he says. The study also proved the technology’s potential effectiveness in reducing the cost of goods required to manufacture the therapies, Hewitt says, by addressing two main cost drivers: cleanroom space and skilled labor. "A traditional open manual process uses Class B cleanroom space, where the closed system with integrated culturing can run in Class C space. Even a back-of-the-napkin calculation suggests a 40% reduction in costs," he says. Lonza is now looking at ways to integrate manufacturing execution systems and electronic batch recordkeeping functionality and logistics tracking into the software. The company is also exploring the addition of beads that would allow for magnetic separation as well as the incorporation of new sensors (e.g., for glucose) and process analytical technology (PAT) that would enable setpoint-based control, Hewitt says.

Identifying CQAs sooner

More “forward facing” approaches to process development and scale-up, with Phase III and commercial stages firmly in sight, are also boosting manufacturing improvements, says Thomas VanCott, PhD, global head of product development at Catalent Cell & Gene Therapy. For example, he says, pre-process performance qualification activities (e.g., designing target product profiles, identifying critical quality attributes [CQAs] and critical process parameters [CPPs], and considering optimal scale-down models) are being done earlier in the cycle.

Before any process-development effort begins, or any external customer process is transferred to the company, initial gap analyses and risk assessments are done for both the process and raw materials to determine whether the process can be scaled to meet the product’s long-term clinical production needs, VanCott says. Analytical needs must also be determined, to assess whether the desired quality attributes are being achieved and in evaluating any critical raw materials.

Quality problems can stem from manufacturing, when parts of the AAV’s native genetic material are removed and replaced by a transgene, the therapeutic gene and genetic elements that support the gene’s activity and expression, explains Stephen Gacheru, vice-president at PPD Laboratories GMP Lab. For recombinant AAV (rAAV) vectors, good quality equates with having a high level of capsids that contain the full transgene, Gacheru explains. Empty and partial capsids are considered product-related impurities, which can impact product efficacy and safety, posing risks of increased immunogenicity to the therapeutic vector and related immune responses, he says.

At Catalent, assessing the analytical requirements for rAVVs at the earliest developmental stages has led to significant improvements, says VanCott, allowing quality deviations to be found before scale-up, reducing the risk of cost overruns. In addition, there is an emphasis on scaling out, rather than simply scaling up, VanCott explains, and this is true for both suspension and adherent viral vector manufacturing processes, as well as autologous cell therapy production.

There may be an evolution in approaches to scaling up allogeneic therapies, he says. Currently, larger scaleup has been precluded by the absence of stable producer cell lines and transient transfection processes in viral vector manufacturing. “For gene therapies, scaling out and combining multiple upstream runs into downstream processes has been more common,” notes VanCott.

Perfusion and lyophilization

For the viral vectors used to make gene therapies, use of perfusion, seeding, and intensification has been less critical than it is for some traditional biologics because of unique processes associated with the transient transfection process used to produce viral vectors, VanCott says. However, per-
fusion is an advantage for other viral vectors such as the baculovirus/Sf9 platform, he says.

In addition, lyophilization strategies are being explored because liquid formulations require storage below -20 °C, posing challenges for formulation and vial composition. Formulation research projects are underway to address these challenges, VanCott says. Stable producer cell lines for AAV production will be key to reducing costs and improving scale-up (e.g., by obviating the need for clinical-grade plasmid DNA for transient transfection processes), he says.

New equipment designs are helping to advance scale-up goals. For example, Univercells Technology recently commercialized a platform (NevoLine) that enables viral manufacturers to chain, integrate, and intensify processes, explains Mohammed Elfar, product innovation manager at the company, while the company’s fixed-bed bioreactors (Scale-X) have been improved to enable linear scalability from the bench to the plant.

Similarly, Pall Corp.’s fixed-bed bioreactors (iCELLis) have been optimized to improve scale-up from the bench to the production floor. As Byron Rees, Pall’s senior manager of process development services notes, cell and gene therapy developers often choose to adapt adherent cells to suspension for viral vector manufacturing because they think this approach will speed scale-up. However, that approach can add months to process development time. As an alternative, he says, iCELLis can be used to scale up adherent cell-based processes to commercial scale while cutting process development times down to three months.

Further upstream, the company’s nano bioreactor (iCEL-Lis Nano) has been designed to optimize benchtop-scale (i.e., 0.53 m² – 4 m²) work and transfer to the large-scale manufacturing bioreactor (iCELLis 500). Using the larger bioreactor, customers can scale their production from 66 m² – 500 m² within the same footprint, allowing more manufacturing flexibility with the ability to accommodate various molecules with different scales of demand, says Rachel Legmann, director of technical consultancy for gene therapy and viral vectors at Pall.

At Cytiva, equipment lines used for traditional biopharmaceutical manufacturing are also being optimized for use with cell and gene therapies. Not only single-use process equipment, but harvest clarification equipment, affinity resins, and low-shear pumps are areas of focus, says Joe Makowiecki, director of business development for FlexFactory and KuBio products.

**Standards setting**

Industry standards promise to clarify best practices and requirements, and help move more cell and gene therapies to market. The International Organization for Standardization’s (ISO)’s Standard 21973 (3) outlines best practices for manufacturing and distribution, Sawicki told webcast attendees (2).

Most notable have been its provisions for full traceability and the management of equipment used to ship the therapies, he said. “This equipment gets reused, so requalification processes are crucial to preventing product failures from occurring,” he told webcast attendees.

Sawicki expects future work to focus on cleaning recommendations to reduce risk of cross contamination. One area that regulators may need to address is establishing universal conventions around label templates, said Vineti CEO Amy DuRoss. “Different labeling conventions in different markets introduce unnecessary risk,” she said on the BioPharm International webcast (2), noting a need to move to on-demand printing capability.

**Quality testing**

There will also be a need to optimize analytical testing to ensure quality control with cell and gene therapies. In January 2020, FDA released preliminary guidance clarifying some aspects of this problem. Various analytical methods have been developed to determine an rAAV product’s composition of full vs. empty/partial capsids, says Gacheru, including analytical ultracentrifuge, transmission electron microscopy, spectroscopy (A280/260 ratio), anion-exchange high-performance liquid chromatography, size-exclusion chromatography with multi-angle light scattering, and capillary isoelectric focusing assays. Efforts are underway to make these methods faster and easier to use for release testing, says Gacheru. Cleaning validation also needs to be optimized for cell and gene therapies. Based on traceability requirements mandated in Australia, Cryogen developed a specialized cleaning validation approach for cell and gene therapies, as well as a customized shipping container to move C&GT products.

**Future developments**

New technologies promise to bring additional improvements to innovative therapy development and manufacturing. Ahlgrimm sees artificial intelligence playing a key role and notes that digital technologies, such as augmented and virtual reality, are already being used to help Discovery Labs improve employee onboarding.

The new industry faces a lot of questions. Will production become decentralized and move entirely to healthcare centers or points of treatment in the future? DuRoss doesn’t expect that shift to be possible for at least another 15 to 20 years. As the market grows, every new C&GT submission and product in development will continue to educate the industry and regulators. “We can only expect that more will be learned and that requirements will change as the field of C&GTs matures,” Ahlgrimm says.

**References**

Process development is moving at unprecedented speed as manufacturers race to produce COVID-19 vaccines and treatments and the products needed to make them, such as viral vectors, as well as keep up with the burgeoning cell and gene therapy sector. Optimizing single-use bioprocessing equipment, including both upstream and downstream equipment as well as consumables and starting materials, is a crucial piece of process development. Knowledge of the equipment, the process, and the product are paramount, and successful projects rely on experts embedded throughout the supply chain. Close cooperation between equipment suppliers and the users of the equipment is a key to success, as the industry seeks to address the expanding need for process development, manufacturing capacity, and training.

**Inter-company collaboration spurs innovation and speed**

At EMD Millipore, the Life Science business of Merck KGaA (operating as MilliporeSigma in the US and Canada), process development is provided through the company’s contract development and manufacturing organization (CDMO). The CDMO works closely with the other parts of the company’s business, including the consumable products businesses, such as filters and media, and the company’s bioprocessing equipment business, says Sébastien Ribault, vice-president and head of end-to-end CDMO Services, Process Solutions at Merck Life Science. As users of the equipment, the CDMO gives feedback to the equipment business.

“When we have an idea at the bench or in the manufacturing area, where we see we could manufacture faster, cheaper, with higher quality, or with fewer mistakes by users, we reach out to our equipment and product suppliers so that they can translate these ideas into new products,” says Ribault. He points to a 2000-L bioreactor that MilliporeSigma’s equipment business introduced in 2015 as an example. “The team members on this product included our head of process development who brought experience in scale-up and scale-down. Now we can scale up directly from 3-L bench-scale to 2000-L commercial scale. We can save two months by not having to do an engineering run at intermediate scale (100–500 L), and we optimize our use of good manufacturing practice (GMP) suites.”

Since 2020, EMD Millipore has been hard at work supporting developers of treatments for COVID-19. In one example,
the CDMO worked with an innovator of an antibody that needed to speed the development process. “We reinvented the process development template and went from DNA to final drug substance in nine months, when a more typical timeframe is 15 months. We could do this because of the close connection between our process developers and the EMD Millipore equipment business,” says Ribault.

The product is now moving through tech transfer to GMP production. “This new way of process development took into account expectations from regulators and also adapted to quality requirements. The use of pre-packed purification columns instead of manually assembled is one good example to speed up processes through the use of products that did not exist years ago. It is faster to implement, easier to use, and eliminates a sometimes-difficult packing step,” he says.

In the fast-growing cell and gene therapy area, projects are also moving quickly. “Clients want to get to first-in-human stages quickly,” says Ribault. “The process needs to be developed to allow rapid advancement to clinical stages that match with the regulatory framework that will be needed to move to GMP manufacturing.”

While cell and gene therapy has been more research-oriented, it now needs to move to a focus on robust, reproducible processes, says Ribault. “Here is where a connection between the equipment developers and the process developers is key to make a templated approach and create the equipment,” he notes. Automation is becoming a more visible part of cell and gene therapy processes. “For some, the importance of automation is that it eliminates the risk of error. For others, automation is key for gaining throughput and allowing the process to run continuously,” explains Ribault.

**Equipment builder expands development resources**

Cytiva has long offered its Fast Trak process development services to customers developing processes using the company’s bioprocessing equipment. The company’s seven Fast Trak centers—in Korea; Japan; Cambridge, UK; Uppsala, Sweden; Shanghai; Toronto; and Marlborough, MA—house processing equipment that can be used for training, development, and manufacturing. In December, Cytiva announced that it had expanded its services at several of the sites, so that all now offer process development, media and assay development, and contract development services. The expansion supports the cell and gene therapy industry and small to mid-sized biotech companies in particular.

“Start-up biotech companies that can’t yet afford space, labor, and time until they have clinical data are benefiting greatly from this initiative,” says Shannon Eaker, Cell and Gene Therapy’s FastTrak leader at Cytiva. He adds that large pharma companies with large product pipelines can also benefit from the company’s process development services. “Companies are looking to expand their pipelines. Starting with Cytiva’s platform processes, which have supported the cell therapy field for many years, Fast Trak saves customers time and money in doing the
R&D work. Starting with Cytiva’s platform processes, which have supported the cell therapy field for many years, saves the customer time and money in doing the R&D work,” says Eaker. A key area of development is developing scalable processes that are flexible for multiple cell types and processes, such as both autologous and allogeneic therapies, notes Eaker.

**Consortium expedites vaccine project**

Pall Biotech supplies single-use biopharmaceutical manufacturing equipment and also has a process development services team that designs processes and performs tech transfer to GMP manufacturing; the group has developed more than 30 viral vector-based processes in the past three years. In April 2020, Pall joined a consortium started by Oxford University and funded by the government of the United Kingdom (UK) to develop Oxford’s COVID-19 vaccine candidate based on its adenoviral vector vaccine platform. The consortium included the University of Oxford Jenner Institute, University of Oxford Clinical Biomanufacturing Facility, UK non-profit Vaccines Manufacturing and Innovation Centre, Pall Corporation, Oxford Bio-medica, Cobra Biologics, and Halix. The group was joined in late April by AstraZeneca, when the company partnered with Oxford University’s vaccine developers and licensed the vaccine technology. As of early January 2021, the vaccine being marketed as COVID-19 Vaccine AstraZeneca (formerly AZD1222) was authorized for use in the UK, India, and others and was in the midst of a large Phase III clinical trials in the US.

The consortium members worked closely together to develop and enable manufacturing of the vaccine in record time, says Clive Glover, director of strategy at Pall Corporation and the lead on the vaccine project. He noted that Pall designed the commercial manufacturing process and installed the equipment at a contract manufacturing partner within two months, breaking Pall’s previous record of nine months.

One of the keys to this success was starting with a standard manufacturing process. Glover suggests that for viral vector-based therapeutics, such as this vaccine, 80% of the manufacturing process is standard—the same no matter what the product—and the remaining 20% needs to be tailored. “The process can vary in several ways,” explains Glover. “For example, on the upstream, each process will rely on different cell lines, each of which may have slightly different growth rates, which will drive different feeding strategies. On the downstream side, viral vector products will vary in their physical properties and so require optimization of each downstream step to affect stability and ability to be concentrated. Finally, different products will need to be put into different concentrations for administration to patients, [which] has to be customized to each process.”

With Pall’s standard manufacturing process and the University of Oxford’s research as starting points, the consortium collaborated to optimize the process. “Decisions around the process were data-driven, based on initial pilot scale runs done by the University of Oxford,” notes Glover. “This process was then recreated by the Pall team at our Process Development Services laboratory in Portsmouth, UK, and developed into a small-scale process. [The process] was designed as a scaled-down model of a commercial process, and it allowed us to determine the specific parameters that would work at larger scale. Following successful runs at the small scale, we then did commercial runs to ensure the process was fit for purpose, before transferring that process to the various contract manufacturing organizations (CMOs). It’s important to note that the whole time we were doing these scale-up runs, we were constantly collecting data that helped with filing of the CMC [chemistry, manufacturing, and controls] section for the regulatory authorities.”

Because rapid scale up to high volumes of commercial product were needed, AstraZeneca called on multiple CMOs for production. Glover notes that, through the consortium, the CMOs worked to each use as similar a process as possible, which simplified the supply chain for equipment and raw materials.

A challenge Pall faced was supplying equipment in the short time that was required to set up the manufacturing process. “We did this by working very closely with our manufacturing sites and manufacturing some units at risk in order to compress timelines,” says Glover.

Another challenge addressed by a team of 20 that Pall had dedicated to the project was tech transfer. “Ensuring that the process is well characterized is critical for a smooth tech transfer. Given that speed was critical in the case of COVID-19 vaccines, we sent Pall personnel who were involved in the process development onsite to the CMOs for their initial runs to make sure that everything went smoothly,” reports Glover.

In addition to the efforts of Pall personnel, keys to the record speed of process development included “a combination of ground-breaking innovation, secure funding streams, relentless effort from some of the greatest scientific minds on the planet and, crucially, a consortium-wide commitment to the principles of lean process development and production,” concludes Glover.

**Building industry capabilities**

Although different ways of collaborating are being employed, the need for a growing body of experts with the knowledge and ability to move manufacturing processes into commercialization is crucial for all. The rapid growth of the cell and gene therapy industry, as well as biopharmaceutical manufacturing for COVID-19 vaccines and therapies, is creating a greater need for training and education as companies add staff who need to learn how to use the equipment.

For new therapeutics, equipment suppliers play a crucial role because of their detailed knowledge of process technologies. “Unlike more established therapeutics like monoclonal antibodies, with many of the novel therapeutics, such as viral vectors, there is not yet a critical mass of knowledge on how to design and run large-scale commercial processes,” notes Glover. “Over time, manufacturers will have much greater expertise on their specific therapeutic and manufacturing process, but even then, they [can benefit from] the depth of knowledge that we have as an equipment supplier. This [knowledge] is why we build long-term partnerships with customers in this space, because we can add real value to them throughout the whole process.”
To achieve delivery of a facility that operates at design capacity upon handover, there is a dual-pronged approach to consider: the facility and the product. Drug sponsors want to bring new products to market as quickly as possible to reach patients and positively impact lives. The current speed of new product drug discovery by many companies simultaneously creates a pace of market competition that does not allow for delays. Historically, contract development and manufacturing organizations (CDMO) have been a good option for bringing products online quickly, but new product demand is outpacing even this capacity, leading drug sponsors to choose building their own factories as a faster avenue to the marketplace. When relying on CDMOs, drug sponsors can focus on the drug product and drug substance; however, when choosing to build their own facilities, the process characteristics and facility design are both critical and must be tied together to achieve success.

In-house or contract manufacturing

When deciding between using a CDMO or one’s own facility, several considerations exist that take into account time and available resources. It is best to have vertical integration when a new product has the potential to become profitable and successful over a short time interval. Other considerations are when time to market is of the essence, coupled with limited CDMO availability and the possibility of capital investment. The advantages for owning one’s own factory include drug sponsors having control over business priorities from project execution through manufacturing and maintaining ownership of product and process aspects as a core competency. It also provides self-reliance for all aspects of delivering product to market; the drug sponsor chooses the priorities of the teams that are making and releasing product. The drug sponsor does not need to have concern about another customer of the CDMO taking priority over their product or having to navigate the CDMO with their own person-in-plant acting as an advocate. Building one’s own factory puts the control over business priorities from project execution through manufacturing directly into the

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drug sponsor’s hands. This control can be vital to the successful launch of the new venture; however, with a capital investment, focus must shift from simply producing goods to the design and oversight of a best-in-class facility.

**Process and facility in sync**

A product in early phase needs to evolve to be usable for commercial manufacturing. What is done in lab scale for early-phase trials is not scalable without significant impact to the operation or to the manufacturing environment. Hand manipulations on a tabletop in a good laboratory practice environment must mature to a fully characterized process that will likely be automated by Phase III to commercial launch and full-scale production. The requirements for lab facilities, including environmental monitoring and frequency, are substantially less stringent than full-scale good manufacturing practice (GMP) manufacturing. GMP facilities require, for example, cleanable surfaces throughout the facility; walls or floors with coved bases; step down between room classifications; segregation between personnel and material entry and exit; or dedicated heating, ventilation, and air conditioning systems dependent upon biological classification.

**Keeping in mind operational readiness activities from early-project phases will be advantageous at project completion.**

Synchronizing process development with facility capability will result in a facility that can more readily realize design capacity upon startup. Appropriate project scope definition and priority setting can facilitate project execution and successful delivery. Current practices employed by drug sponsors have shortcomings that can be minimized with the proper effort and planning. For example, understanding the true performance criteria for the facility by using sufficient process data related to critical quality attributes of the product during design leads to improved decision-making and mitigates schedule delays. Examples of critical quality attributes range from hydrophobic or hydrophilic products requiring humidity control capability, or equipment performance characteristics such as what process gases are required and ensuring that those gases are available in the production suites.

**Creating a team**

Although no amount of planning can fundamentally eliminate all risks, evaluating the needs of the project team, including both team size definition and composition, early in the process can prepare a project for its best trajectory for success. A project team will include a project manager and team members needed for executing design, construction, fit out, and testing to start up the facility. Problems that arise can be remedied early by providing adequate resourcing to accomplish timely decision-making when chance events occur. In addition to having an experienced project leader who is skilled at consensus building and conflict resolution, a key concept for success is to have the same project team members throughout the project lifecycle to provide continuity. When project team members understand the nuances of the drug substance and drug product as well as the requirements for facilities, they will keep the project moving ahead in a linear direction and not fall victim to rework.

Additionally, oversight by drug sponsor leaders who possess the appropriate expertise and dedicated bandwidth to focus on the project is extraordinarily valuable. By using the leadership’s expertise to establish key project success metrics associated with decision making throughout the project, and early definition of key considerations such as factory flexibility and time to market, project goals and team members will be aligned, and project trajectory will be linear. For example, using tools such as decision trees and a methodical approach will align to structured decision making which, in turn, will drive results. Project oversight by leadership will keep things moving in the right direction, as long as that leadership is committed to the success of the project and has backed the decision-making process where the new facility was chosen in lieu of using a CDMO.

**Facility design decisions and risk**

As the design of a new best-in-class facility unfolds, drug sponsors find themselves facing many decisions that are similar to the criteria that would be used to choose an appropriate CDMO, but they also face additional decisions that include a clear understanding and early definition of business performance drivers, such as supply-chain considerations and amount of risk tolerance. It is important to consider factors such as projected timing for return on investment (ROI), information technology systems selection, space allocation, and accounting decisions for a facility that will be depreciated and carry a longer-term impact to the balance sheet. Rather than relying on others to perform manufacturing processes, the drug sponsor must now monitor the course of the project and make decisions along the way to stay on track to guide the project to on-time completion.

**Single purpose or polyvalence**

The initial project definition must include performance characterization and operating assumptions such as whether the facility will be product-specific or a flexible model for multiproduct use. With a traditional singular design, the path is more straightforward. Process definitions will
need to be clear, including accurately defined and appropriate critical quality attributes and critical process parameters to provide the quickest path to project completion. Conversely, if the process is ill-defined at project inception and the trajectory for final product in unknown or still not well defined, a flexible facility could be the best choice. The agile nature of a flexible facility lends itself to easier changes in use as the product and process definition matures.

Whether the choice is for a nimble, flexible facility or a quick, traditional facility, keeping in mind operational readiness activities from early-project phases onward over time will be advantageous at project completion. Activities including items such as defining the quality management system, writing standard operating procedures, and preparing facilities maintenance inventory will minimize impact and prevent delays during start up by integrating these and similar activities into the overall project schedule.

Value engineering is an organized and systematic approach to examining required functions in a project and their associated cost. The key to successful value engineering is to reduce cost without sacrificing quality. Another advantage throughout the project design phases is executing value engineering as a trade-off exercise during the programming phase, which proves more valuable than as a point-in-time exercise during the project detail design phase. Lifecycle implementation of value engineering then can be viewed more positively by the project team and not seen as simply a cost-cutting measure by ensuring that selected low cost options still provide high value.

**Collaboration and leadership**

Throughout the life of the new building project, the team itself becomes crucial to project delivery. From effective leadership to accurate communication, project success is a collective effort between the project team and drug sponsor whose goal is getting product to market. The project plan and schedule must contain accurate requirements for regulatory approval based on the defined differences between clinical manufacturing and commercial manufacturing of the product. This will require that the team understand and remain focused on those changes so that they are effectively incorporated into the new facility design and implementation. This will lead to the volume of supply being at design capacity at startup and not requiring rework when the project is handed over to manufacturing operations.

Success hinges upon considering performance definitions and operating assumptions throughout the project lifecycle that in turn will lead to seamless project execution. When facilities meet design criteria at handover, their products save money and reach patients faster. Keeping focused on the synchrony between process and facility throughout the project can lead to optimal project execution and may prove one’s own factory is the best choice. **PT**

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Biologic drug products are typically formulated into a liquid or lyophilized powder form for the fill/finish step during biomanufacturing. As the much-anticipated COVID-19 vaccines move through the pipeline, and some are already in use under emergency authorization, manufacturers will need to optimize vaccine formulation and establish robust fill/finish operations.

**Liquid vs. lyophilized product**

In general, biomanufacturers face challenges in the fill/finish step when dealing with biologics that have been formulated into either a liquid form or a lyophilized powder. One main challenge is understanding the product’s characteristics and behavior under different circumstances, including what parameters may be necessary to lyophilize the product, for instance, says Dhaval Patel, senior manager, Manufacturing Science & Technology, Catalent. It is also important to understand the inspection requirements for the product because there could be different criteria for liquid vs. lyophilized drug products, he adds.

The difference in formulation may also require different approaches to fill/finish. For instance, Patel notes that different sizes of filters and membranes for sterile filtration may be required. “For a manufacturing partner, the biggest challenge is to build a catalogue of capabilities that cover different customer and product needs, and to be able to incorporate realistic lead times associated with having to source any new or additional equipment/components needed for manufacturing,” he says.

Christy Eatmon, senior scientist, pharma services, at Thermo Fisher Scientific says that, sometimes, liquid biologic products have stability challenges that can be overcome by formulating the product as a lyophilized biologic. “Lyophilization may be necessary to decrease prohibitive storage temperature requirements, allowing for shipment and storage in areas of the world where refrigeration isn’t as easily accessed. Lyophilization also extends the shelf-life of the biologic and can protect a labile molecule from degradation in an aqueous environment,” she says.

Eatmon does note that lyophilized and liquid biologic drug product vials are both filled in a similar manner, but the different formulations do pose different processing challenges. “The hold times during compounding of a lyophilized product are typically
shorter than those of a liquid product and affect the production timeline and planning that must be done in advance of the API addition,” she explains.

A major difference regarding these two types of formulations for biologic drug products, Eatmon points out, is the varying fulfillment times for each project. For instance, liquid products require less time for development and, thus, have shorter lead times. On the other hand, she emphasizes, the lead time for lyophilized products must incorporate the freeze-drying cycle and characterization of that cycle. “Characterization is important because the parameters of that cycle affect the production of a high-integrity cake, and producing a cake without collapse, melt-back, or shrinkage requires additional development,” she explains.

In both cases, Eatmon continues, it is necessary to understand the stability of the formulation, but for lyophilized products “we need to develop the cycle through calorimetric measurement, define critical process parameters, and optimize the cycle,” she says. “We also must do characterization of the lyophilized product and complete the stability profile work.”

“Lyophilized products require more preparation in choosing the right excipients, bulking agents, and cryoprotectants as well as the cycle development,” Eatmon adds.

**Vaccine fill/finish**

Fill/finish for vaccines requires a similar approach to biologics, Patel notes. In addition, the nature of the incoming vaccine drug substance will determine what equipment, filters, and other components are needed for formulation. “From a fill/finish perspective, vaccines and typical biologics require either a thaw, pool, and filtration process of the final product; or a thaw, pool, dilution with buffer, and then filtration of the final product. The configuration of the vial or syringe components, together with any additional packaging requirements, will determine what labeling or packaging of the vaccine or biologic is necessary,” he states.

It is also important to note that some of the COVID-19 vaccines are multidose and require the use of an evaluated preservative, includes Eatmon. For example, messenger RNA (mRNA) vaccines use nanoparticle technology to enhance stability, as opposed to the aqueous-soluble molecules that are typical of standard biologics. Furthermore, with recombinant protein vaccines, the use of an adjuvant could be needed in order to stimulate immune response. There are also unique differences between live vaccines and attenuated or inactivated vaccines, Eatmon notes.

“These differences require considerations in terms of facility classification and engineering controls as live viruses must be separated from other types of vaccines,” Eatmon says.

At the end of the day, COVID-19 vaccines are no more challenging than any other biologics from a fill/finish perspective, assures Patel. Where the real issue sets in, however, is in the management of time when the vaccines are out of controlled storage. This time management issue poses an additional challenge because of the requirement to freeze the filled product within a certain amount of time, he observes.

“Ensuring operations are managed in a timely manner means all the necessary resources for the process must be staged and be ready to perform manufacturing activities as soon as product moves to the next stage, minimizing the time out of storage,” Patel emphasizes.

“The challenge posed by the COVID-19 vaccines at the fill/finish stage of manufacturing stems from the fact that these candidates are dispersions,” adds Eatmon, who explains that the dispersion factor makes the vaccines sensitive to shear stress because they are a lipid nanoparticle rather than a solution.

“CDMOs/CMOs [contract development and manufacturing organizations/contract manufacturing organizations] must account for the different types of COVID-19 vaccines,” Eatmon states. “For some of the mRNA-based vaccines, once the drug substance has been manufactured, it must be frozen to maintain stability. The temperature-sensitive liposomes typically require additional monitoring during processing to ensure that filtration pressures are not exceeded and that temperature excursions do not occur,” she explains.

Eatmon further explains that facility capacity and suite segregation must be considered, noting that these vaccines must also be filled almost immediately after the end of the compounding process.

“For this type of drug product manufacturing, you want to make sure your CDMO/CMO has end-to-end experience and is knowledgeable in starting from drug substance production. A skilled CDMO/CMO will have the experience to know how to handle specific vaccine challenges that increase substantially as these products become more complex,” Eatmon adds. For example, it is strategically beneficial for a CDMO/CMO to understand that facility design is integral to efficient manufacturing, not only due to rapid hold times, but also due to the need for segregated suites for live viruses and compounding areas that require organic solvents, she says.

**Excipient considerations**

The use of particular excipients also plays a factor for ensuring vaccine stability as well as bioavailability *in vivo*, but determining which excipients to use may itself be a challenge. Some excipients used to enhance the stability of a vaccine, such as polysorbate, for example, are often foamy, Eatmon points out. As a result, the manufacturer or CDMO/CMO must pay close attention to foaming during liquid formulation filling and must reduce the rate of vial filling to accommodate excipients that foam, she notes.

Other excipients can also be adhesive, Eatmon explains, meaning that they cling to the product contact surfaces, such as filter membranes and disposable tubing. “Excipients such as these can dilute the concentration in the formulation, so we must compare component compatibility prior to use in fill/finish,” she states.

“In some cases, the need for an adjuvant could pose significant challenges to the process as a proper recirculation loop needs to be included as part of the line and can impact the overall filling strategy,” she adds.

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The audit function of a pharmaceutical company is one cornerstone of an effective and efficient quality management system. There are several types of audits that comprise a robust auditing program, including supplier audits, internal audits, and regulatory audits. Each of these specific audits requires preparation to make sure the audit is productive and accomplishes its intended purpose, which, in the manufacturing world, is to ensure facilities are manufacturing fit-for-use products in full adherence (hopefully more) to current good manufacturing practice (CGMP) requirements.

Supplier audits are performed to confirm that the suppliers of raw materials, packaging, and labeling components, etc., are able to provide a continuous, uninterrupted supply of the materials that are compliant with CGMPs. Regulatory authorities perform inspections to determine if the manufacturing company is providing materials that comply to CGMPs. Internal audits are performed by the company as a self-assessment for the purpose of identifying areas/issues that might affect their compliance status. Internal audits are solely under the purview of the company, while regulatory/supplier audits involve two distinct entities. Supplier audits are conducted using personnel from the supplier company and the client, and regulatory audits are conducted using personnel from the regulatory authority and the company being inspected.

Pre-pandemic, preparing for a supplier or regulatory audit typically consisted of the regulatory inspector or the auditor for supplier/internal audits providing the facility being audited with an agenda listing the areas to be toured (e.g., incoming raw material area, quality control [QC] chemistry and microbiology laboratories, manufacturing, etc.) and a list of documents to review (e.g., quality manual, list of standard operating procedures, open deviations, and corrective and preventive actions [CAPAs]) and any additional supporting evidence the auditor chooses to review. This information helps auditing authorities assess and decide the compliance status of the facility.

With appropriate planning and the proper use of technology, remote auditing can be as effective and informative as in-person auditing.

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Performing external audits during a pandemic

The documentation that would have been reviewed on-site pre-pandemic is the same documentation that is needed for review during and post the COVID-19 pandemic. The documentation and supporting evidence review conducted pre-pandemic would most likely have occurred at the facility. However, audits conducted during the pandemic require the documents and supporting evidence to be shared electronically to the auditor using secure electronic systems. This electronic exchange helps make time more efficient for both the auditor and the facility being audited. The documentation can be reviewed by the auditor, and questions can be communicated to the audit manager via email or conference/video calls. While this may not be ideal, because it eliminates the in-person interaction, it is still an effective way to conduct an audit when there are conditions prohibiting face-to-face interaction.

Touring the facility is challenging when the audit is conducted during a pandemic, but the challenges are not insurmountable. Live video feed could be streamed to the auditor, while the company’s audit manager and/or subject matter experts are available to answer questions that might arise during the live feed. Additionally, operations could be recorded, and that recording could be provided to the auditor, again with the understanding that the audit manager would be available to answer any questions posed by the auditor upon the review of the video. While the recorded version of the tour is probably not the most ideal, because the auditor needs to see things in as real time as possible, it does allow for the auditor to pause and go back to review a specific operation in more detail if warranted.

Supplier audits during a pandemic

Preparing for a supplier audit requires the same discipline as preparing for internal and regulatory audits. During the COVID-19 pandemic, many companies reduced the number of employees allowed at the site, and many of the quality personnel that conduct audits are allowed to work remotely.

Conducting a supplier audit is different from the other audit types, whether it is pre-, during, or post-pandemic. If designed and implemented appropriately, the value of the supplier audit is that it allows both the supplier and client company to find vulnerabilities in their existing supply chain and remediate them before they are discovered by an external auditor. Supplier audits should not be looked at as punitive from the supplier perspective. The best supply audits are ones where the client auditors are looked upon as partners in the overall continual improvement efforts of the supplier company.

Supplier audits can provide valuable information that can be used to prevent issues at the supply company before they become compliance concerns that may disrupt the supply chain. Issues that can be discovered during a regulatory inspection may be identified during a supplier audit. If these issues can’t be completely remediated before a regulatory audit, a plan to correct them can be established and action taken to mitigate them. Having corrective actions in place before others identify the issue may lessen the impact of the observation and instill confidence that the quality system is under control and there is a process in place for continuous improvement. In addition, the results from the supplier audit can be used for training staff and communicating valuable information to the organization.

The objective of a client when conducting a supplier audit is not to pretend to be the regulatory authority and show up unannounced, but rather to work in cooperation with your supplier to identify and solve potential issues. An effective program establishes a partnership between the client and the supplier so they can work together to solve issues before they affect the ability of either partner to supply material/product that complies to current standards. The ideal tone for a supplier audit should be a collaborative team-oriented activity that is instructive, informative, open, honest, and inclusive.

There are several factors that help contribute to establishing this tone, even during a pandemic. One way to set the proper tone is to publish the audit schedule/agenda in advance and make sure the functional areas personnel are informed of the schedule. During a pandemic, the agenda takes on another level of importance because it ensures that the site can have the proper documents ready to go and upload them either before or during the audit. Prior planning precludes poor performance in this area. Also, the audit itself should be forward thinking and unlimited in scope, even during the pandemic.

The auditor’s behavior is also important to obtaining valuable information. Auditors should be direct and avoid asking questions designed to intentionally stump people. Another important behavior is the ability of the auditor to listen to the answers personnel give and refrain from judging. The exact same behavior defined for the auditor should also be the exact same behavior displayed by the auditees. Auditees should be direct and avoid deflecting or obfuscating answers and take the time to explain why they do things the way they do them. They need to listen to the auditor’s concerns and not overreact to questions being asked. They should be proactive and point out things of concern and seek advice on how to remediate them. Both parties need to remember they are not enemies, rather they are the partners in improving their organization together.

Conclusion

The pandemic has allowed the industry to creatively utilize technology-based applications to communicate and perform an effective audit. The documentation and supporting evidence review can be conducted remotely, and confidentiality can be maintained. After reviewing the documentation and supporting evidence, the auditor can request interviews with various personnel, which can then be scheduled via video conferencing to accommodate both the auditor and the facility personnel.

The outcome is that, with appropriate planning and the proper use of technology, remote auditing can be as effective and informative as in-person auditing, as well as being more time and cost effective for companies who typically allocate a great deal of budgetary resources to an audit program. The post-pandemic sweet spot will likely be balancing remote and in-person audits.
Developments in biologics and personalized medicines are reshaping the clinical trial landscape. According to Grandview Research, the global biologics market is anticipated to reach $398 billion by 2025, with growth supported by faster drug approval processes (1). Simultaneously, the increasing prevalence of cancer and rare diseases is providing the catalyst for investment in the development of targeted therapies. These precision medicines, which are tailor-made to meet unique patient needs, are expected to reach $85 billion over the next five years, representing a substantial 9.9% compound annual growth rate (2).

The increase in complex, targeted, large-molecule products brings with it disruption to traditional drug development. In an increasingly competitive market, expediting biologic drug development, approval, and commercialization in a bid to achieve timely return on investment is key. As such, clinical trials are shifting from developed nations to emerging countries, including Latin America and Western Europe, which possess greater disease variations (1) and can represent more efficient and cost-effective operations that promote faster completion of key study milestones.

Exploring the conditions for a perfect storm
While developing biologics and personalized medicines present clear opportunities to advance human health, it also makes designing strategic and streamlined supply chains more challenging and risk intensive.

The larger financial investment synonymous with developing and manufacturing biologics makes the existence of waste and inefficiency in the supply chain commercially unviable. This puts pressure on sponsors to optimize supply and minimize waste. This pressure is magnified by the lower product yields associated with biologics. This is largely attributable to the complex manufacturing process, which involves living systems that are sensitive to very minor deviations in the manufacturing process. Short expiration dates are also typical for complex biologics. A lack of stability data means biologics can easily become unstable if not maintained at precise temperature ranges through the process of development to patient delivery.
When combined with the standard study-based challenges of operating global clinical trials—from mid-study protocol amendments or unplanned delays, to navigating multiple country-specific regulatory requirements, to managing bulk drug availability and enrollment changes—the conditions for a perfect storm are evident.

To mitigate these risks to better serve patients and enhance performance, it is necessary to re-examine the approach to and management of the clinical supply chain. As the industry evolves, sponsors should prioritize exploring new ways of conducting and managing clinical supplies geared more toward biologics and personalized medicines. Clinical packaging strategy is a good place to start.

**Critical considerations for biologics packaging planning**

For supply chains to be flexible and viable, clinical packaging should be planned with the complexities of biologics products in mind, and at the earliest opportunity. There are several critical factors that must be considered to inform a fit-for-purpose packaging strategy that can respond effectively to the complex challenges associated with biologics and personalized medicines.

First, the proposed depots and sites should be checked to establish capacity to appropriately store materials during the last leg of the cold chain. Shipping conditions and processes also need to be scrutinized to ensure product integrity can be upheld. Shipping requirements are often overlooked, yet failure to obtain a firm grasp of the average quantity of material sponsors plan to ship at a time can lead to disruption and delay, while heightening the risk of waste and negative patient impact. At this point, sponsors should consider development of kit designs that will fit within the core of cold-chain shippers. When dealing with high-value biologics, separating products into multiple shipments may increase overhead but mitigates the risk of loss, should temperature be compromised during distribution.

Another crucial factor is assessment of the material-handling capabilities of each step of the process and party involved. This will ensure processes are in place or can be implemented to effectively and safely handle biologics material within the required storage conditions, while prioritizing end-to-end patient safety and product integrity.

Packaging design, materials, and processing options are influenced by a number of product, study, and sponsor-specific requirements. Perhaps the most obvious is clinical trial timelines. If timelines are short, typically it will be harder to use booklet labels and may necessitate use of a previous kit design. Contrastingly, if enough time is provided, a bespoke packaging solution can be designed that meets unique kit requirements and decisions made based on what is best, not what is possible.

It’s also important that sponsors define all packaging and distribution requirements prior to finalizing packaging design, as last-minute changes have the potential to delay the start of a clinical trial.

Although not unique to biologics, blinding can impact packaging strategy and is a prime example of why developing adaptive supply chains is important. For example, when using commercial comparators within a blinded study, the commercial packaging may change throughout the life of the study. Strategies designed to adapt to evolving program requirements will enable sponsors to take additional steps to ensure proper blindness is maintained. Unexpected comparator changes can also have a domino effect on costs, which can be especially detrimental to the performance of programs that involve high-value, low-yield products.

The amount of label text sponsors require can also present challenges when labeling small vials and prefilled syringes. As most biologics-based products are stored within vials, the fragility of the packaging can increase the risk of breakage and require the addition of a bag or pouch into the design of the final unit for shipment or storage. Not only are glass vials more susceptible to breakage during distribution, but the thaw-and-freeze cycle of a product can lead to cracks in glass vials, making plastic vials a better choice in some scenarios.

Fragile packaging components can also limit packaging speed and efficiency if handling requirements prevent the product from spinning, thus removing the option of labeling automation. Biologics product that are sensitive to light and temperature will further inform handling requirements, options, and limitations for not just packaging design, the types of materials, and production environments, but for storage and shipment, also.

Biologic drugs with special packaging requirements demand a more complex kit design and more time to label or assemble materials. Likewise, if biologics products need to be processed in ultra-low temperature conditions, the choice of materials must be carefully considered. For example, adhesives behave differently based on the application temperature, the storage temperature and duration, and the material to which they are applied. Some adhesives will not hold in ultra-low temperature ranges; cartons may need to be mechanically designed. Products being processed in frozen conditions will require plastic coatings to strengthen the carton and protect from potential moisture damage. Most tamper-evident seals are not effective when applied to plastic; packaging must be adapted to ensure kits that require tamper seals remain both functional and compliant.

Finally, the frequency in which sponsors anticipate updating the expiry dates for biologics products will shape supply chain and packaging approaches. Factoring this into packaging planning at the earliest opportunity will help minimize waste.

Being clear about requirements for packaging and distribution prior to finalizing packaging design will help manage risk and empower sponsors to operate optimized and flexible supply chains that keep timelines on track.

**Embracing new tools for new challenges**

To respond to the challenges presented by biologics, supply chains need to be nimble and adaptive to change. When it comes to a packaging strategy capable of ensuring costly, temperature-sensitive products remain viable and flexible for wider use across a study’s lifecycle, traditional production models may not deliver in every scenario.
Instead, new approaches are needed to effectively maintain control over high-cost, high-demand clinical supplies, while decreasing waste, increasing product availability, and effectively managing limited stability profiles within the clinical supply chain to meet the specific needs and timelines of biologics trials.

One strategy sponsors can utilize to achieve these goals and inject flexibility and viability into biologics supply chains is just-in-time manufacturing (JTM). Unlike standard batch manufacturing, developed to meet the needs of lower-value, small-molecule products, and less complex program models, JTM offers a more flexible and lower-risk option for sponsors of studies involving biologics and targeted therapeutics.

The production strategy, which can be practiced on its own or as part of a wider LEAN manufacturing initiative, refers to the late-stage customization of clinical kits and is becoming more prevalent across trials involving gene therapies, rare or orphan diseases, oncology, and immunotherapy treatments. It is also becoming increasingly popular for sponsors of targeted therapeutics and patient-centric trials that necessitate patient-specific labeling and kit configuration, for trials operating a pooled supply strategy, and for trials involving drugs with short stability and a need for frequent retesting.

JTM makes it possible for stock materials to be packaged and labeled just prior to shipment to effectively meet varying global need, once demand is known. This approach better supports variable demand typical with biologics programs and patient-specific requirements, while mitigating the risk of high-value investigational medicinal product exceeding its expiry date while awaiting distribution. Implemented appropriately, JTM can reduce the need to pre-package bulk supplies before a study commences and facilitate pooled supply across protocols.

JTM can also reduce over-production leading to enhanced commercial performance. With a recent Tufts study estimating that almost 50% of clinical sites failing to recruit patients in line with estimates (3), significant quantities of seeding stock, produced as part of a batch manufacturing approach, can often remain unused and require destruction and replacement, due to limited expiration.

By combining careful consideration of the critical factors needed to plan a robust biologics packaging strategy with adaptive production methods, sponsors can overcome the challenges of operating complex global trials of biologics and targeted therapies. Through embracing this best practice, sponsors can operate supply chains with the increased flexibility and performance needed to promote timely and successful program completion, all while keeping patients at the heart of operations.

References

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Patel, meanwhile, explains that, for vaccines, the API itself can be considered the most conducive component. “All vaccines are based on a different platform; some are based on antigen and some of the recent COVID-19 vaccines are based on mRNA. Other than the API, excipients sometimes include: antibiotics, to prevent contamination by bacteria; adjuvants that help stimulate a stronger immune response; and stabilizers, to keep the vaccine potent during transportation and storage,” he notes, further explaining that the types of API used all help to ensure the product’s stability, and that each type plays a different role while in storage.

CMO/CMO readiness

As fill/finish operations are predominantly outsourced to CDMOs/CMOs, these organizations are well suited to handle fill/finish of COVID-19 vaccines as they start to hit the market. Catalent is an example of a manufacturing partner that is well positioned to deliver on both scale-up and meeting demand, Patel notes. He says that additional capacity can be created by effective management and by expediting expansions.

“The supply of excipients and drug substance is obviously critical to the scale-up of drug product manufacturing, but the procurement of components used in manufacturing, such as vials, stoppers, seals, filters, labels, cartons, and other consumables is also important,” Patel says. He emphasizes that creating partnerships between suppliers can help alleviate some of these challenges as well as streamline manufacturing efficiencies to meet demand and timelines.

“Additionally,” he continues, “storage can become a challenge for vaccines without sufficient warehouse space, especially where specific storage conditions are necessary.” Normal production of a typical biologic, in contrast, does not require storage of both empty and filled components in such large quantities, which makes it much easier to manage. The situation with COVID-19 vaccine production, however, is slightly different because of the extremely high number of doses needing to be manufactured. “This constraint can be rectified by utilizing a third-party storage partner,” Patel asserts.

Eatmon points out that one of the biggest challenges for CDMOs/CMOs, even before the COVID-19 vaccines and therapies entered clinical trials, is capacity. “At Thermo Fisher, we have continued to invest in our facilities and build new lines. We are currently expanding sites across North America, APAC [Asia Pacific], and Europe to add development and CGMP [current good manufacturing practice] commercial production lines to support a range of capabilities, including live virus, aseptic liquid, and lyophilized vial filling,” she says. Equally important, she adds, is maintaining robust quality standards.
A key driver of the massive effort to manufacturer and deliver COVID-19 vaccines in record time has been the development and production support provided by contract manufacturing organizations (CMOs) and contract development and manufacturing organizations (CDMOs). This article, which was sourced from news reports and press releases, takes a look at announced contracts and partnerships to produce the lead vaccine candidates in recent months.

**Pfizer-BioNTech mRNA-based vaccine**
Pfizer will use its extensive manufacturing network to handle much of the manufacturing for its messenger-RNA COVID-19 vaccine, BNT162b2, developed with BioNTech. Raw material manufacturing will be performed at the company’s St. Louis, MO, facility; drug substance manufacturing in Andover, MA, and formulation and fill in Kalamazoo, MI. A Pfizer plant in Belgium will produce vaccines for the European market. In September 2020, BioNTech added a third manufacturing site in Germany with the acquisition of a Novartis GMP production facility in Marberg (1).

Even with expanded inhouse capacity, BioNTech contracted with contract service providers for specialized processes. Rentschler Biopharma will provide large-scale downstream processing of the mRNA vaccine drug substance at its headquarters in Laupheim, Germany (2). Siegfried agreed to dedicate a production line at its Hameln, Germany site for aseptic fill/finish and storage (3).

To accommodate the vaccine production, Pfizer reported in May 2020 that it planned to outsource production of other drugs to free up capacity for the vaccines (4).

**Moderna: mRNA-based vaccine**
Moderna’s messenger RNA-based COVID-19 vaccine was granted Emergency Use Authorization by FDA in December 2020 (5) and conditional marketing authorization from the European Medicines Agency in early January 2021 (6). The company has contracted with a number of contract manufacturing facilities to fill expected production demands.
In May 2020, Moderna entered into a 10-year strategic collaboration agreement with Lonza to enable larger-scale manufacture of the vaccine (7). The companies plan to establish manufacturing suites at Lonza's facilities in the United States and Switzerland and will manufacture the vaccine at both sites. Technology transfer began in June 2020, and the companies manufactured the first batches of the vaccine at Lonza US in July 2020.

Also in May 2020, CordenPharma was contracted to manufacture large-scale volumes of Moderna's lipid excipients to be used in the vaccine (8). The companies have expanded their original 2016 agreement to meet the increased demand and will focus on securing a future long-term supply.

Recipharm's drug product manufacturing facility in France will be used for formulation and fill/finish of Moderna's vaccine supply outside of the US (9). Laboratorios Farmacéuticos Rovi was selected by Moderna in July 2020 to provide large-scale, commercial fill/finish manufacturing of the vaccine at its facility in Madrid, Spain (10). Rovi will handle vial filling and packaging capacity via a new production line and equipment for compounding, filling, automatic visual inspection, and labeling to produce hundreds of millions of doses of the vaccine outside of the US.

For the US market, Catalent will provide vial filling, packaging capacity, and additional staffing at its Bloomington, IN biologics facility to support the production of 100 million doses of the vaccine (11).

**Johnson & Johnson adenovirus-based vaccine**

Production of Janssen Pharmaceuticals', a Johnson & Johnson company, adenovirus-based vaccine, was planned for the company's facilities as well as supporting contract manufacturers. Emergent BioSolutions has been selected to provide large-scale drug substance manufacturing of J&J's vaccine via a five-year, $480 million manufacturing services (12). Emergent will offer large-scale manufacturing at its Bayview facility in Baltimore, MD.

Catalent's Biologics' Bloomington, IN facility will also provide large-scale commercial manufacturing of the J&J vaccine along with accelerated availability of manufacturing capacity (13).

**AstraZeneca: adenovirus-based vaccine**

Three contract manufacturers announced contracts for drug substance manufacturing and fill/finish of AstraZeneca's COVID-19 vaccine, AZD1222, co-developed with the University of Oxford and authorized for emergency supply in the United Kingdom in December 2020 (14); clinical trials are ongoing in the US.

HALIX will handle large-scale commercial manufacturing of the drug substance at its current good manufacturing practice (CGMP) facility at the Leiden Bio Science Park in the Netherlands. The company will also continue its role as one of the original partners in the University of Oxford's consortium for the manufacturing of the vaccine (15).

Catalent has announced the company will manufacture drug substance for AZD1222 at its commercial gene-therapy manufacturing facility in Harman's, MD (16) and will provide large-scale vial filling and packaging of the vaccine at its facility in Anagni, Italy (17).

**Novavax: protein-based vaccine**

Phase III trials for Novavax's NVX-CoV2373 protein-based vaccine are underway in the UK and US with contract manufacturers engaged in production and filling. Novavax contracted Fujifilm Diosynth Biotechnologies (FDB) to manufacture bulk drug substance for the vaccine, and in July 2020, FDB's site in Morrisville, NC began production of the first batch of NVX-CoV2373 under Novavax' $1.6 billion award by the US government as part of Operation Warp Speed. In January 2021, FDB reported that the company completed expansion at its College Station, TX facility to accommodate large-scale bulk drug substance production (18).

**References**

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