TODAY'S BIOMANUFACTURING OPTIONS:
Build, Broker, or Blend

AZZUR GROUP

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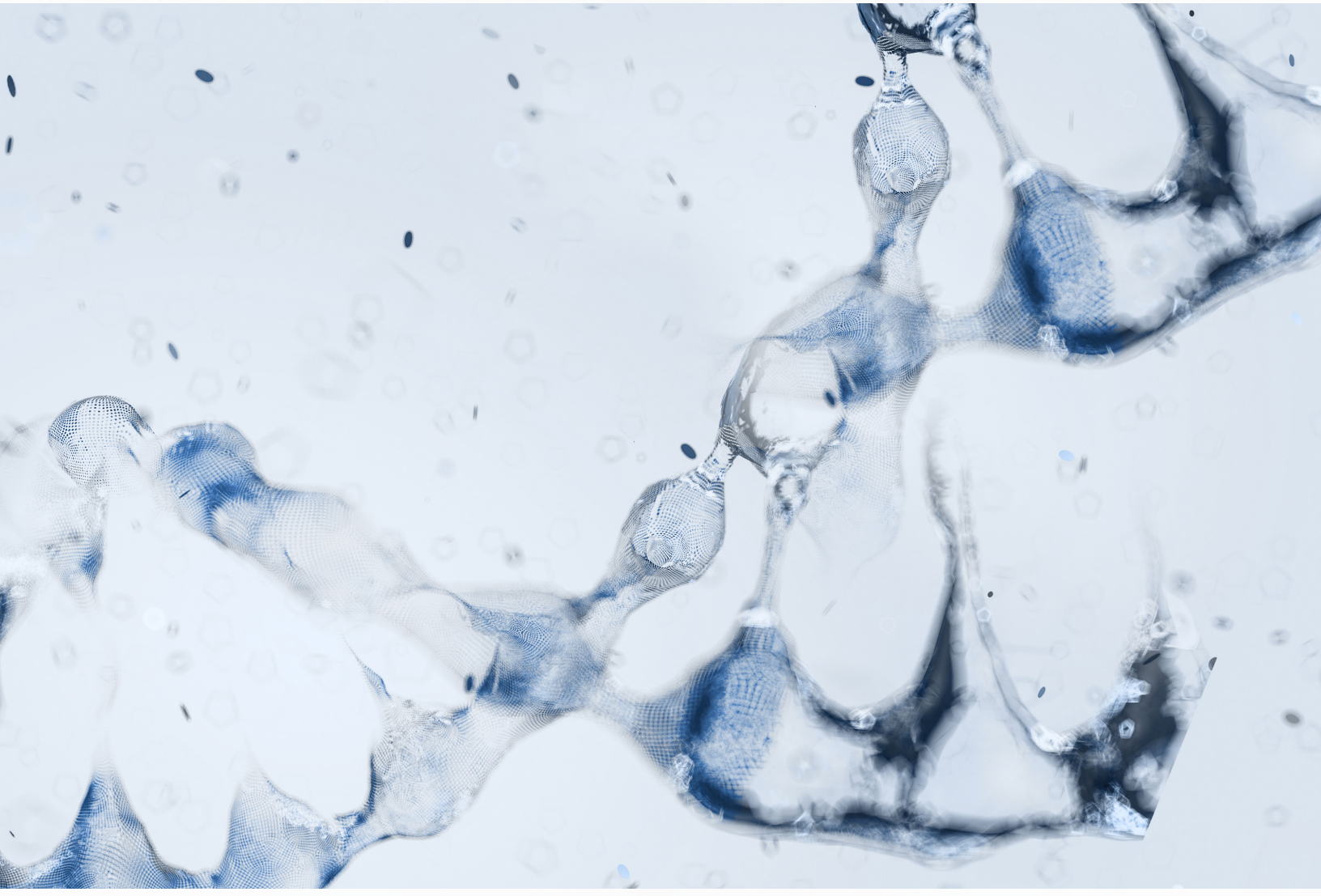


Introduction

With more than 400 registered gene therapy clinical trials worldwide[1] and a compound annual growth rate of more than 25% since 2015[2], there is no doubting the impact of cell and gene therapy (CGT) innovation on the market.

In fact, the industry is expected to grow at a rate of 28.7% through 2025. With capacity constraints, it's no longer a question of if cell and gene therapies will come to market, but how and who will win the race.

Traditionally, biomanufacturing innovators have two choices when it comes to early clinical trial manufacturing: build or broker, and both options come with significant trade offs. With more virtual companies on the scene, the capital expense and time needed for brick and mortar is a non-starter.

According to studies, almost 90% of CGT developers would prefer to manufacture using contract manufacturing organizations (CMOs), but current lead times are soaring past 18 months with no relief in sight. In both options, further risk lay in the lack of the necessary in-house good manufacturing practice (GMP) expertise to scale up and out.

Today, however, hybrid options exist that allow a risk-based approach to early CGT manufacturing. It's critical for developers to understand the risks they face and be proactive in their approach to quality and regulatory compliance.[3]

Areas of Growth in Life Science
A History of Manufacturing Options

There once was a time when the development of new drugs and therapies was primarily done in-house. Prior to 1996, the concept of outsourcing production was first done informally among "big pharma" companies as a way to maximize efficiency without enabling competition.

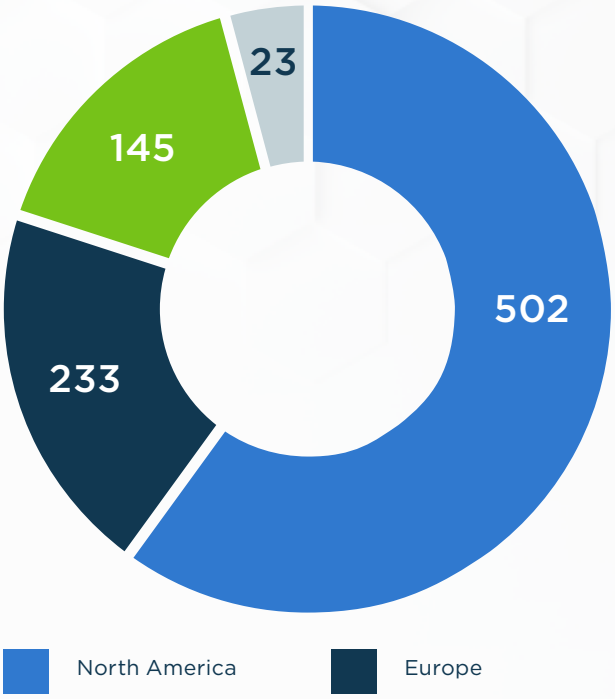
Then, from 1996 to 2007, there arose an outsourcing phenomenon in pharmaceutical manufacturing. The contract development and manufacturing organization (CDMO) market started to expand with companies looking to broaden their businesses. At the same time, big pharma looked to shed excess capacity for products coming off patent. Biopharma began to take off, and contract research organizations (CROs) were able to provide data validating outsourced production as an effective alternative to in-house capacity.

Following the financial crisis of 2008 and a downturn in CDMO production, private equity investors saw an opportunity to take advantage of the low valuations and interest rates to invest in the CDMO community with the hopes of long-term gains. Fast forward from the year 2009 to 2022, and there's a demand for GMP manufacturing space outpacing availability, waitlists 18+ months long, and companies of all shapes and sizes scrambling for production capacity and space.

Looking at numbers from 2018, pharmaceutical manufacturing brought in $485B and is estimated to bring in $625-655B by 2023. By 2025, cell and gene therapy is projected to grow from about $1B to $12B. Biotechnology growth will top $300B moving from $417B to an expected $729B, and medical device will move from $426B to $613B.[4]

Areas of Growth in Life Science
A History of Manufacturing Options

The Numbers: CTG Clinical Trials



- Activity is increased in clinical space
- 1,060 trials worldwide (Q1 2019)
- 9 approvals in US / FDA
- 19 aprovals in EU / EMA

Gene Therapy
Total: 372
Ph. I: 123
Ph. II: 217
Ph. III: 32

Gene-Modified Cell Therapy
Total: 374
Ph. I: 160
Ph. II: 197
Ph. III: 17

Cell Therapy
Total: 268
Ph. I: 55
Ph. II: 182
Ph. III: 31

Tissue Engineering
Total: 46
Ph. I: 11
Ph. II: 22
Ph. III: 13

Source Q1 2019 Report – Alliance for Regenerative Medicine

Over the last 10 years, there has been an increase of 10X the number of cell and gene clinical trials - almost 1,000 drugs in the pipeline at the end of 2019.

Fast forward to 2020 and the COVID-19 pandemic. The 1,000 drugs that were in the clinical trial pipeline now take a backseat to the vaccine and therapies associated with COVID-19.

With the pent-up demand in the marketplace, limited space, and CDMOs that are often at full capacity for 18-24 months, pharma and biotech are forced to reconsider the need for a capital build. The question, then, is: Is build a better option, is brokering still a better choice, or is there something else?

Areas of Growth in Life Science: A History of Manufacturing Options

Where the Market Stands Today

What's next for the life sciences industry? Buildouts are capital intensive for burgeoning companies and a 90% failure rate across the board in clinical trials makes it difficult to justify the investment. For those companies where capital is not a concern, the multiyear buildout, infrastructure demands, and staffing remain a challenge.

Early-phase customers have said CDMOs offer a proven alternative to build, but the timelines are not always favorable, and the cost of failure remains high.

Now, biotechnology companies have more than just the option of building their own facility or going into production at a third-party CDMO - a hybrid approach utilizing on-demand cleanrooms coupled with good manufacturing practices (GMP) support, materials management, and facility services.

Understanding the Use of Manufacturing in Biotechnology & Pharmaceuticals

83% of Companies have a CDMO Product Development & Manufacturing Strategy

In 2022, Azzur Group commissioned a third-party research study to give additional context to the needs of start-up and mid-sized pharmaceutical and biopharma companies throughout the country.

Azzur Group was keen on a deeper understanding of the development and manufacturing paths clients were engaging in for their pipeline drugs and therapies. In addition, a hybrid alternative was introduced to elicit feedback on the model.

Key Insights

- Modern pharma development, fueled by early-to-mid-stage virtual companies, has generally moved towards the use of CDMOs rather than building infrastructure as a way to preserve capital
- Some of the key disadvantages when using a CDMO are the loss of control over scheduling, prioritization, and timelines
- The description of a hybrid on-demand cleanrooms model presented to respondents was considered attractive, allowing pharma developers to cost-effectively regain control over scheduling, prioritization, and timelines
- An equipment/operator lease model may significantly expand the potential base of pharma developers who would value regaining control via a hybrid model, yet avoid capital investment risk

Understanding the Use of Manufacturing in Biotechnology & Pharmaceuticals

Manufacturing Strategy

In one of the key findings, utilizing a CDMO as a clinical trial supply manufacturing strategy has become more common in recent years, and 83% of the respondents from the research study have a CMO or CDMO product development strategy in place.

For some of the respondents in the study, the current use of internal manufacturing resources is substantially based on existing infrastructures and the type of investments associated with it. It was reported that respondents believe the creation of future internal manufacturing capability is declining due to the virtual nature of today's pharma development companies as well as the high costs associated with building and maintaining internal manufacturing capability. The costs particularly become oppressive when the failure rate for compounds in development stands at 92%.[5]

With CDMOs carrying the weight of the preferred current manufacturing strategy, the research study was able to depict why this is the favorable option compared to an infrastructure buildout.

CDMO Strategy Benefits

- Faster speed to market as traditional buildouts add time to the manufacturing process
- Flexibility to pivot quickly with less cost: To meet changing business needs, respondents mentioned that pivoting on formulation, therapeutic areas, dosing, and other modalities could be a potential benefit
- It is more customizable as it can be turnkey, or the manufacturer can specify the services needed
- There is an availability of SMEs and experienced staff ready to assist with the development process
- The facility has established and streamlined standard operating procedures (SOP) and quality control (QC) services for various manufacturing needs
- More easily allows manufacturing to expand into new geographic locations to support clinical trials

Research study respondents identified some pain points associated with the CDMO strategy that cause frustration, delay, and uncertainty.

Understanding the Use of Manufacturing in Biotechnology & Pharmaceuticals

CDMO Strategy Challenges

- A lack of control over manufacturing schedules
- Several clients competing for the same manufacturing time
- Overall resource availability
- Varying levels of subject matter expertise require finding the right CDMO
- Long lead times (eclipsing eight months) and multiple clients create an unfriendly environment for unanticipated changes
- Contract terms can be restrictive, including cancellation penalties and high project start-up costs

Decision Process and Criteria

According to respondents, the key decision maker for most organizations seeking out a hybrid manufacturing model will be the research and development executive. Additionally, executives associated with the organization's commercial and regulatory strategies will be favorable to the decision-making process.

When identifying the highly influential aspects of the decision-making process critical to the ensuing commercial success of drug development, the research showed the following three factors to be most important:

- Speed to market
- Risk versus capital balance
- Human resources limitations in regards to subject matter experts (SMEs) and staff

The study shows that an early-stage company with a lack of internal SMEs is likely swayed in a direction favoring the CDMO expertise. The same is mentioned for organizations that want to develop a one-off or franchise molecule where favoring the CDMO route with more in-development assets could be a factor in the manufacturing strategy process.

Other factors to consider when deciding on a manufacturing strategy are the compound's stage of development, the compound/drug requirements, the size and scale of needed materials, and environmental specifications.

Build vs. Broker

Between the typical build and broker options, there are key considerations for early phase current good manufacturing practices (cGMP) that are associated with costs and time.

Cost Considerations

BUILD OPTION

- Facility capital expenses include design/build, qualification, personnel, quality management systems, equipment, and electronic systems
- Facility operational costs including ongoing maintenance, cGMP compliance, utilities, and licenses

BROKER OPTION

- Upfront non-refundable costs to a third party
- High penalties for early contract termination
- Technology transfer costs
- Costs associated with pivoting/downtime after schedule changes

Time Considerations

BUILD OPTION

- Facility buildout time and product wait time
- Time to establish cGMP readiness, including quality management systems (QMS), personnel, training, monitoring systems, and suppliers
- Process equipment and consumables availability
- The team's readiness to pivot

BROKER OPTION

- Wait times at third parties and product wait time
- Time for technology transfer and training/retraining of the third party
- Time lost due to technology transfer failures
- Time to implement process changes
- The team's readiness to pivot

A Hybrid Model for Early-Phase Manufacturing

In 2018, Azzur Group recognized the risks that early-phase and start-up biopharmaceutical manufacturers faced when choosing between building and brokering.

Introducing its on-demand cleanroom model to the market, the organization helped life science companies reduce the risks associated with moving through clinical trials and into GMP manufacturing; maintain process knowledge, intellectual property ownership and production control; and improve speed to clinic and commercialization.

The hybrid on-demand cleanrooms model provides the benefits of in-house product development and manufacturing without the burden of constructing, managing, maintaining, and staffing a GMP facility by providing:

- Multi-tenant GMP facilities with turnkey cleanroom suites for drug development and manufacturing
- 750-sq.-ft. ISO7/8 cleanroom suites, including a 500-sq.-ft. ISO7 core, anteroom, airlocks, and gown in/out
- Panel-based modular construction allowing for configurations of single suites with up to a 3,000 sq.-ft. ISO7 core
- Clients receive dedicated office space, shared conference and breakrooms, and various dedicated business services

The study shows that an early-stage company with a lack of internal SMEs is likely swayed in a direction favoring the CDMO expertise. The same is mentioned for organizations that want to develop a one-off or franchise molecule where favoring the CDMO route with more in-development assets could be a factor in the manufacturing strategy process.

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Bridging the Gap During Greenfield Construction

The hybrid on-demand cleanrooms model was initially introduced to the market for start-up clients looking to reduce risk and win the race to clinic. However, since its inception, the model has resonated with larger, more established pharma powerhouses.

With never-before-seen manufacturing backlogs in the wake of COVID-19, the on-demand model provides a bridge space for clients during greenfield construction or brownfield retrofits, as well as a supplement to current space and resource constraints for production overflow capacity and storage needs. The model can also be used to experiment with new modalities that are not suited to be collocated with current processes and products.

The Build, Broker, Blend Breakdown

A comparison of the key considerations build, broker, and blend offers biotechnology companies and their investors for emerging programs.

	Risk Capital	Speed to Market	The Process is the Product	Fail Fast & Optimize Cost
HYBRID	Fully refundable deposit & no penalty for cancellation with 90 days written notice	Up and running in as few as 1-3 months	Full control of your process and intellectual property	Shortest lead time to occupancy, fail today start again tomorrow, you control the manufactuing timelines
BUILD	Build, Qualify/Commission & Operate costs roughly $10 million year 1	24-36 Months from design through completion	Full control of your proocess and intellectual property	Longest lead time, you are still in control but real estate and significant capital risk
CDMO	30%+ up front with no refunds. On average $500,00 in initail investment	Minimum 18-month wait time to production, plus tecchnology transfer and CDMO training	Process and intellectual property knowledge transferred to CDMO with risk of enabling their other customers to tag along	Long lead time to occupancy and potential technology transfer delays/failures mean you go back to the end of the line extending timelines to clinic

Time is Money: The Blend Approach

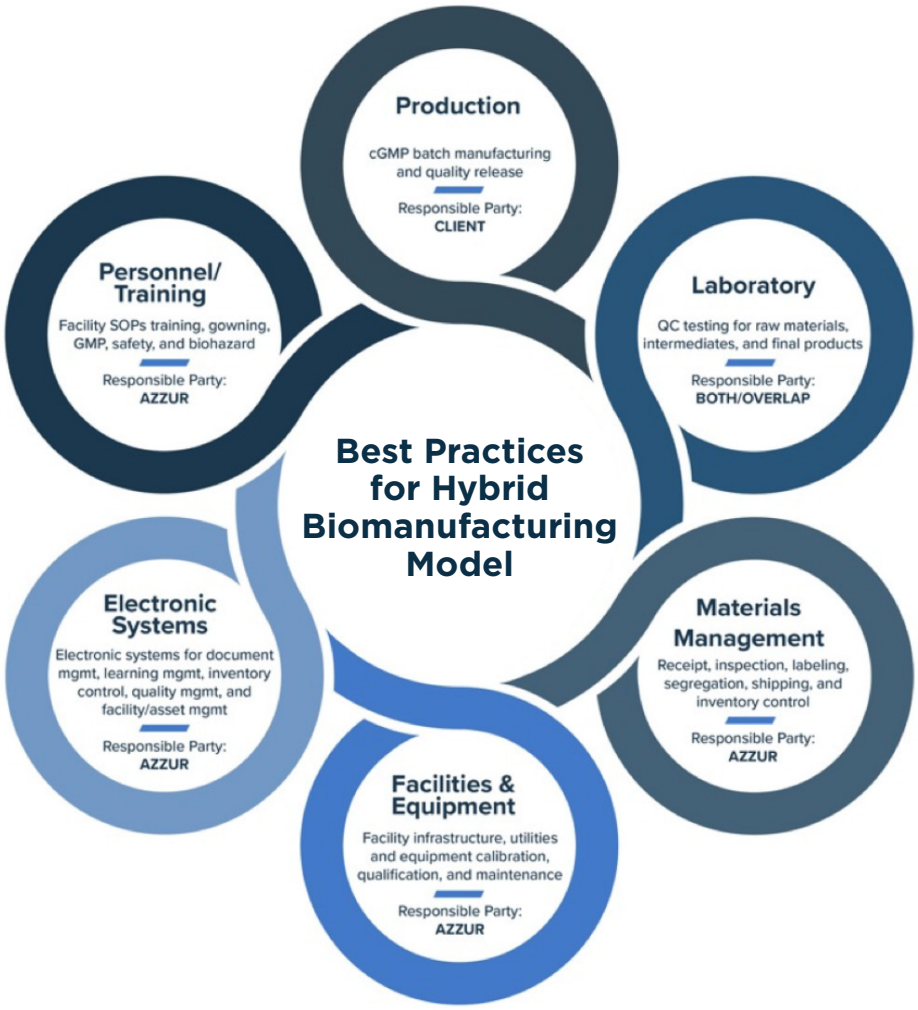
With the cost and time considerations, Azzur Group gathered another insightful piece of information from the research study - intellectual property protection and the process itself.

Oftentimes, in CGT and biologics manufacturing, the process that is used to do the manufacturing is the actual product. It is something that is novel. Once a third party helps in the development of the product, they leverage that information to enable their other clients' development. In the race from clinic to commercialization, enabling competitors to speed up is not an ideal outcome.

After many years of hearing client pain points and taking in the considerations between both parties of build and broker, Azzur Group recognized that GMP and manufacturing space is at a premium. So in 2018, the first Azzur Cleanrooms on Demand™ facility was launched.

The new hybrid model addressed the ongoing concerns of biotechnology companies.

How Blend Works



Production
The client is the responsible party for cGMP batch manufacturing and quality release

Laboratory
The client and Azzur Group are responsible for QC testing for raw materials, intermediates, and final products

Materials Management
Azzur Group is the responsible party for receipt, inspection, labeling, segregation, shipping, and inventory control

Facilities and Equipment
Azzur Group is the responsible party for facility infrastructure, utilities, equipment calibration, qualification, and maintenance

Electronic Systems
Azzur Group is the responsible party for electronic systems for document management, learning management, inventory control, quality management, and facility/asset management

Personnel Training
Azzur Group is the responsible party for facility SOPs, training, gowning, GMP, safety, and biohazard

Conclusion

Innovation and agility have long been the cornerstones of the pharmaceutical and biotechnology industries. Rooted in the necessity to solve some of humanity's most critical challenges, life science discoveries continue to grow at exponential rates.

To further enable these discoveries and bring them through clinic and into the hands of treatment providers, it's essential that the manufacturing mindset evolves alongside the science.

Looking to the future, green- and brownfield construction and CDMO/CMO utilization will continue to be essential options for biopharmaceutical manufacturing. However, new, proven options are available for innovators looking to move from bench to batch.

New hybrid manufacturing models, such as on-demand cleanrooms, make it possible for up-and-coming innovators (and their investors) to fail fast, pivot efficiently and bring their science to market while retaining process knowledge, controlling IP, and maintaining flexibility. Additionally, models such as Azzur Cleanrooms on Demand™, in-house GMP advisory services, laboratory services, and training ensure that manufacturers are prepared to take the next step when it comes to commercialization.

About the Author: David Frank

David Frank, VP of Client Development, leads customer-facing initiatives for Azzur Group nationwide including Azzur Cleanrooms on Demand™, Consulting and Advisory Services, Labs & Training.

For the past decade, David has consulted some of the world's largest companies in pharmaceuticals, medical devices, technology, and financial services, aligning people, processes, and technology to drive sustainable business results.

He has been recognized over the past 20 years for leading award-winning teams and is passionate about developing individuals into leaders. David received his Bachelor of Arts in Economics from The Pennsylvania State University and is a Lean Six Sigma Master Black Belt and PMP.

About Azzur Group

From Discovery to Delivery™, Azzur Group provides the life science community full life-cycle solutions for all of their GxP needs.

From Azzur Cleanrooms on Demand™ facilities, to our labs, training centers and consulting offices across the nation, Azzur Group helps organizations start, scale, and sustain their growing enterprises. With nearly four decades of service to the life science community, we have become a trusted partner to the world's leading pharmaceutical, biotechnology, medical device, and healthcare companies, as well as their supply chain.

For more resources on this topic, or to learn about solutions Azzur Group provides to organizations in the life science community visit: azzur.com/cleanrooms.

Sources

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[2] The business research company Cell And Gene Therapy Global Market Report 2020-30: COVID-19 Growth And Change

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