EXECUTIVE INSIGHTS

Drug Manufacturing Trends Impacting Biopharma Stakeholders in the Post-COVID-19 Era

A distinct group of therapeutic assets comprise approximately 20% of biopharma clinical and commercial pipelines (2022 estimate). Advanced therapeutic modalities, (ATMs) including adeno-associated virus (AAV) gene therapies (GTx), engineered cell therapies (CTx) and nucleic acid therapies (NATs), have had a significant clinical impact in hereditary disease, for hematological malignancies and, perhaps most acutely, against COVID-19.

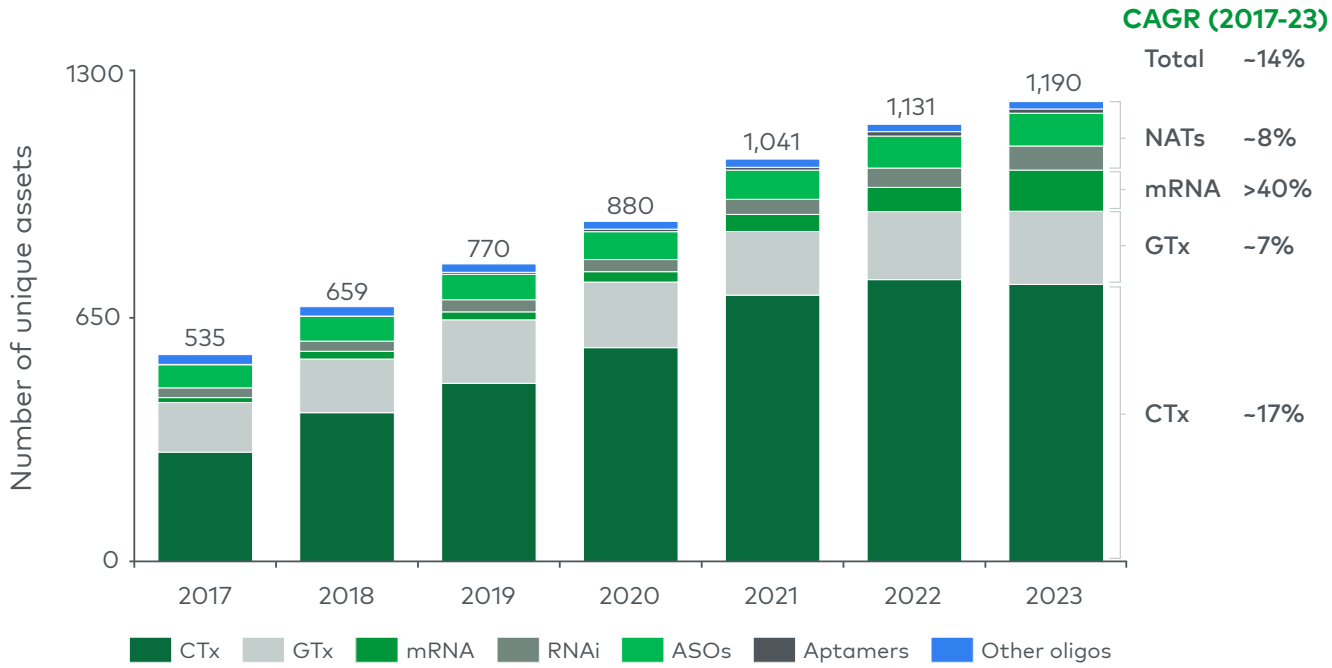
As interest in ATMs grew during the 2010s, manufacturing challenges were top-of-mind for C-suite stakeholders, given technological novelty, complexity and capacity constraints (both in terms of facility infrastructure and experienced talent). These challenges were further exacerbated during the COVID-19 pandemic as manufacturing sites were shut down and supply chains were disrupted. In response, biopharma and contract development manufacturing organizations (CDMOs) aggressively invested in ATM manufacturing capacity expansion while taking advantage of historically low interest rates.

Today, manufacturing leaders are at a crossroads as capacity outpaces demand and facilities may not be fully utilized due to pipeline failures, clinical delays or shifting development priorities. Raising capital for continued process development, clinical development, scale-up and manufacturing is now difficult and expensive in the current macroeconomic environment, prompting executives to reexamine their insource vs. outsource strategy and broader manufacturing strategic approach.

Pre-pandemic: The emergence of advanced therapeutic modalities

Early clinical trial success signaled a need for novel manufacturing technologies and know-how as well as capacity planning for upcoming commercial yields. Initially, early biopharma adopters built internal capacity for the first wave of ATMs because there was not the external expertise or infrastructure to support their new manufacturing needs. The early clinical trial successes drove pipeline growth, which drove demand for rapid capacity and subsequent infrastructure investment. In turn, the expanding and maturing pipeline ultimately created an incentive for CDMOs to invest in capabilities and capacities to address ballooning demand (see Figure 1).

Figure 1
Historic ATM pipeline growth – GTx, CTx, NAT (split by mRNA and other oligos) (2017-23)



Note: ATM=advanced therapeutic modalities; mRNA=messenger ribonucleic acid; CAGR=compound annual growth rate; GTx=gene therapies; CTx=cell therapies; ASO=antisense oligonucleotides; RNAi=ribonucleic acid interference; NAT=nucleic acid therapy
Source: PharmaProjects (April 2024)

- **GTx:** The first successful AAV gene therapies were typically manufactured in-house, including Zolgensma production by AveXis/Novartis and Luxturna production by Spark/Roche. The success of these gene therapies sparked an influx of emerging biotech innovators in gene therapy research and development. With a record increase in the number of gene therapy pipeline assets between 2017 and 2020 (about 28%) and record-level financing in 2020 (about US$20 billion), CDMOs proactively accounted for capacity, opening new facilities and acquiring existing facilities (e.g., Thermo Fisher's acquisition of Brammer, Catalent's acquisition of Paragon) to meet growing demand.

- **CTx:** The manufacturing of commercialized chimeric antigen receptor T cells (CAR-T) therapies was generally outsourced: Oxford Biomedica struck a deal to be the sole manufacturer of Kymriah, Juno/Bristol Myers Squibb (BMS) outsourced production of Breyanzi to Lonza, and Kite/Gilead also started out with CDMOs for Yescarta. Investment in cell therapy biomanufacturing continued to follow a steady upward trend, with the expectation of production capacity of CTxs to increase around 30% (BioPlan 2021 report). With the increasing demand for CTx production, an anticipated "capacity crunch" drove the need to innovate CTx manufacturing processes.
- **NATs:** Early approvals in rare indications (e.g., Spinraza for spinal muscular atrophy and Exondys 51 for Duchenne muscular dystrophy in 2016) validated the technology. However, the first wave of NATs (mostly ribonucleic acid interference and antisense oligonucleotides therapies) were less of a focus in biopharma pipelines given that other ATMs were being developed with increased durability of response and curative potential. Given NATs were largely targeted for rare diseases and thus had smaller patient populations, clinical and commercial manufacturing demand remained manageable and relied on established chemical oligo synthesis methods, which created less of a strain on capacity than that from cell and gene therapies.

During this time, demand started to exceed the supply of experienced and capable CDMOs across all ATMs. This created a capacity bottleneck for clinical assets because of the fast-growing pipeline, and for commercial therapies because scaling up is nontrivial and generally requires separate, larger and overall different equipment needs.

During the pandemic era: Accelerated investment in ATM manufacturing

The COVID-19 pandemic required an immense effort from global biopharmas and CDMOs to develop, scale and manufacture vaccines and treatments to address the outbreak. Given the heavy reliance on CDMOs, ATM manufacturers were acutely exposed to the disruptions brought on by the pandemic. CDMOs faced challenges that complicated the manufacturing process of ATMs in several ways:

- Viral vector vaccines under development (e.g., J&J, AstraZeneca, Sputnik) required viral vector manufacturing capacity, and CDMOs ultimately minimized any nonurgent viral vector agent manufacturing
- All parts of the manufacturing supply chain were strained, including interrupting new facility construction and inspection, illness, and quarantine that limited worker availability, leading to staff shortages, and shipping and air transportation routes falling by more than 90%, disrupting operation and manufacturing requirements

- Competition for talent and supplies (e.g., culture media, filters) against COVID-19 vaccines and therapies became prevalent with a pressing need to prioritize COVID-19 vaccines and therapies versus others

Despite the strains of the COVID-19 pandemic, demand for ATM manufacturing persisted. The COVID-19 messenger RNA (mRNA) vaccine was a major catalyst for investment in advanced therapies. Outside of mRNA vaccines, economic stimulus, soaring valuations and near-zero interest rates allowed biopharmas to easily raise capital, which was used to invest in the expansion and maturation of ATM pipelines and to invest in internal manufacturing capabilities/capacity, including:

- Gilead Sciences subsidiary Kite Pharma built a new viral vector manufacturing facility in Oceanside, California, in 2019, approved by the FDA for commercial production in October 2022
- BMS strengthened its CTx capabilities by adding a new U.S. manufacturing facility for viral vector production in Libertyville, Illinois, which amplified both internal CAR-T cell therapy development and relationships with external partnerships for future capacity requirements
- Spark Therapeutics, a member of the Roche group, invested $575 million in a 500,000-square-foot GTx innovation center in Philadelphia, dedicated to becoming a global center of excellence for GTx manufacturing

Ultimately, the pandemic created a supply-disrupted environment where the strategic value of capacity, coupled with a favorable economic/capital environment, heavily outweighed the cost of capital and downside financial risk of building in-house. This resulted in the building out of internal infrastructure, with a myriad of facility developments and expansions seen over the course of a short period of time (see Figure 2).

Figure 2
Announced facility developments and expansions

Company	Investment ($M)	Date announced	Location	Investment type	Company type
Thermo Fisher	$450	Mar-20	Global	Capacity expansion	CDMO
Merck KGaA	$110	Apr-20	USA	Capacity expansion	CDMO
Emergent	$75	Jun-20	USA	Capacity expansion	CDMO
Minaris	$64.5	Nov-20	Germany/Japan	Capacity expansion	Biopharma
Ultragenyx	$45.5	Nov-20	USA	New facility	Biopharma
Taysha Gene Therapies	$75	Dec-20	USA	New facility	Biopharma
Biogen	$200	Mar-21	USA	New facility	Biopharma
Fujifilm	$2,000	Oct-21	USA	New facility	CDMO
Catalent	$230	Oct-21	USA	Capacity expansion	CDMO
Spark	$575	Dec-21	USA	New facility	Biopharma
Amgen	$550	Mar-22	USA	Capacity expansion	Biopharma
Alexion	$68	Jun-22	Ireland	Capacity expansion	Biopharma
J&J	$250	Oct-22	USA	Capacity expansion	Biopharma

Note: CDMO=contract development manufacturing organization
Source: Biopharma-Reporter; company websites; Outsourcing-pharma.com; Reuters; L.E.K. research and analysis

Situation today and outlook going forward

Today, biopharmas find themselves in a much different macroeconomic environment. The market has experienced historically high inflation that has resulted in the fastest interest rate hike in four decades with rates unlikely to return to the historically low level of the 2010s and into the COVID-19 era (see Figure 3).

Figure 3 (part 1)
ATM manufacturing capacity shifts among notable biopharmas/CDMOs

Level of capacity change (directional) — Increase; Stagnant; Decrease
Potential planned closing; Potential planned opening

	Company*	Asset(s)/ modalities	Facility sq. ft. (thousands**)	Commentary	Capacity change
mRNA	Moderna	COVID-19 vaccine	200	• Ramps down production of mRNA and expects to absorb the demand currently supported by Lonza at its internal manufacturing site in Norwood, Massachusetts, for 2024-25	↘
AAV GTx	Pfizer	COVID-19 vaccine	680	• Amid $3.5B cost-cutting campaign, closes facility in Peapack, New Jersey, effective early 2023, cutting 791 jobs (595K sq. ft.)	↘
		Various early-stage clinical programs		• Trimming viral vector manufacturing and selling off a gene therapy manufacturing facility in Durham, North Carolina (85K sq. ft.)	
	NorthX Biologics	GTxs	45	• NorthX acquires a multipurpose biologics manufacturing facility in Valneva, Sweden, in order to work with ATMPs and advanced biologics during process development and manufacturing for clinical trials and commercial requirements	↗
CTx	Thermo Fisher Scientific	Various CTx and GTx	290	• Announced the development of a facility to expand its CTx and GTx capabilities located in New Plainville, Massachusetts; the site was opened in August 2022 and helped double the company's commercial viral vector capacity; estimated investment was $180M	↗
	Bayer	Various CTx	100	• Opens new cell therapy launch facility in Berkeley, California, for $200M, bringing modular space for cell culture, viral transduction and automated filling of clinical to commercial-scale cell therapies	↗
	AstraZeneca	CTx	85	• Announced planned investment to build a new cell therapy manufacturing facility in Rockville, Maryland • Total investment is expected to be ~$300M for the 85K sq. ft. facility and will be operational by 2026	↗

Figure 3 (part 2)
ATM manufacturing capacity shifts among notable biopharmas/CDMOs

Level of capacity change (directional): Increase; Stagnant; Decrease
Potential planned closing; Potential planned opening

	Company*	Asset(s)/ modalities	Facility sq. ft. (thousands**)	Commentary	Capacity change
CDMO	Lonza	GTx, mRNA	500	• Bluebird and Lonza recently amended their production contract for the second time since the deal was announced in summer of 2016; under the updated deal, Lonza has agreed to increase manufacturing capacity for bluebird's therapies Zynteglo and Skysona • Moderna ramps down production of mRNA drug substance for its COVID-19 vaccine at Lonza's site in Visp, Switzerland, in Q3 2023	→
	Fujifilm	CTx	2,000	• Launches commercial office in Tokyo to provide enhanced sales support and customer service for CDMO services for biologics and advanced therapies to Asia-based pharma and biotech • Expects to begin producing CTx at a nearly 2 million-square-foot plant in Holly Springs; by the end of 2028, it has promised to create 725 jobs at the site 20 miles southwest of downtown Raleigh	↗
	Genezen	CTx, GTx	25	• Announced the closing of an $18.5 million follow-on growth equity investment to accelerate Genezen's growth trajectory in retroviral, lentiviral and AAV vector manufacturing and support the execution of a robust pipeline of customer projects for innovators developing groundbreaking cell and gene therapies	↗

*Nonexhaustive; publicly disclosed facilities both operational and planned
**Combined manufacturing, office, R&D space or non-ATM related operations
Note: ATM=advanced therapeutic modalities; CDMOs=contract development manufacturing organizations; SEC=Securities and Exchange Commission; mRNA=messenger RNA; GTx=gene therapies; CTx=cell therapies; AAV=adeno-associated virus; ATMPs=advanced therapy medicinal products
Source: Company websites and press releases; SEC filings; news websites (FiercePharma, BioPharmaDive, Endpoints)

The interest rate spike has made raising capital more expensive and has reduced available funding for emerging biotechs. Given these headwinds, biopharmas are likely to react in the following ways:

- **Focused investment on late-stage assets:** Biopharmas, both large and small, have been forced to scrutinize R&D pipelines and the associated spend. In many recent cases, biopharmas have prioritized investment in late-stage clinical programs with near-term returns on investment at the expense of early-stage programs or assets with limited scientific validation. Rationalizing the pipeline increases per unit cost of goods sold (COGS), as the fixed cost/overhead with the facility is spread across a smaller number of batches that need to be produced. This more prudent R&D investment is likely to continue in the near-to-midterm.
- **Increased rate of outsourcing:** In addition to R&D spend, biopharmas have had to reevaluate manufacturing infrastructure investment strategy. During the COVID-19 boom when valuations were at all-time highs, financing was essentially free and funding was prevalent, the business case to build internal manufacturing capacity/capabilities was much easier to make than in today's environment. In parallel, many CDMOs used the financial tailwinds to expand capacity/capabilities and continued to gain ATM manufacturing experience. As such, the high rate of ATM manufacturing outsourcing is likely to further increase as biopharmas look to avoid the fixed cost and overhead associated with incremental manufacturing infrastructure.
- **Increased biopharma-to-biopharma partnerships:** While many biopharmas require incremental manufacturing capacity/capabilities to keep up with growing pipelines and commercial scale, others that have cut programs have unwanted excess capacity. ATM manufacturing facilities are typically designed for a specific modality and are challenging to retrofit or repurpose, so the idle capacity becomes a drag on the balance sheet. As a result, biopharmas with excess ATM manufacturing capacity are increasingly likely to explore partnerships or joint ventures with other biopharmas to increase absorption on fixed assets and avoid costly write-offs.

Despite several financial and operational challenges, there often remains strategic value in building and maintaining internal manufacturing capabilities. Having internal manufacturing capabilities reduces or eliminates reliance on external partners that may have competing incentives or priorities. It allows for the manufacturer to have complete control over the tech transfer, process and quality of the facility instead of outsourcing regulatory risk to a third party. It also allows for complete control over the prioritization and timing of batch manufacturing, which creates flexibility in the event of a failed batch or a shift in demand

that is difficult to address when leveraging a CDMO. This strategy is on full display in the Eli Lilly/Novo Nordisk GLP-1 battle where Novo Nordisk recently acquired several facilities from Catalent to help alleviate supply constraints, potentially putting it in the pole position to win in the market.

Drug manufacturing investment strategy considerations

While there are many detailed aspects of an insource vs. outsourcing decision, several key questions will help assess operational, financial and strategic trade-offs:

1. **How baked is the demand forecast?** Forecasting is always an estimate, but some forecasts are built on more "baked" assumptions than others. For example, an ATM entering an indication with a known, small patient population and limited competition may be easier to estimate demand versus an indication with a large patient population and many current and future competitors. This becomes even more complex when considering a portfolio of assets with various likelihoods of approval and thus a wide range of demand scenarios.
2. **What is the time to market?** Even if leveraging an existing facility, it can take three to five years to procure, design, build, install and validate manufacturing infrastructure to make good manufacturing practice materials. Investment decisions must be made early enough to not be a critical path for clinical or commercial material, but late enough to where the process can be designed appropriately to manufacture the drug and that the program has been sufficiently de-risked to justify large investment.
3. **Will COGS be competitive?** For portfolios with low volume and/or a high degree of variability in product type, internal manufacturing investments may be inefficient. For assets that are entering highly competitive indications or markets with strong pricing headwinds, keeping COGS in line or below that of peers is important to maintain profitability. It is imperative to develop a robust COGS model that accounts for potential low-demand scenarios to help understand the financial risk of the internal manufacturing investment.
4. **Is the process technology a competitive advantage?** For many ATMs, novel process technologies are designed and leveraged to manufacture cutting-edge therapies. If the intellectual property behind the manufacturing process is what creates a competitive advantage, then making strategic internal investments will help retain the differentiator versus working with a CDMO that may be able to apply the process more broadly.

While this analysis has been specific to ATM manufacturing, the framework is applicable more broadly across other modalities (monoclonal antibodies, small molecules, etc.). As we continue into this nonzero interest rate era, having answers to these questions will help inform the financial and strategic considerations that are inherent in making internal manufacturing investment decisions.

To find out more and for further discussion, please **contact us**.

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