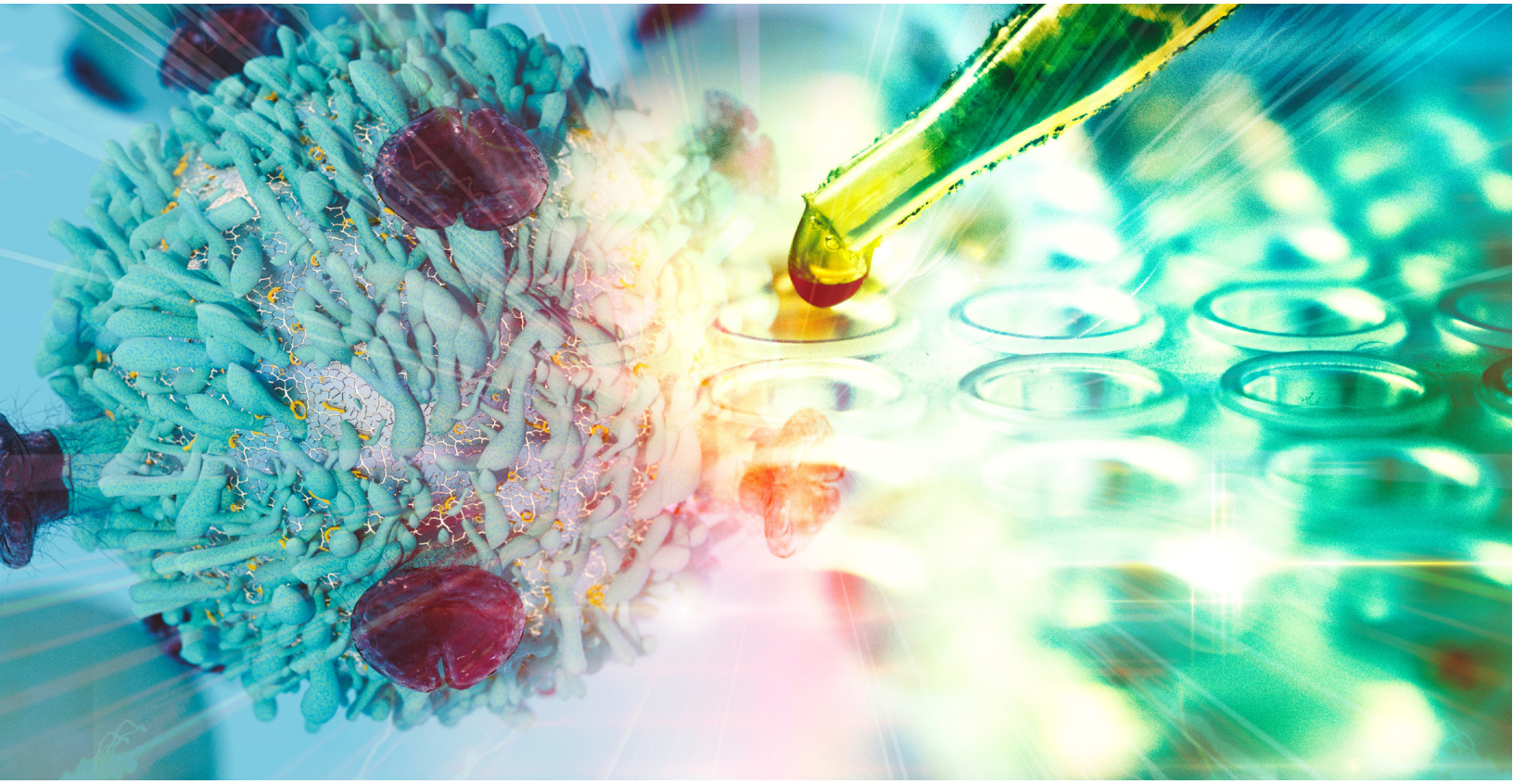

Cell and Gene Therapy: 2022 Recap and Observations

By Jeff Boesiger and Ben Spink, PhD

Despite considerable headwinds confronting the entire biopharmaceutical industry, 2022 has been a banner year for approvals in the cell and gene therapy space. While investment in the sector is not yet back to where it was two years ago, the industry is once again trending up when it comes to research and development spending and forging partnerships. The success of innovative products launched over the next few years will likely depend on the ability of companies both to gain access to new markets and implement value-based pricing arrangements. However, meeting program timelines and delivering on commitments to the investment community will also be critical for firms to achieve future commercial success and to maintain momentum in the space.

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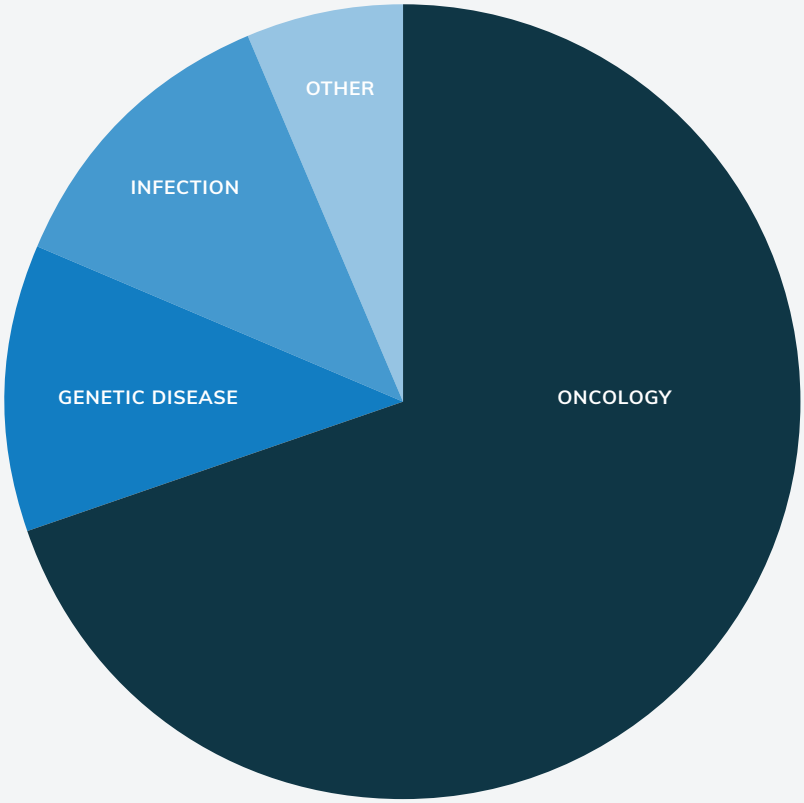
Cell and Gene Therapy Pipeline is Growing Rapidly

Based on an ever-expanding cell and gene therapy pipeline, analysts forecast a wave of new cell and gene therapy approvals in the coming years across numerous therapeutic areas. With more than 1,000 clinical trials now underway worldwide, cell and gene therapies are becoming so prominent that they make up about one-third of the approximately 6,000 clinical stage assets in development. These investigational therapies almost exclusively target therapeutic areas with high unmet need and limited availability of treatments. To illustrate, oncology and rare diseases remain the top areas of cell and gene therapy development in both the overall pipeline (preclinical to pre-registration) and in the clinic (Phase I to pre-registration). Note that there is significant overlap between oncology and rare diseases, as many cancers are considered rare diseases. This focus on genetic diseases and oncology is reflected in the preregistration filings in 2022, shown in Table 1, which indicate robust years ahead for cell and gene therapy.

GRAPH 1: DISORDERS TARGETED BY GENE THERAPY CLINICAL TRIALS, 2010-2020



Source: "Gene therapy clinical trials, where do we go? An overview", Biomedicine & Pharmacotherapy, 153 (2022)

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Table 1: Multiple New Therapies are Nearing Approval

THERAPY	SPONSOR	THERAPEUTIC AREA	MODALITY	INDICATION	JURISDICTION
Lenadogene nolparvovec	GenSight Biologics	Ocular	Gene therapy	Leber hereditary optic neuropathy	EU, UK
Beremagene geperpavec	Krystal Biotech	Oncology	Topical gene therapy	dystrophic epidermolysis bullosa	US
Delandistrogene moxeparvovec	Sarepta Therapeutics	Genetic Disease	Gene therapy	Duchenne's muscular dystrophy	US
Tabelecleucel	Atara Bio-Therapeutics	Oncology	Allogenic cell therapy	Epstein-Barr virus (EBV) positive post-transplant lymphoproliferative disease (EBV+ PTLD)	EU
Exagamglogene autotemcel	CRISPR/Vertex	Genetic Disease	Autologous cell therapy	Beta thalassemia / Sickle cell disease	EU, UK, US
Adstiladrin	Ferring/FerGene	Oncology	Gene therapy	Bladder cancer	US

Source: ASCGT; Q3 report

2022 has been a strong year for cell and gene therapy approvals with the CAR-T space in particular thriving. Carvykti (ciltacabtagene autoleucel) a novel CAR-T therapy developed by Legend Biotech and Johnson & Johnson, was approved in the US in late February for multiple myeloma. Since its February approval in the US, Carvykti has gained conditional marketing authorization by the European Medicines Agency in the summer and Japanese regulators in Q3. The product has demonstrated impressive durability data, which extends to 28 months post initial treatment. Also, three supplemental indications – in large B-cell and follicular lymphoma - were approved by the FDA and EMA for three existing CAR-T therapies: Kymriah, Breyanzi, and Yescarta. As such, CAR-T remains the most common technology used in the pipeline of genetically modified cell therapies.

9 regulatory approvals in 2022

In the second half of 2022, the gene therapies Upstaza and Roctavian were approved in the EU for AADC deficiency and hemophilia A, respectively. Additionally, three gene therapies were approved in the US: Zynteglo for beta thalassemia, Skysona for cerebral adrenoleukodystrophy, and Hemgenix for hemophilia B. This trend looks to continue for cell and gene therapies in the year ahead as there are multiple candidates in pre-registration trials, as Table 1 shows.

98% of CAR-T therapies are for cancer indications

Success has Arrived and Markets are Growing Rapidly

While the pipeline is promising, commercialization has had its challenges. A few years ago, many analysts predicted that the industry would feature several blockbusters (products with more than $1 billion in annual sales) by 2022. But that assessment turned out to be far too optimistic. Today, only Zolgensma, which was first approved in 2019, qualifies as a blockbuster.

However looking at the global sales of selected cell and gene therapies and their projected growth, Table 2, this is expected to change in the next five years Abecma, Breyanzi, and Yescarta may join the blockbuster club by 2024, as supplemental indications and approvals for earlier lines of treatment take hold.

In 2021, cumulative worldwide sales of cell and gene therapies came to

$3.3 billion

Table 2: Existing Approved Therapies Poised for Significant Growth

THERAPY	SPONSOR	THERAPEUTIC AREA	MODALITY	INDICATION	PREVIOUS 5 YEARS	NEXT 5 YEARS
Zolgensma	Novartis	Genetic Disease	Gene therapy	Spinal muscular atrophy	**$2.6B**	**$8.5B**
Yescarta	Gilead/Kite Therapeutics	Oncology	Autologous cell therapy	Diffuse large B-cell lymphoma; nonHodgkin's lymphoma; follicular lymphoma	**$1.9B**	**$7.0B**
Abecma	BMS	Oncology	Autologous cell therapy	Multiple myeloma	**$0.2B**	**$4.3B**
Breyanzi	BMS	Oncology	Autologous cell therapy	Diffuse large B-cell lymphoma; follicular lymphoma	**$0.1B**	**$4.2B**
Kymriah	Novartis	Oncology	Autologous cell therapy	Acute lymphocytic leukemia; diffuse large B-cell lymphoma; follicular lymphoma	**$1.4B**	**$3.2B**
Roctavian**	BioMarin	Genetic Disease	Gene therapy	Hemophilia A	-	**$2.6B**
Tecartus	Gilead/Kite Therapeutics	Oncology	Autologous cell therapy	Mantel cell lymphoma; acute lymphocytic leukemia	**$0.2B**	**$2.2B**
Carvykti	Legend/J&J	Oncology	Autologous cell therapy	Multiple myeloma	-	**$1.2B**
Hemgenix*	CSL Behring/ uniQure	Genetic Disease	Gene therapy	Hemphilia B	-	**$1.2B**
Luxturna	Roche/Spark Therapeutics	Ocular	Gene therapy	Leber's congenital amaurosis; retinitis pigmentosa	**$0.3B**	**$0.7B**
Zynteglo	Bluebird bio	Genetic Disease	Autologous cell therapy	Beta thalassemia	**<$0.1B**	**$0.6B**
Upstaza**	PTC Therapeutics	Genetic Disease	Gene therapy	AADC deficiency	**<$0.1B**	**$0.4B**
Libmeldy**	Orchard Therapeutics	Genetic Disease	Autologous cell therapy	Metachromatic leukodystrophy	-	**$0.3B**
Skysona	Bluebird bio	Genetic Disease	Autologous cell therapy	Cerebral adrenoleukodystrophy	**<$0.1B**	**$.01B**
				TOTALS	**$6.7B**	**$36.4B**

Sources for analysis: Evaluate Pharma, Wedbush Securities; *Thus far, only approved in US. ** Thus far, only approved in EU and UK.

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Table 3: Genetic Diseases Represent the Largest Commercial Opportunities in the Pipeline

THERAPY	SPONSOR	THERAPEUTIC AREA	MODALITY	INDICATION	PREVIOUS 5 YEARS	NEXT 5 YEARS
Roctavian*	Biomarin	Genetic Disease	Gene therapy	Hemophilia A	-	$2.6B
exagamglogene autotemcel	CRISPR/Vertex	Genetic Disease	Ex Vivo Gene Therapy	Beta thalassemia / Sickle cell disease	-	$2.5B
Delandistrogene moxeparvovec	Sarepta Therapeutics	Genetic Disease	Gene therapy	Duchenne muscular dystrophy	-	$2.5B
Lovotibeglogene autotemcel	Bluebird bio	Genetic Disease	Ex Vivo Gene Therapy	Sickle cell disease	-	$1.1B
				TOTAL	-	$8.6B

Sources for analysis: Evaluate Pharma, BioPharmaDive; *Roctavian has already been approved in EU and UK.

Precedence Research's forecast for cell and gene therapies calls for worldwide sales of approximately $42 billion by 2026. While that prediction appears optimistic, revenues will likely climb steadily over the next few years. One reason is that a few already approved drugs, such as Abecma, are likely to become blockbusters soon. Another is that several new therapies will have indications that serve larger populations and therefore have a much greater revenue potential. For instance, two new treatments for sickle cell disease - one from bluebird bio and one from Vertex - should come onto the market next year.

Established Biopharma and New Innovators are Capitalize Finding Ways to Collaborate

M&A ACTIVITY

In the last couple of years, small and mid-sized firms, which constitute more than 80% of the 900 firms that are developing cell and gene therapy products, have been hit particularly hard by the downturn in the market and available financing.

As expected, we are seeing a shift towards alliances and mergers with more established firms in order to advance late stage programs. Inadequate cash on hand to move projects along from phase to phase is the main reason why smaller firms often can't follow through to the pre-registration and approval phases. Particularly for Phase 3 clinical trials, the expense is often prohibitive for all but the large and established firms.

Table 4: Notable Deals in 2022

PARTIES INVOLVED		DEAL TYPE	POTENTIAL VALUE
Novartis	Voyager	Partnership	$1.75B
Novartis	Precision Biosciences	Partnership	$1.5B
Eli Lilly	Akous	Acquisition	$487M
Vertex	Verve	Partnership	$340M
AstraZeneca	Neogene	Acquisition	$320M
Pfizer	Beam	Partnership	$300M

PARTNERSHIPS

In 2022, several large pharmaceutical firms stepped in to collaborate with small and mid-sized firms. For example, this fall, Vertex Pharmaceuticals broadened its reach in gene editing, as it finalized a deal with Verve Therapeutics to develop a one-time treatment for an undisclosed liver disease. Vertex will pay Verve $25 million in cash and make a $35 million investment in the smaller biotechnology company to kick off the four-year alliance. Verve could receive another $66 million in unspecified "success" payments, and $340 million more if the program hits certain development and commercial targets.

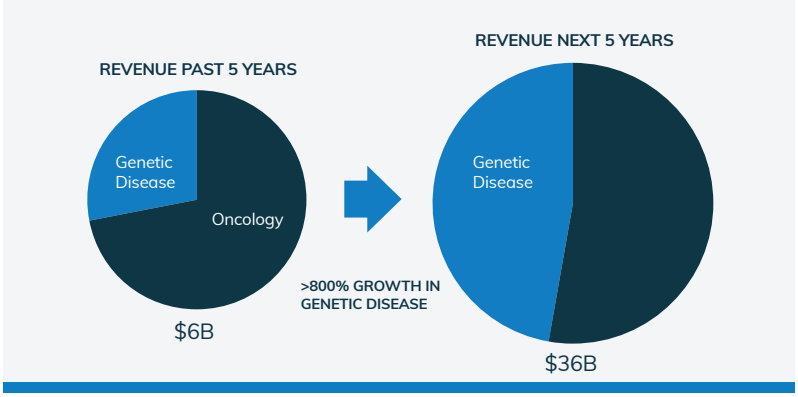
Topping the list of partnerships forged in 2022 was the Novartis licensing deal with Voyager, which is potentially worth $1.75 billion. Also, in a $1.5 billion deal, Novartis brought in another biotech partner – Precision BioSciences - in its quest to create an in vivo gene editing therapy for sickle cell disease and other similar blood disorders.

COMMERCIAL SUCCESS DRIVES INVESTMENT IN MANUFACTURING

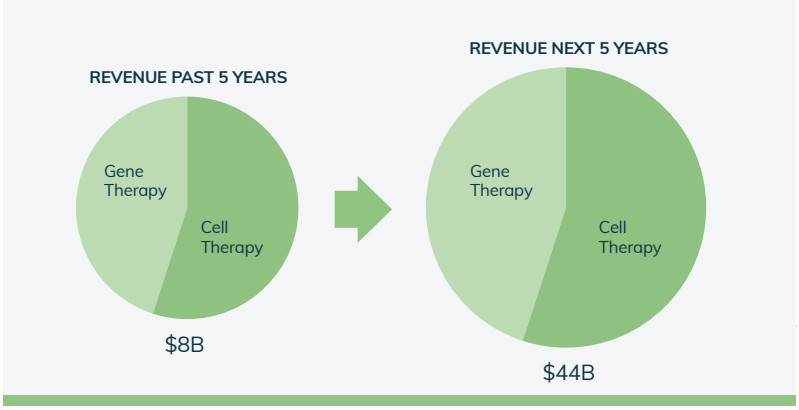
This ever-increasing number of therapeutic candidates is also stretching manufacturing capacity. In some cases, this is limiting the potential of approved products and showing that these operational challenges can be just as impactful to growth as market access and reimbursement issues. This was exemplified in 2022 by the $500 million investment in manufacturing by Legend Biotech and Johnson & Johnson as announced in November.

A need for capacity and know-how has also triggered investment by manufacturing service providers to prospectively expand to serve the growing market. For example, SK Inc, the South Korean conglomerate, started the year with an announced $350 million investment in the Center for Breakthrough Medicines. In September, ARCH-backed manufacturer Resilience pulled in a massive $625 million in Series D financing. Prior to this haul, Resilience had already secured manufacturing deals with several major industry and academic players, including Takeda, Moderna, Be Bio, bluebird bio, and Harvard University.

Graph 2: Genetic Disease with Catch-up to Oncology



Graph 3: Revenue Split Between Modalities Expected to Remain Constant



IPOs

In 2022, there were very few IPOs, which is more likely a reflection of the general downturn in the stock market than a long-term reduction in the appetite for cell and gene therapy public offerings. But two notable IPOs did occur; Prime Medicine raised more than $200 million, and Arcellx raised $120 million.

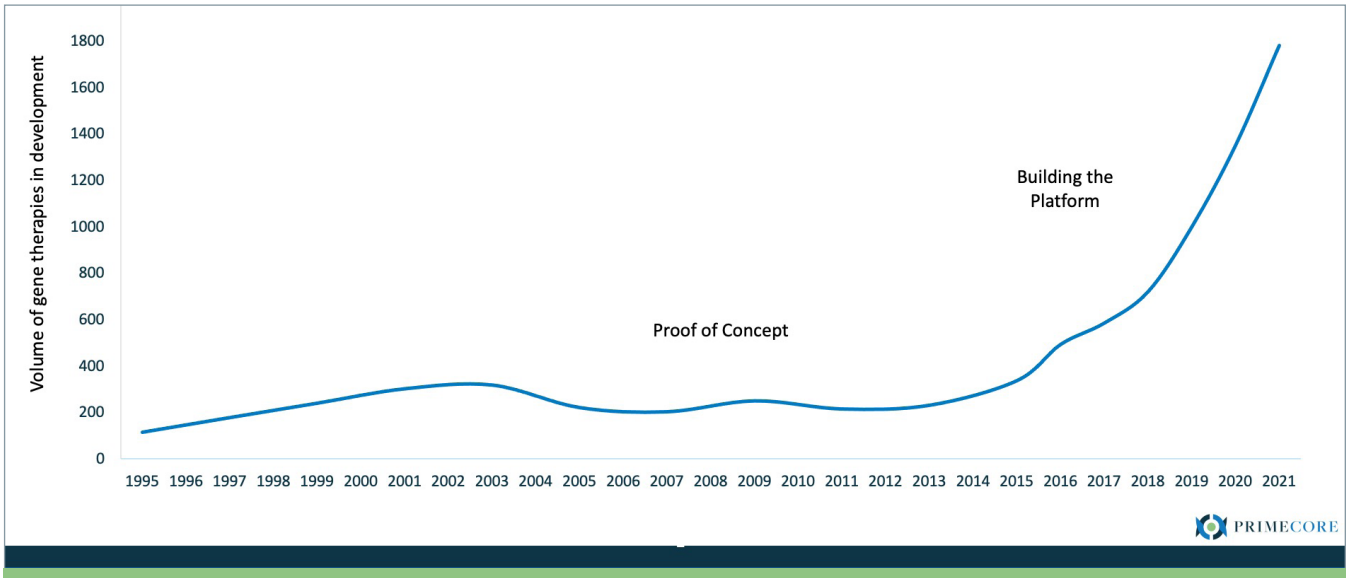
Though the market has faced obstacles during the last 18 months, the biotechnology sector may be seeing a respite of sorts. As of mid-December, the XBI - a biotechnology index widely seen as the sector's barometer - is up 30% in the past six months. By contrast, the S&P 500 is up only 8% over the same timeframe.

FINANCE AND INVESTMENT

While there's been a retrenchment in cell and gene therapy investment - from venture capital to IPOs - there still have been plenty of deals involving more than $100 million. In Q2 of 2022, 17 start-ups raised $793 million in seed and Series A funding - an increase in numbers of deals and value ($250 million more) compared to Q1. Tessa Therapeutics led start-up financing with a $126 million Series A round to develop allogeneic CAR-T therapies against CD30-positive cancers.

In Q3 of 2022, combined seed and Series A financing for 19 cell and gene therapy companies totaled $569 million. While down by $225 million compared to Q2, there were more deals closed in Q3 than in Q2. Furthermore, the amount raised in Q3 was higher than in Q1, indicating that perhaps financing bottomed out in Q1.

Graph 4: Programs in Development have been Growing Exponentially Since 2014



Source: Pharmaprojects Informa, April 2021

POTENTIAL IMPACT ON OPERATIONS

Overall, the growth in the Cell and Gene Therapy space over the last decade has been impressive. With approximately 2,000 therapies currently in development, the number of programs in the pipeline has been doubling approximately every 3 years. The industry has moved past proof of concept and is now building on proven platforms requiring ever more processing capacity. The ability to find the right operational partner, either internally or externally, may limit the ability of companies to create supply and pull programs through their pipeline. Just as the explosive growth of mAbs in the late 1990s and early 2000s spurred a flurry of investment in operations and manufacturing capacity, the cell and gene therapy space seems primed for a similar response.

About Primecore

Primecore is a life sciences consulting firm focused on operations including product strategy, pipeline program management, manufacturing, CMC, supply chain, information technology, capital projects, and delivering on strategic initiatives. Using best practice program management skills, they help life science companies deliver on their commitments and realize the full potential of their product portfolio. Primecore partners with their clients to roll out strategic programs designed to create optimum value for patients and shareholders alike. They do this by providing all operations services (instant "COO") so that their clients can fulfill their clinical and commercial ambitions. **Please see www.primecorepm.com for more information.**

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