Simplification Of The Supply Chain Process For Advanced Therapies

The current Advanced Therapy procurement process is complex, costly and likely too slow for customers with US Food and Drug Administration [FDA]/Medicines and Healthcare products Regulatory Agency [MHRA]/European Medicines Agency [EMA] fast track status. **Cobra Biologics** is an international contract development and manufacturing organization (CDMO) with a wealth of experience currently at the forefront of this rapidly evolving market with its nascent regulatory climate. This article explains the global pressures on CDMOs, including addressing technology challenges to maximize productivity of these new therapies, and how the UK government is supporting the sector through the Life Sciences Industrial Strategy to anchor manufacturing in the UK for the benefit of both patients and the economy.

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COBRA AND MARKET OVERVIEW

I have been the CEO of Cobra since 2011 and have overseen a remarkable growth in the business, driven mainly by the global demand in Advanced Therapy services. Since 2012, Cobra has seen a four-fold increase in its manufacturing of pDNA. Advanced Therapies are now very much an established and rapidly growing market segment of biologics product development. There are nearly 900 companies developing Advanced Therapy products with more than 1,000 clinical trials underway, with 93 now in Phase III. Fundraising for these products year to date was $2.6bn for a market that is predicted to be worth up to $14bn in product sales by 2025.

THE QUEEN'S AWARDS FOR ENTERPRISE 2018

Cobra has a track record in gene therapy stretching back to 1998 and in recent times we have seen rapid growth with $46m worth of orders taken in 2017. Revenue has increased in the UK three-fold since 2013 with 98% of our business coming from outside the UK. This remarkable growth has seen us recognized with numerous awards over the last 12 months, culminating in the Queen's Award for Enterprise earlier this year.

Cobra has had to be nimble as we have grappled to keep pace with the relentless needs of our Advanced Therapy customers.

GLOBAL PRESSURES ON A CDMO TO DELIVER ON FAST TRACK STATUS THERAPIES

By 2022 there are expected to be 40 product approvals in gene therapy with numerous products granted "Breakthrough Therapy" designation by the regulatory authorities, resulting in rapid to market clinical development plans. However, these products require multiple manufacturing sites. There is currently limited capacity for both viral vector and DNA manufacturing and many of the manufacturing processes are complex and unproven. Scott Gottlieb, the commissioner of the FDA, commented in July 2018 prior to the agency's Chemistry, Manufacturing and Controls (CMC) guidance on Advanced Therapy products, that unlike traditional biopharmaceuticals, a lot of the risk in gene therapy product development, around 80%, lays in the CMC rather than clinical development plan.

In a typical Advanced Therapy supply chain, even before the viral vector is induced into the engineered cell, there is the potential for up to 17 GMP campaigns for one single product: 15 pDNA runs (5x cell banks, 5x drug substances and 5x fills) followed by a viral vector drug substance manufacture and fill.

Dose levels can vary a million-fold and patient numbers can range from hundreds for rare genetic diseases to millions for more common diseases such as wet macular degeneration. This is compounded by the uncertainty around adoption levels and potential treatment price indications, which have been quoted up to $4m per patient. All of these issues impact a CDMO's future capacity investment decisions.

The pDNA quantity requirements for different indications can vary significantly, with treatments for choroideremia and hemophilia A having forecast plasmid requirements ranging from less than 1 g to 340 kg per annum. Again this variability requires an adaptive approach by CDMOs to meet an as yet unknown market demand.

The dynamic for pDNA manufacturing is changing rapidly, with customers sourcing pDNA from multiple suppliers that face increasing pressure to squeeze the cost per gram as quantity requirements increase with pDNA becoming a commodity product. However, pDNA supply is absolutely critical to the viral vector production

process and clinical timelines. Consequently, I believe there will be more alignment between pDNA and viral vector manufacturers in the near term as this market matures.

The manufacturing requirements for viral vectors are equally complex if you take adeno-associated virus (AAV). For example, the amount of vector required for the treatments of choroideremia and hemophilia A and their patient populations varies a million-fold, which for the CDMO means that one size of capability will not fit all indications and there will be a high degree of variability on both the process and the cost of goods.

The production of Lenti viral vectors also presents its own set of manufacturing complications. First, with productivity levels that are in the region of a 100-fold lower than those seen for AAV, significant challenges are created for host contaminant removal and in-process monitoring. Second, the size of the vectors at 80 to 120 nm in diameter makes basic operations such as sterile filtration highly problematic. Of course, such challenges are not insurmountable but require close collaboration between suppliers and manufacturer to develop more optimal solutions than those presently available.

I am personally intrigued by competitors' claims on their viral vector platforms. There are multiple vector and serotype options that can provide a 1,000-fold range in productivity outcomes, ensuring that each product indication requires a unique solution, with no one-size-fits-all manufacturing platform. A further complication is the history of biotech, with biopharmaceutical process equipment and analytical techniques tailored specifically to antibody production. If you compare the relative size of, say, a Lentivirus, it is 12 times bigger in diameter and 1,700 times greater in volume than a standard antibody. This can have a profound impact on production efficiency of the viral vector when using traditional equipment especially in the critical areas of purification, product characterization, quality control and analytics.

Back to the all-important timelines. Fast track designation means that product approval timelines have reduced from the traditional 15 years to five years. This places considerable pressure on the CDMO to deliver multi-dimensionally as we tech transfer in a rapidly developed sub-optimized process, likely from a university lab, that we are obliged to run in parallel – process development, scale-up, clinical supply and even BLA submission. This is further complicated by a lack of clarity around process classification and even regulatory product designation.

COBRA ADDRESSING THE CHALLENGE WITH UK GOVERNMENT SUPPORT THROUGH THE LIFE SCIENCES INDUSTRIAL STRATEGY

Cobra is addressing these challenges through: **expansion**, **innovation** and **collaboration**, along with active participation in the UK's **Advanced Therapy Manufacturing Task Force**, from which many recommendations have been included in the UK Government's Life Sciences Industrial Strategy published late last year.

Cobra has a considerable track record dating back to 1998 when we made our first batch of pDNA for GSK and we believe that Cobra is one of five independent commercial CDMOs that can provide both DNA and viral vector supply.

We are expanding our capacity to meet demand from both our existing and new customers. In Keele, Staffordshire, UK, we are investing **$9m** to double our viral vector capacity and gain a MHRA commercial license in 2019. In Matfors, Sweden, we are investing **$10m** to add to our UK pDNA capacity with a range of commercial services by 2020, from small-scale high-quality [HQ] pDNA to a large-scale 500 L capability. This will create **50 jobs** supported in the UK by our participation in the **Advanced Therapy Apprentice Scheme** with two new apprentices starting at Cobra this year. Our **$19m** expansion plan is supported by both the UK and Swedish governments, with Innovate UK in particular supporting our Keele project with a **$4m** capital grant.

Alongside our expansion plans we add to our technical process capability with external collaborations – key equipment, consumable and process industry experts – to enhance both our DNA and viral vector offerings. These include Centre for Process Innovation [CPI], Cell & Gene Therapy Catapult, GE Healthcare [GEHC] and Pall Corporation. This again has been supported in the UK by grant funding to the tune of **$3m** in total over the last three years.

COBRA & SYMBIOSIS VIRAL VECTOR OFFERING

I am also pleased to announce that Cobra has formed a strategic alliance with **Symbiosis Pharmaceutical Services**, based in Stirling, Scotland, to provide a seamless viral vector offering that combines Cobra's drug substance (DS) expertise with Symbiosis' drug product (DP) fill capability. This gives the UK a unique combined service offering for Advanced Therapies.

This endeavor has been partially funded by Innovate UK to a value of **$3m** with the project providing funding for expansion on both sites alongside technical/quality and commercial alignment for both organizations.

Looking back again at the typical Advance Therapies supply chain, the combination of both Cobra and Symbiosis can now effectively address that 17 GMP potential batch requirement, referred to earlier, under one comprehensive commercial agreement that will reduce supply chain complexity for our future customers.

*symbiosis Pharmaceutical Services

cobra:bio

Cobra's Advanced Therapy CDMO development plans over the last few years and the support we have received, I believe, are very much in keeping with the recommendations of the UK government's Life Sciences Industrial Strategy.