

# Bridging Vaccine Translational Research

**Crawford Brown and Roger Lias of Eden Biodesign, Inc argue that in order for outsourced manufacturing strategies to work for vaccine development as they do for monoclonal antibodies, manufacturing development needs to account for the unique properties of vaccines**



Dr Crawford Brown, Chief Executive Officer, co-founded Eden Biodesign, Inc in 2000 from Celltech-Medeva where he was Director of Product Development and was responsible for developing and manufacturing the biotech product pipeline. Among his achievements Crawford managed and led a successful pan-European submission for a complex recombinant vaccine which included an EMEA sponsored pre-approval inspection. Crawford has held senior technical management positions in both biotech and pharmaceutical companies and has been actively engaged in commercial biopharmaceutical development for over 20 years. As well as leading the company, he retains a major role in Eden Biodesign's consultancy services.



Dr Roger Lias is President of Eden Biodesign, Inc and Group Commercial Director. Roger's responsibilities include identifying and establishing strategic business partnerships and expanding Eden Biodesign's offer to the large North American biopharmaceutical sector. Prior to joining Eden, Roger held the position of Vice President, Sales and Business Development at Cytovance Biologics. At KBI BioPharma, a start-up contract biomanufacturing company, he played an active role in securing funding, building revenues and was responsible for identifying and establishing strategic business partnerships and new business relationships. Prior to this, he was Vice President, Business Development, at Diosynth where he had global responsibility and headed North American sales and marketing for Lonza Biologics.

Interest in vaccines has never been greater, as shown by substantial high-profile private and public investment in the sector. For example, the market for vaccines for children and adolescents, is estimated to grow from \$4.3 billion in 2006 to \$16 billion by 2016 (1). Product development service providers, including contract manufacturing organisations (CMOs), can bridge vaccine translational research, enabling sponsors to rapidly develop and access new vaccines during early-stage clinical trials. Many companies developing vaccines, unlike biotech companies developing monoclonal antibody products, need to make considerable capital investment in establishing their own manufacturing facilities, often at a time when capital is required to support clinical development. Table 1 shows a selection of top-tier biotechs that are developing vaccines and have established internal manufacturing capability.

This trend reflects, in part, the unique process and analytical challenges faced in developing each new vaccine, when compared to the platform approach that is more readily adopted for monoclonal antibody products (MABs). This article focuses on process design issues for the development of vaccines, comparing current commercial, technical and regulatory trends

**Table 1:** Cross-section of top-tier biotechs that are developing vaccines and have in-house manufacturing capabilities

Company	Products
Acambis	Anthrax
AlphaVax	Viral
AVANT Immunotherapeutics Inc	Viral and bacterial
BioVex	Oncology
Bavarian Nordic	Smallpox
Emergent Biosolutions Inc	Anthrax
Intercell	Japanese encephalitis

with the issues faced by companies developing highly characterised monoclonal antibodies.

## RAPIDLY EXPANDING MARKET OPPORTUNITIES FOR BIOTECHS DEVELOPING VACCINES

The adage that 'prevention is better than cure' has been the basis for substantial interest in vaccines over the past few years from:

- ◆ Governments
- ◆ Pharmaceutical companies
- ◆ Not-for-profit organisations

For governments struggling with rising healthcare costs, vaccines represent a cost-effective investment: for preventing illness; for government personnel rapidly mobilised for overseas operations; for use against pandemics, such as influenza; and more recently for preventing cancers caused by viral infections. For example, there are well documented US Department of Defence supply agreements intended to create stockpiles of vaccines, such as those against adenoviral infection within recruitment camps (Barr Laboratories Inc) and anthrax (Emergent Biosolutions Inc). The US has led the way in financial terms. For example, it has spent \$200 million purchasing the H5N1 influenza vaccine from major pharmaceutical players through supply agreements to prepare against pandemic influenza (2). However, government action is not restricted to the US. In Europe, for example, the UK Health Protection Agency is adopting an increasingly proactive approach to developing interventions (3).

For pharmaceutical companies, vaccine development represents an important element of their strategic goal to increase the proportion of biopharmaceuticals within their development

portfolios. There are substantial market opportunities, for example, the flu vaccine market is expected to double from \$2.2 billion (2006) by 2016 and recently introduced blockbuster vaccines, such as Wyeth's pneumococcal vaccines with sales of \$2.4 billion in 2007, have been very successful (4,5).

Last but not less significant, charitable or philanthropic investments by organisations – such as the Bill and Melinda Gates Foundation and Wellcome Trust – have targeted funds for vaccine research to tackle neglected diseases in developing countries. Investment trends from these three groups are creating an increasingly broad range of potential partners available to finance biotech companies developing promising new technologies and vaccines. This is, in turn, driving demand for vaccine manufacture.

## **DESIGN AND DEVELOPMENT: CHALLENGES FACING VACCINE MANUFACTURERS**

While it is recognised that biologics face different manufacturing and associated technical-regulatory challenges to small molecule products, it may be less apparent that vaccines are even more complex than a typical monoclonal antibody (MAB) biologic. We can identify four fundamental differences in vaccine manufacture when compared to a typical mammalian produced MAB:

- ◆ A much wider range of product technologies
- ◆ An associated wide range of necessary production technologies
- ◆ The need to manufacture on a relatively smaller scale
- ◆ Vaccines are not perceived by regulators as being well characterised

Vaccines can be a purified protein similar to a MAB, but are frequently based on other product technologies and formulations such as conjugated polysaccharide vaccines (pneumococcal); virus-like particles (HPV); live attenuated bacteria (BCG); live attenuated virus (MMR); partially purified fractions (influenza); and inactivated bacteria (cholera). These diverse products in turn require diverse production technologies, particularly for: upstream production of crude antigen; bacterial and yeast fermentations; cell cultures based on a range of cell substrates; and baculovirus-based expression. Vaccine doses are typically much smaller than for a MAB. Vaccine doses are in the µg range, meaning market volumes can be obtained at production scales of 100s or even 10s of litres, rather than 1,000s or 10,000s typically associated with commercial MAB production. Manufacturing some vaccines at small production volumes means vaccine production technology is even more diverse. Commercial vaccine manufacture can use cell cubes (hepatitis A), roller bottles (Japanese encephalitis) and other production systems more typically used for pre-clinical development of MABs. Variability in product chemistry, biological production system, production technology and scale precludes the establishment of a single dominant 'plug and play' approach to vaccine purification. Development of purification processes for vaccines remains more technically challenging and typically requires considerably more expertise than the MAB purification scheme design.

An additional subtle but important difference between vaccines and MABs is that regulators perceive that vaccines are generally poorly characterised products. The principle that biopharmaceutical products cannot be defined through analytical characterisation alone but are inexorably linked to a specific process, continues to dominate for vaccines. In contrast, there has been a trend with MABs, especially by the FDA, towards using product characterisation data to support process change and scale-up. Trends in MABs, such as CDER's regulatory stance on comparability protocols and adoption of quality by design (QbD), indicates that, in future, post-approval scale-up for recombinant protein-based therapeutics may be simpler and faster. Over time, therefore, MAB development may become more closely aligned with small molecule development, meaning the post-approval process change will be easier. While the EMEA appears to have less enthusiastically adopted comparability protocols, European public assessment reports (EPARs) demonstrate that similar trends are appearing in Europe (for example herceptin) (6). In contrast, CBER and EMEA's approach to MABs and other well-characterised recombinant proteins indicates that, for vaccines, the paradigm that 'the process equals the product' is unlikely to decrease any time soon. The implication remains for vaccines that the definitive process design and facility needs to be used to produce Phase III clinical materials. This, of course, introduces major associated costs, commercial risks and time implications.

## **VACCINE PRODUCT DEVELOPMENT CONSTRAINTS AND MARKET SEGMENTS: THE IMPACT ON OUTSOURCING VACCINE MANUFACTURE**

As described above, a biotech company with a vaccine portfolio has to overcome a range of challenges due to vaccine-specific constraints when outsourcing. Different product types require the use of multiple production technologies such as viral, microbial and mammalian production. Very few CMOs have the expertise and facilities required for all these technologies, meaning that vaccine developers must manage multiple vendors, relationships and locations to manage their vaccine portfolio. Biotech companies developing MABs can establish small-scale in-house processes for candidate screening with confidence that basic unit operations can be readily transferred to a variety of CMOs for scale-up. Vaccine developers do not often have this luxury and have to engage more quickly with CMOs to ensure that the basic





process design can be used. If they do not, they risk needing to introduce fundamental process design changes later, with the potential that disastrous fundamental changes to immunogenicity associated with either product or process impurities will be introduced. Most CMOs focused on MABs will have a standard set of in-process and release tests already in place that can be qualified for the sponsor's specific MAB. In contrast, before vaccine development can begin, many tests may require technology transfer protocols to be developed, new reagents of appropriate quality to support cGMP production to be sourced and purchased and the establishment of reference materials.

Formulation is sometimes taken for granted or viewed as a formality when developing MABs; however, it is a vitally important process during early vaccine development which helps to avoid problems at later stages. Linking the quality of antigen generated by transitional process to preclinical and clinical studies can be vital to integrating safety and immunogenicity patient exposure databases. Development of purified bulk antigen and final dosage needs to be carefully managed and may require the engagement of multiple outsourcing partners. While several contract service providers can provide fill and finish of protein-based MABs, there are very few CMOs globally with capabilities and expertise in formulation of purified multicomponent vaccines. There are even fewer with the ability

to handle fill and finish of live bacterial or viral vaccines along with the associated real-time stability studies.

The highly specialist nature of vaccine development means few capable CMOs are available to support a growing pipeline of products. Even companies developing vaccines funded under lucrative government contracts who need to demonstrate their logistical supply capabilities frequently have to manufacture in different countries or on different continents. The impact of this is that many mid-cap biotech companies seek to establish their own facilities, despite the considerable capital risk.

#### **ACCELERATING VACCINE TRANSLATIONAL RESEARCH**

Investments by governments, the pharmaceutical industry and not-for-profit organisations are accelerating vaccine research and development and are, in turn, creating unprecedented opportunities for biotech companies wishing to develop vaccines. For the majority of biotech companies developing more typical MABs and recombinant proteins, process development uncertainties revolve around the expression system, licensing costs and which of the many global CMOs to select. In contrast, biotech companies developing complex vaccine products, having achieved sufficient financial security, often resort to establishing their own facilities. This is due, in part, to the unique process required and analytical challenges faced with



each new vaccine. It is also as a reflection of production scale and the lack of vaccine specialists in the CMO sector. Before this situation will change, it is necessary for biotech companies and CMOs to adopt a ‘beginning with the end in mind’ philosophy to manufacturing design, with clearly defined endpoints informing process design specifications. It is clear that not all CMOs dealing with MABs and similar products have the necessary expertise and experience. Regulatory trends for MABs that permit more flexibility during manufacturing development are not, as yet, emerging for vaccines. Therefore, biotech companies developing vaccines must take an extremely detailed regulatory-led design philosophy at the product concept stage that not only demonstrates an understanding of market need and immunology, but also examines, in detail, manufacturing strategy and its implications.

In turn, CMOs need to change from offering a pure manufacturing service to working as an extension of a biotech company’s vaccine development team. They must understand the market that the vaccine serves and the differences in both technical and regulatory challenges compared to MABs and similar products. To reflect vaccine product diversity, CMOs specialising in vaccines must deliver broad technology capabilities and associated multi-technology cGMP infrastructure and expertise. Both the commercial and non-

commercial sectors within the vaccine market demand portable process designs, with associated analytics. These must enable transfer to other global locations – should a pharmaceutical company license the product for later phase development and commercialisation, for example. Products targeted at developing countries may require the CMO to support basic cGMP, as well as product-specific training and to make allowances during product design for limited infrastructure at the final manufacturing site. Expert CMOs specialising in vaccines must be able to develop vaccine products for delivering commercial scale production that passes pre-approval inspections, or must establish suitable satellite facilities, thus avoiding the need to change manufacturing site during development and minimising technical and regulatory risk.

## CONCLUSION

The wide variety and complexity of vaccine products and their production processes require technologies, expertise, production infrastructure and regulatory insight that are not widely available. In order to bridge the gap between translational research and vaccine development a careful selection of qualified partners is crucial. Companies that can identify and forge strategic partnerships with the few CMOs that hold the relevant vaccine expertise and experience necessary to create specific development programmes and identify critical endpoints, will be at a significant advantage. Simply offering process development services appropriate for development of MABs may not be enough for vaccine development. Partnering with a CMO which has a broad understanding of clinical vaccine development – together with the insight and ability to anticipate development challenges early on, as well as a clear understanding of the impact of early process development decisions on later stage development – will save significant time and investment over the life of the development programme. It is important to identify a partner that has the ability and infrastructure necessary to continue to support the project over its lifetime. Careful selection of the right biomanufacturer will enable companies to overcome the regulatory gauntlet and technical hurdles to ultimately bring the biologic to market. ♦

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