

## Review

# Collaborative vaccine development

## Partnering pays

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Vaccine development, supported by infusions of public and private venture capital, is re-entering a golden age as one of the fastest growing sectors in the life-sciences industry. Demand is driven by great unmet need in underdeveloped countries, increased resistance to current treatments, bioterrorism, and for prevention indications in travelers, pediatric, and adult diseases. Production systems are becoming less reliant on processes such as egg-based manufacturing, while new processes can help to optimize vaccines. Expeditious development hinges on efficient study conduct, which is greatly enhanced through research partnerships with specialized contract research organizations (CROs) that are licensed and knowledgeable in the intricacies of immunology and with the technologic and scientific foundation to support changing timelines and strategies inherent to vaccine development. The CRO often brings a more objective assessment for probability of success and may offer alternative development pathways. Vaccine developers are afforded more flexibility and are free to focus on innovation and internal core competencies. Functions readily outsourced to a competent partner include animal model development, safety and efficacy studies, immunotoxicity and immunogenicity, dose response studies, and stability and potency testing. These functions capitalize on the CRO partner's regulatory and scientific talent and expertise, and reduce infrastructure expenses for the vaccine developer. Successful partnerships result in development efficiencies, elimination or reduced redundancies, and improved time to market. Keys to success include honest communications, transparency, and flexibility.

Vaccines save lives, reduce transmission rates of infectious diseases, and trim potential health care spending to provide society with positive, tangible benefits. Immunization programs have revolutionized standards of healthcare around the world by eliminating or reducing diseases that once wiped out entire populations (i.e., smallpox, polio). Yet, with all the progress, there is still great

unmet need in this specialty. Unmet need comes in many forms and includes demand for access, portability, potency and alternate modes of administration. Just a few diseases for which preventative or therapeutic vaccine options are lacking include AIDS, hookworm, malaria, many cancers, viruses, and potent bacterial strains (i.e., tuberculosis, *Staph aureus* and influenza).

Investment capital is available in both public and private sectors for vaccine ventures. Governments recognize the positive externalities of preventative care and acknowledge the global, social, economic and public policy implications by requiring and underwriting national immunization programs. Recognition of the public good compels the government [i.e., National Institute of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID), Centers for Disease Control & Prevention (CDC)] to devote public funds and appeals to private charities, such as the Bill & Melinda Gates Foundation, to invest enormous sums of money and intellectual capital in the quest to find new and improved vaccines for acute and chronic diseases around the world.

### Balancing Risk with Reward

Despite the benefits, vaccine development remains a risky business. Instant expertise in this rapidly evolving field is available to innovators from CROs that specialize in immunotechnologies and vaccinology. Successful partnerships require collaboration and excellent communication, with each enterprise knowledgeable and experienced in immunology methodologies, processes, best practices, quality assurance, and regulatory guidelines inherent to vaccine and biologic product development.

Good manufacturing practices (GMPs) and rigorous quality assurance processes implemented in the 1980's contributed to skyrocketing costs, lean profit margins, and an exodus of US manufacturers in the 1990s.<sup>1</sup> The high fixed costs, rigorous regulatory compliance, uncertain demand, long time-spans for conducting efficacy studies, and multi-million dollar litigation suits further reduced vaccine providers in the US from 26 licensed producers in 1967 to only 12 (supplied by four manufacturers) in 2002.<sup>2</sup> The economics of vaccine production rely on volume and are highly sensitive to principles of supply and demand. For many diseases prevented by vaccination, only a single US manufacturer of a given vaccine exists, thereby leading to vulnerability and concerns about national vaccine supply and scale-up.

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With the successful launch of Merck's human papilloma virus (HPV) vaccine Gardasil®, and the blockbuster status of Wyeth's pediatric conjugate pneumococcal 7-valent Prevnar® vaccine, a shift in momentum and renewed interest has occurred in vaccine development from both pharmaceutical and emerging biotechnology enterprises.<sup>3</sup> The pool of potential partners that specialize in the intricacies of vaccine development is limited; therefore it is crucial to select firms with the experience, facilities, flexibility, and requisite project management skills required to navigate the development and regulatory challenges that inevitably emerge.

Although older conventional vaccines lack the profit margins of other biologics and small molecule compounds, the tide is turning and Big Pharma (including Glaxo, Pfizer, Merck, Wyeth, J&J, Novartis, Astra-Zeneca, Sanofi-Aventis, and others) is expanding operations in vaccine production even as layoffs in other internal divisions occur.<sup>4</sup> Incentives are up as reimbursement levels for higher-priced vaccines approach those of therapeutic drugs. Demand for vaccines in the US has grown at an annual rate of 10%, from \$2.9 billion in 1992 to \$6.9 billion in 2002, and prospects for global vaccine market growth are predicted to exceed \$26 billion by 2012.<sup>5</sup> There are approximately 350 vaccines in preclinical and clinical development,<sup>6</sup> and a never-ending pursuit for improvements in safety, efficacy, potency, and expanded claims. Venture capitalists recognize the potential and for the first quarter of 2007, invested \$192 million in emerging companies working in the infectious-diseases category (includes but not limited to vaccine development, but does not include vaccines outside the field of infectious diseases).<sup>7</sup>

### Arriving at the "Go/No-Go" Decision

Vaccine manufacturers are always under pressure to achieve certain milestones and timelines for continued product development funding (i.e., influenza vaccine availability by October/November for northern hemisphere markets). As a result, strategies may change on a continual basis and flexibility, responsiveness, and tolerance from the development partner are required. Communication must be candid, and many times it is easier for an outsourcing provider to objectively review development programs since their investment is often motivated from a business, rather than personal, perspective. Both sponsor and contractor understand that it is better to kill a project early and devote those precious resources to other projects rather than have it fail in a later phase of development.

Vaccine development specialists provide pre-R&D and preclinical animal model platforms for testing vaccine proof-of-concept before moving into more expensive clinical trials. With definitive results gathered at these early stages of development, the information necessary to make practical go/no-go business decisions is available very early in development, so strategic planning is facilitated and tactics for further development are considered in an optimal way.

### Evolution of Vaccine Administration & Production

The time-tested embryonic egg-based vaccine manufacturing method is the "gold standard" used for killed, attenuated, and modified live virus in flu vaccine production. Largely grandfathered in prior to institution of cGMP regulations in the 1980's, it has shortcomings, but nonetheless is the backbone of current influenza production systems. Influenza vaccine is particularly

challenging given the yearly fluctuations in genetic drift and often great differences in strain virulence from one year to the next. Influenza vaccine development is characterized by extended times for strain identification and manufacturing (6–9 months), with often less-than-optimal yields and gaps in availability when and where it is needed when flu season hits.<sup>8</sup>

Research into new and more efficient methodologies for vaccine administration and to improve yield and production is underway. Faster onset of immune response, dose-stretching strategies, and addition of adjuvants that increase potency are tangible results from an increasingly sophisticated understanding of human immunobiology. For many parts of the world, storage of vaccines under controlled conditions is problematic, and research progresses for temperature-stabilized, needle-free, alternative delivery systems.

New technologies and funding offer promise for growth, purification, and harvest of vaccines. The CDC and NIH offer grants to support investigative efforts geared toward speeding up disease analysis, shortening manufacturing periods, and dose-stretching strategies; these items are critical for response to national or local pandemics. Likewise, the Department of Health and Human Services (HHS) seeks proposals from manufacturers to test cellular and recombinant vaccines that may eliminate dependence on embryonic egg-based systems altogether. HHS also offers funding for development of dose-stretching and new, more effective formulations, purification, and manufacturing methods.<sup>9</sup>

A CRO vaccine development partner often brings key learnings from previous assignments and incorporates the knowledge gained into new strategies for clients that encompass genomics, proteomics, bioinformatics, immunology, vaccinology and molecular biology.

### Vaccine Development: Building Operational Efficiencies

Bringing new vaccines to market is a multi-year effort that requires a team approach to streamline discovery, development, and business processes. It is no longer necessary for developers to allocate resources for Quality Assurance, elaborate, expensive, scientific tools, and build multi-million dollar testing facilities. Properly selected drug development service providers with the requisite set of skills, facilities, and organizational talent are available "for rent" and can facilitate milestone achievements for developers by reducing or eliminating organizational and infrastructure redundancies. For example, CROs that specialize in immunotechnologies and customized vaccine program management cater to the seamless, "one-stop-shopping" needs often required by vaccine clients.

Contractors must appreciate the client challenges and balance the science and need for speed with a competitive price to become valued partners. Excellence in client communication is crucial to the success of any partnering or outsourcing venture, as is confidentiality, responsiveness, flexibility, and realistic expectations. An experienced vaccine Study Director will recognize pitfalls, ask the sometimes difficult questions and have alternative strategies to pursue if and when the unexpected occurs. These experts understand timelines and the financial aspects of vaccine development (i.e., internal quoting systems and actual costings for different vaccine types and the platforms necessary to bring them to market) and have the real-life experience to improve study conduct efficiencies. They keep projects on track by avoiding lengthy negotiations and have the flexibility to make adjustments when study plans are

altered by experimental results. Drug development service providers are often able to navigate complex problems and the national and international regulations more efficiently because of experience amortized from work with numerous vaccine developers across the globe.

### Attributes for Economies of Scale

New generations of vaccines are extremely diverse and savvy developers look for partners with flexibility, capacity, and resources to complement their development efforts. A vaccine-specific contractor's infrastructure may include ABSL-2 facilities, a ready pool of research animals, and the requisite testing platforms that conform to both national and international regulatory specifications and safety guidelines. The corporate culture and policies of the development service provider are a reflection of the organization and serve clients best when they are grounded in scientific expertise, operational excellence, and honest communication. If appropriate equipment or technologies are not available, outsourcing providers often have access to resources and are able to acquire, install, and train technicians faster than sponsors.

Outsourcing frees the client to focus on R&D innovation while vaccine development work continues, including assessment of efficacy, quality, and product safety. This practice can also result in lower costs due to volume testing and standardized processes, while still ensuring access to world-class scientific expertise and resources specific to vaccine development. The innovator gains from the "lessons learned" of previous challenges encountered in development programs, while financial savings and economies of scale are realized through infrastructure reductions, quick study start-up and turn-around times, scientific talent and expertise, flexibility to accommodate study schedule changes, and diminished in-house regulatory burden.

A vaccine "sponsor champion"<sup>10</sup> within the developing company utilizes the outsourcing partner's scientific talent and expertise for complete vaccine development, licensing, and marketing authorization. A comprehensive package of vaccine development services includes animal model development, immunotoxicity/ safety studies, immunogenicity studies, efficacy studies, dose-response studies, stability testing, adjuvant testing, assay development for lot/batch release, potency testing, and post-manufacturing/post-licensing testing. Full service integration, or "one-stop shopping," offers opportunities for synergy and improves service delivery.

### Conclusion

Vaccines and biologics represent one of the fastest growing sectors in the life-sciences industry due to the quest for improvements in safety, efficacy, and expanded claims. Achieving development and clinical milestones is integral to vaccine company survival. Partnering with a vaccine development specialist offers instant expertise and economies of scale through strong project management, financial controls, flexibility, scientific innovation, and the technical and regulatory expertise necessary to realize study efficiencies.

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