DDT Vol. 6, No. 11 June 2001

Challenges and new approaches for the vaccine industry

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The economic forecast for the vaccine industry has never been better. The market is growing faster than pharmaceuticals and is estimated to reach 15 billion Euro by 2010. Growth in the industry has been fueled by strong investment and commitment from both public and private sectors with an aim towards lessening the burden of communicable diseases. Recent G8 and EC initiatives have shown willingness to invest in the fight against poverty linked disease and improve health levels, particularly in less developed countries (LDCs). The treatment of vaccine-preventable disease is seen as the most cost-effective solution to achieve this. Nevertheless, the vaccine industry is facing new and evolving difficulties. The *World Vaccine Congress* (Montreal, Canada, 3–5 April 2001) focused on three broad, yet interrelated, aspects of this challenge: vaccine pricing, novel vaccine strategies and vaccine strategies for LDCs.

Vaccine pricing

The forum identified that vaccine manufacturers today face a challenge that provides a conundrum. That is, to protect profitable markets and develop strategies to achieve this, while maintaining an ethical duty to develop, produce and supply vaccines for LDCs. These two aspects must be achieved hand-in-hand. The poorer countries of the world are experiencing the greatest global health crisis of our times, with 36 million people infected with HIV and millions dying yearly from malaria and tuberculosis. Keynote speaker Jean Stephenne (GlaxoSmithKline Biologicals, Rixensart, Belgium) stressed that the failure of industry, government and international organizations to achieve the right balance between economic and ethical considerations will not only lead to a tragic human cost, but will undermine political stability and global markets for all products.

The difficult scenario of today

It is becoming increasingly difficult for large pharmaceutical and biotechnology companies to invest in vaccine development. The commitment for vaccine R&D is associated with high risk and is exemplified by the fact that, of 25 vaccines entering Phase I trials, only five will enter Phase III trials, and of these only one is likely to reach the market. Conservative estimates of time and cost for vaccine R&D were reported to be ten years and >US$100 million. Peter Paradiso (Wyeth Lederle Vaccines, Philadelphia, PA, USA) reported that the heptavalent, pneumococcal conjugate vaccine Prevnar, saw 14 years' development time and three company mergers. C. Boyd Clark (Aviron, Mountain View, CA, USA) compellingly described the difficulties for biotechnology companies attempting to commercialize vaccines. Flumist will have taken six years since the initiation of Phase III trials and US$400 million to reach the market. This is a daunting risk that prompted King Pharmaceuticals (Bristol, TN, USA) to discontinue the development of a nasal flu vaccine after US$100 million investment.

Kevin Reilly (Wyeth Lederle) explained that vaccines are now among the most expensive pharmaceutical products. The reasons for this are numerous. The biotechnology revolution has provided great technological advances in vaccines and immunology but this is associated with markedly increased research costs. A further consequence of technological advances is shorter life-cycles for products: early vaccines had 30–40 years before replacement but this period today is ~5 years. Increased R&D costs are also being driven by more stringent safety requirements. In developed countries, the public is less inclined to accept personal risk, particularly against the background of 'seemingly' rare disease. The notion of zero-risk vaccines, although an impossibility, is in the public realm. Consequently clinical trials have tripled in size. Regulatory bodies, in an attempt to screen for rare adverse effects, have proposed increasing the number of subjects in Phase III trials to a minimum of 20,000. Furthermore, the standards for licensing vaccines have become as stringent as those for conventional drugs and the size and duration of Phase III studies are now comparable. The idea to reduce the size of Phase III studies and perform more extensive post-marketing Phase IV studies was touted. In addition, intellectual property concerns, the trend toward combination vaccines, uniform labeling and adapting to changing regulatory standards as a result of public health concerns (Thiomersal and BSE are examples of this[1]) all add complexity for manufacturers.

A panel discussion highlighted the differing European and US regulatory standards. The example was an incongruity

 PII: S1359-6446(01)01811-6

where vaccines marketed in Europe for two years with extensive Phase IV surveillance cannot be marketed in the US until additional Phase III studies on 5000 US citizens are completed – the reverse does not hold true.

Strategies for the future

How is the industry dealing with the challenges? The cost of vaccines represents only 5% of total US expenditure on pharmaceutical products, yet they remain the most cost-effective form of health spending. For example, *H. influenzae* conjugate vaccine costs US$150 million per year, but returns healthcare savings of US$2.5 billion per year. Kevin Reilly suggested that the perception that vaccines are good value encourages high-risk investment by industry. Therefore, it is imperative that the government and the public agree with this to achieve fair pricing and a reasonable balance between cost and profit. Policy makers must consider the cost:benefit ratio and humanitarian aspects in the price of a vaccine. The public is, and must, be prepared to pay for the many health benefits associated with vaccination. Indeed, spiraling production costs might even require society to accept cost-neutral vaccination programs in the future. A challenge for the industry is to focus public attention on these aspects.

Indeed, the public perception of vaccination and the anti-vaccine lobby was a well debated topic. One incident cited was the reduction of vaccination against hepatitis B in France following an unsubstantiated rumour of an association between hepatitis B vaccination and multiple sclerosis. The challenge for the industry will be to educate the public on the undeniable benefit of vaccination. This is no easy task in a world where the specter of polio victims requiring artificial lungs is removed from public awareness. The necessity for public education was deemed essential by the panel. Proposals to educate the public ranged from using primary healthcare workers to corporate style advertising campaigns. The novel concept of establishing an independent body to investigate adverse effects associated with vaccination was proposed by Robert Chen (Center for Disease Control, Atlanta, GA, USA). He suggested such a body could operate in a way analogous to National Transport Safety Board's role in investigating air crashes.

The identification of strategic technical and project challenges is crucial in accelerating development times and bringing a product to market for both pharmaceutical and biotechnology companies. This theme was discussed in detail at the meeting. Ronald Ellis (BioChem Pharma, Quebec, Canada) pointed out the need for recognizing and addressing key strategic issues as early as possible in development programs. Key issues include vaccine design, formulation, adjuvants, delivery systems, production, clinical and regulatory issues, and marketing. Addressing these concerns will define a strong course to market but not necessarily an accelerated development time-line.

Identifying new vaccine markets represents an opportunity. Targeting specific groups, such as adolescents, adults, elderly and travelers is thought to have potential. Key targets for the future and continuing development include HIV, malaria, tuberculosis, respiratory syncytial virus (RSV), *Meningococcus B*, herpes, chlamydia, human papilloma virus (HPV), and new and emerging pathogens.

Perhaps the most important new direction for the vaccine industry that emerged from this meeting involves changing the focus of vaccines from prophylaxis to therapeutic use. Indeed, it is estimated that if therapeutic vaccines realize their potential, the estimated 15 billion Euro market of 2010 could double or triple in size. Alf Lindberg (Aventis Pasteur, Paris, France) was of the opinion that therapeutic vaccines will prove effective for the treatment of cancer, allergy, auto-immunity and chronic disease. Challenges for therapeutic vaccines include increasing our knowledge of their mechanism of action, safety issues, determining levels of efficacy, regulatory hurdles, cost, and industrialized versus ethical issues. Nevertheless, with profit returns for immunotherapeutics more in-line with conventional pharmaceuticals, therapeutic vaccines are viewed as a profitable future direction for the industry.

Novel vaccine strategies

The meeting also addressed the concept of immunotherapeutics and rational targeting of the immune system. In the genomics era of antigen discovery, the need for new adjuvants was identified as crucial for future advances. Several examples of improved adjuvant technology that directly exploit the pattern recognition system of the immune response were presented.

Immunostimulatory sequences (ISS) based on CpG motifs have been characterized as patterns that are recognized by antigen-presenting cells in murine models. Both Dino Dina (DynaVax, Berkeley, CA, USA) and Heather Davis (Coley Pharmaceuticals, Wellesley, MA, USA) presented ISS that could be optimized for humans. Some sequences turned out to be species-specific, whereas some worked in numerous species. First trials in humans demonstrated that optimized ISS were effective at boosting antigen-specific B cell responses and were 10^6-fold more effective than bacterial DNA. B cell responses were stimulated more by ISS that were covalently linked to antigen compared with ISS mixed with antigen. Moreover, Th1 type responses were induced making ISS attractive for immune deviation (e.g. from Th1 to Th2). It is hoped that ISS could be applied to allergies, infectious disease and chronic inflammation. Heather Davis addressed the issue of dose for ISS: she presented data from

humans and orangutans indicating the amount of ISS required for an adjuvant effect was only moderately higher than that required for mice (~1.0 mg).

Davis Persing (Corixa, Seattle, WA, USA) presented novel adjuvant formulations based on lipopolysaccharide-derived monophosphoryl lipid A (MPL), which is currently in Phase III trials. MPLs represent an alternative approach to targeting the innate immune system, which is achieved by selectively triggering Toll-like receptors 2 and 4. Altering the length of the lipid side-chains permits fine-tuning of the response to selectively stimulate either nitric oxide synthase or chemokines.

An alternative approach to enhance the immunogenicity of vaccines by targeting the adaptive, rather than the innate, immune system was described by Martin F. Bachmann (Cytos, Zurich, Switzerland). Target antigens were rendered highly ordered and oriented by covalently linking them to virus-like particles (VLPs). Using this technology, Cytos demonstrated potent B cell and CTL responses in the absence of adjuvant. Th1 responses were generated, affording the opportunity to induce immune deviation for allergy treatment. Furthermore, it was possible to break B-cell tolerance in mice by coupling self-antigens to VLPs. This latter approach could be used to block self-molecules such as tumor necrosis factor (TNF) or IgE *in vivo*, and offers potential to replace monoclonal antibody therapies. VLPs, therefore, represent a promising new technology for immunotherapy in general.

Despite the initial hopes raised by DNA vaccination strategies, results in clinical trials have remained disappointing, a finding summarized by Myron Levine (Center for Vaccine Development, University of Maryland, Baltimore, MD, USA) as 'paradise lost', or at least 'paradise postponed'. However, Alf Lindberg suggested that prime-boost strategies involving canary pox and specific peptides or DNA-vaccination might be effective for treatment of melanomas in some patients. In addition, Robert Whalen (Maxygen, Redwood City, CA, USA) showed how PCR-based promoter reshuffling can be used to enhance the immunogenicity of DNA-based vaccines.

Vaccine strategies for LDCs

The take-home message from the conference is that partnerships provide better purchase-mechanisms and certainty to the industry. LDCs suffer most from infectious diseases, with the major diseases to be addressed including HIV and AIDS, malaria and tuberculosis. It is, therefore, imperative that LDCs have access to new vaccines. One way of ensuring adequate supplies and the earliest available access is through partnerships between international agencies, government, philanthropic organizations and industry. The role of partnerships is crucial for ensuring purchasing power for the third world and the Global AIDS Vaccine Initiative (GAVI) has adopted a leading stance in this respect. Novel financing models are required to supply LDCs with affordable vaccines, and tiered pricing might be the optimal solution. However, industrial partners are concerned with preventing parallel trading and ensuring fair pricing in developed countries. Also, once developing countries become wealthy enough, it can be expected that they will pay for future value and innovations; South America was cited in this respect. Guaranteed-purchase mechanisms and facilitated procurement might be additional incentives for the industry; GFCV (Global Funds for Children's Vaccines) and UNICEF are currently serving this role.

Seth Berkeley from the International AIDS Vaccine Initiative (IAVI, New York, NY, USA) offered a novel concept to ensure supply of an AIDS vaccine to LDCs. IAVI finances the R&D of AIDS vaccines, but leaves the intellectual property with the partner. However, IAVI demands and enforces that the vaccines are sold in the Third World at an affordable price. Additionally, to protect the needs of LDCs, IAVI only finances prophylactic, and not therapeutic vaccines. Jose Esparza, from the World Health Organization and the United Nations Program against AIDS (WHO–UNAIDS) reported that, to date, of the 30 HIV vaccines tested, more than ten trials have been performed in LDCs.

In conclusion, the public sector and industry are well aware of the devastating situation in LDCs with respect to infectious diseases. There is hope that the relevant measures are being employed to begin to resolve this problem.

Reference

1 Anon. (2000) Thiomersal as a vaccine preservative. *Wkly Epidemol. Rec.* 75, 12–16

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