Commercial Opportunities Created by New Vaccine Adjuvant Technologies

Introduction

Of all medical innovations, vaccines have had by far the greatest impact in reducing the morbidity and mortality of infectious diseases. Although antigens have always been the lead products of the vaccine industry, over the last decade adjuvants have received far greater attention. The first vaccine adjuvants were developed in the 1920’s, when it was found that addition of irritant substances such as aluminum hydroxide (alum) or mineral oil enhanced vaccine immunogenicity. Thereafter, many different substances were tested for their ability to enhance the effectiveness of bacterial and toxin antigens including agar, saponin, lecithin, starch-oil, and tapioca. Needless to say, although many of these compounds had adjuvant effects when tested in animals, most of them were highly reactogenic and poorly tolerated and thereby deemed unsuitable for human use. This has left alum as the dominant adjuvant in vaccines right up to this day.

Killed or live-attenuated organisms used in older vaccines contain high levels of contaminants that evoke a strong inflammatory response, which in turn enhances adaptive immune responses, such that they generally don’t need an additional adjuvant. However, because of the reactogenicity of such older style vaccines, vaccine manufacture has shifted to highly purified antigens (split and sub-unit antigens). The consequence is that these vaccines often have poor immunogenicity, a problem that could potentially be fixed by addition of an appropriate adjuvant. However, this solution has in many cases been hampered by the lack of choice in approved human adjuvants. In 2009, the FDA approved Cervarix™, a human papilloma virus vaccine containing AS04 adjuvant (a mixture of alum and monophosphoryl lipid A), making this the first new adjuvant approved by the FDA in over 80 years. This approval of a new adjuvant has created a great deal of excitement, that this might mark the start of a trend towards approval of many other innovative new adjuvants in the US and other markets. This article seeks to provide a timely overview of the regulatory and technical hurdles to the development and introduction of innovative adjuvants, as well as the market growth opportunities that new adjuvants would be capable of creating in the vaccine market over the next ten years.

Regulatory Issues in Introduction of New Adjuvants

Regulatory authorities understandably have, with rare exception, taken a conservative attitude towards approval of new adjuvants, given the uncertainty regarding the mechanism of action of most adjuvants and the difficulty this presents in making safety assessments. Despite several adjuvant candidates being in late-stage clinical development, it remains an open question when such adjuvants may obtain marketing approval. A major hurdle is that most candidate adjuvants have a higher reactogenic profile and less certain safety than alum, thereby requiring strong justification that their benefits in terms of enhanced immunogenicity outweigh any potential risks. Moreover, public and professional concerns about adjuvant safety, as highlighted in US and Europe with the highly publicized debate over the use of squalene oil containing adjuvants in influenza and other vaccines, has placed great pressure on regulatory authorities to get it right when it comes to adjuvant approval. The Swedish Medical Product Agency (MPA) recently made a conclusive finding (1) that a squalene-adjuvanted influenza vaccine caused narcolepsy, a serious chronic autoimmune disease, in children receiving the vaccine. It remains unclear as to what component of the vaccine might have caused the narcolepsy,
but the fact that it was an adjuvanted vaccine that caused the problem will no doubt yet again flare the public debate about use of vaccine adjuvants. This highlights just what a difficult job regulators confront when faced with the challenge of assessing the safety of a new vaccine formulation that might include a new adjuvant as this is an extremely complex task.

For an increasingly well-informed public, there is an expectation that any new vaccine, especially for young children will receive adequate assessment to ensure safety prior to its approval. Hence, the critical challenge for vaccine manufacturers, in order to gain approval from regulatory authorities and at the same time ensure a high level of public acceptance for vaccines, will be their ability to convince not just the regulators but also the wider public of their commitment to the development of safer and better-tolerated compounds. This public engagement did not happen in the past when vaccine policy was mandated by government decree and the public support and engagement in the process of setting public health policy was not encouraged. The educated and informed public of today mandates that old-fashioned paternalistic approaches to public health no longer have a place in today's society. Instead it is critical that the public be consulted and engaged in the setting of vaccine policy and the introduction of new vaccines. The old health slogan of "no pain, no gain" carries little weight (2) with today's public with increasing demands that governments fund development of safer and better tolerated vaccines, a development that industry itself may not be excited about given their large capital investment in existing old-style products and infrastructure. Nevertheless, these recent changes have created new opportunities for more nimble small new biotechnology companies to advance new vaccines and manufacturing approaches, unencumbered by these restrictions. This is well highlighted by recent investment by the US government in funding of manufacturing facilities and product development by multiple new recombinant influenza vaccine technology companies, including Protein Sciences, Medicago and Novagen. This in turn creates major new opportunities for market growth of adjuvant companies, given that many if not all of these recombinant vaccines will presumably need adjuvants to be effective. Outside of influenza, other growth opportunities are presented by the attractive pediatric vaccine market segment, where new products including new adjuvants could demand a major price differential, with this market being expected to grow at a compound annual rate of 11% over the next 3 years (3).

### Government Contracts and Grants

The swine flu pandemic highlighted issues including the importance of antigen-sparing to compensate for limited antigen manufacturing capacity. During pandemics, vaccine manufacturers are not able to quickly deliver the number of doses required, impacting on the time it will take to protect the population. Adjuvants provide the most obvious solution, turning one vaccine dose into many, while maintaining or even enhancing vaccine potency. Subsequently, numerous governments around the world have signed contracts with large pharmaceutical companies, in order to stockpile not only flu vaccine antigens, but also potential adjuvants, thus preparing for the next pandemic flu. For instance, the US government has invested over $280 million in purchasing stockpiles of squalene oil adjuvants for potential use in pandemic influenza vaccines. These types of government contracts can be attractive for vaccine developers, because even non-FDA approved adjuvants have been stockpiled giving an opportunity to companies to create a substantial cash-flow with in-development adjuvant candidates.

Government contracts during pandemics do not represent the only source of public funds available for adjuvant developers. For example, the US government has proactively been freeing up funds for both public research centers and private companies to stimulate innovation in the vaccine industry. Innovative adjuvants have been one of the technologies targeted by these grants, with funds made available for early-stage development programs and clinical trials, suggesting that past lack of innovation in the adjuvant field is a major concern for health authorities. Amongst all the programs involving adjuvants, the ones concerning pandemic influenza remain the priority. Many companies have strategically oriented their portfolios to government needs in terms of biodefense products, regularly receiving grants to develop their technology. While these biodefense contracts could present a great opportunity for adjuvant developers to have access to large financing resources, questions have been raised about the reliability and sustainability of these financing options for private companies, as in tough financial periods governments may have to drastically slash budgets allocated to such research, thereby threatening the survival of any company overly reliant on such funding.

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Table 1. Market opportunities for new adjuvants created by their ability to solve specific vaccine technical hurdles

### Seasonal flu market and Targeted Groups Opportunities

Mainly as a result of the recent pandemic threat and increased public awareness of influenza, the seasonal flu vaccine market is
a high-growth market, recording a compound annual growth rate over 12% during the period 2005-2010, out performing the rest of the drug market (4). Valued at US$ 3 billion in 2009/2010, many reports forecast a similar growth rate for the flu vaccine market over the next five years; this is extremely attractive to the vaccine industry. Still, optimism should be balanced by an important consideration, pointed out by many experts: which is the danger of commoditization. This phenomenon creates a growth constraint on this market and is largely driven by two factors. First, the market is overcrowded with multiple major actors competing and little actual product differentiation (4). On the other hand, the conservative attitude of regulators towards new technologies, especially towards new adjuvants, has slowed down innovation and emergence of innovative products in the influenza area. The effect of commoditization is stagnation and even a regression of influenza vaccine prices, resulting in lower incentives for new market entrants. However, extensive market opportunities could be created by innovative companies developing new technologies and well differentiated products. In developed countries, government policy concerning the flu vaccination is to address the vaccine uppermost to high-risk populations: elderly, patients with chronic diseases, and young children. Nevertheless, the current vaccines available on the market have been shown to be less effective in the elderly and in patients with chronic diseases, emphasizing a need for more effective vaccines for these populations. Considering that alum is not effective for influenza vaccines, this represents a major market opportunity for vaccine developers. MF59™ is a good example of an adjuvant that Novartis has been heavily marketing as having a competitive advantage over non-adjuvanted vaccines for the elderly and patients with chronic diseases. Seasonal influenza is not the only indication for which companies are using new adjuvants to develop differentiated vaccine products targeting specific patient groups. For instance, GSK and Dynavax have both taken a similar approach with their respective Hepatitis B virus (HBV) vaccines. GSK has developed Fendrix®, an HBV vaccine containing its AS04 adjuvant that is approved in Europe for patients on kidney dialysis. Similarly, Dynavax is undertaking phase III clinical trials of its CpG-adjuvanted Heplisav™ HBV vaccine in individuals with chronic kidney disease to demonstrate its superior efficacy over standard alum-adjuvanted HBV vaccines. The strategy of targeting specific groups is based on the more flexible attitude of the regulatory authorities concerning vaccine products developed for high unmet medical needs. Moreover, after gaining the approval for a limited indication, the aim is presumably to collect sufficient safety data in order to extend indications to larger populations in the future.

Use of Adjuvants to Extend Indications

Improving the safety and efficacy of existing vaccines is not the only challenge for the vaccine industry: there are many more diseases that could potentially be prevented or treated by new vaccines. Technological hurdles are large as are the market opportunities. For instance, the first vaccine approved for the prevention of cervical cancers, Gardasil™, has already reached blockbuster status, with annual sales in excess of US$ 1 billion. This success is one of the reasons for the renewed interest from large pharmaceutical companies in the vaccine market. In order to create new market opportunities to compensate for the loss of patents for their major blockbusters, these companies have embarked on the development of vaccine products against numerous diseases including staph and strep skin infections, hospital acquired pneumonia, HIV and cancer, amongst others. Companies have spent billions of dollars funding internal research programs, licensing antigens or acquiring whole biotechnology companies to build strong pipelines for potential vaccine applications. As previously stated, because of the poor immunogenicity of these highly purified antigens, new or old adjuvants will be essential to create effective vaccines. The scientific challenge is to develop adjuvants that specifically induce a strong T-cell response (also called cellular or Th1 response), necessary to achieve a protective immune response in many infectious diseases. Several adjuvant compounds currently in development have shown promise as Th1 adjuvants. The quest for innovative vaccines has been underlined by numerous research and development deals, as well as strategic alliances between pharmaceuticals and biotech companies holding promising adjuvants, illustrating the "open innovation" concept. The strategy of small companies has been to maximize the utilization of their technology, trying to make it available for a great number of indications by multiple non-exclusive licensing deals. Partnerships with big pharma not only allow early-stage companies to generate revenues, but also help produce safety and efficacy data on their proprietary adjuvant. As a lack of funds usually slows down product development in small companies, this business model creates the opportunity to generate both revenue and data.

Again with the aim to generate revenues in early-stages, some adjuvant developers have translated their human technology to the veterinary industry. The animal vaccine market is expected to reach US$ 5 billion in 2013, with a compound annual growth rate of 5.9% (2). The need for safer and better-tolerated adjuvants for animal vaccines is increasing, as owners demand higher quality products for their pets. Some biotech companies have been proactive in this area, entering into multiple research collaborations and licensing deals with veterinary companies, allowing them to secure early revenues. Examples of this strategy are small companies like Isconova, a Swedish biotech developing saponin-based adjuvants, or our own Australian-based start-up Vaxine Pty Ltd, which is developing the unique Advax™ line of polysaccharide adjuvants, both of which examples have developed extensive research collaborations and concluded commercial agreements with veterinary as well as human vaccine manufacturers.

Cost of Vaccine Production: an Increasing Concern

The costs associated with vaccines extend beyond research expenses, comparable to the ones associated with drug R&D, to the development of dedicated and specialized production facilities for large-scale vaccine manufacturing. Indeed, fixed costs for a vaccine manufacturer are high for two main reasons. First, building plants to produce innovative antigen expression systems
involve mammalian cells, or insect cells necessitates heavy up-front investments. Moreover, maintaining production standards is essential for regulatory authorities. These two factors combined with low production yields and the fact that health authorities are reluctant to pay high prices for prophylactic vaccine products, can result in a low profit margin. The challenge is for new vaccine technology to be cost-effective and not result in higher costs of production. Technologies that would be able to reduce production costs, by increasing antigen yield or by reducing the antigen dose, represent great opportunities for vaccine manufacturers to increase profit margins. Reduction in production costs is also important to address the increasing needs of vaccines in poor countries, allowing not-for-profit organizations and governments to make this technology accessible to all.

**Conclusion**

While innovation in adjuvant technologies was until recently neglected by industry and policy makers, these sectors now understand that new adjuvant technologies are needed to help create major new market opportunities for vaccine manufacturers while at the same time potentially solving major antigen supply problems for pandemic planners and those involved in biodefense. The development of innovative adjuvants, demonstrating high safety and tolerability profiles, should gain the confidence of regulatory authorities and the public and persuade that introduction of new adjuvants is a major necessity and should be seen as a positive not a negative. New adjuvants may offer the potential to create effective vaccines targeting important indications like HIV and cancer, thereby presenting major growth opportunities for the vaccine market. Furthermore, new adjuvants could play a major role in decreasing the costs of vaccine production, thereby making more vaccines accessible to the developing world, while maintaining vaccine manufacturers’ profitability.

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