FROM THE ANALYST'S COUCH

Influenza vaccine market dynamics

Hedwig Kresse and Holger Rovini

'Rocky recycled chair' image courtesy of Nigels Eco Store.

The market for seasonal influenza vaccines, sized at US$2.8 billion in 2008–2009 across the seven major markets (United States, Japan, France, Germany, Italy, Spain and UK), has had a strong compound annual growth rate of 12.6% since 2005–2006 (REF. 1). In recent years, the sector has benefited considerably from an increase in disease awareness and funding, triggered by the threat of an influenza pandemic. However, owing to increasing competition and market commoditization, maintaining this strong growth momentum will be a key challenge in the future. The cautious stance of regulators towards new technologies inhibits successful product differentiation, particularly in the crucial US market. Improved vaccines for the elderly, alongside faster and more flexible manufacturing technologies, are the key unmet needs.

Challenges of the market

The influenza vaccines market is a challenging sector for several reasons. Besides requiring annual updates, seasonal influenza vaccines have to be produced and shipped within a short time frame of 6 months. Manufacturing delays and reduced output can result in losses of revenue and market share. Additionally, the demand for seasonal influenza vaccines is variable and often unpredictable, being influenced by factors such as the weather, the timing and severity of the influenza season, vaccine availability and public awareness of vaccination. These factors make production planning difficult. The pandemic influenza vaccines business is even more unpredictable and depends almost exclusively on government stockpiling and supply contracts.

A re-emerging focus for vaccine players

Historically, the influenza vaccine landscape has undergone marked fluctuations, particularly in the United States. The country remains the single largest market for seasonal influenza vaccines, accounting for 40% of overall sales across the seven major markets in 2008–2009 (REF. 1). In the 1970s, at least ten US firms were marketing seasonal influenza vaccines. As a consequence of stricter FDA regulations and poor returns on investment compared with other pharmaceutical sectors, only three companies remained in the market in 2002: Wyeth, Aventis Pasteur (now Sanofi Pasteur) and PowderJect (now Novartis). In 2003, Wyeth ceased production of its own vaccines to concentrate on marketing MedImmune's (now part of AstraZeneca) FluMist, but decided to leave the flu space altogether in 2004.

Two factors prompted a change in US policy: the emerging threat of a pandemic caused by the H5N1 avian influenza strain since 2004 and a perceived vaccine supply shortage in 2004–2005 following disruptions at Chiron's (previously PowderJect's) manufacturing facility. The US government subsequently began to invest heavily into establishing US-based influenza vaccine production capacity, aiming to decrease the country's dependence on vaccine imports from few, mostly European, manufacturers. Furthermore, the US provided an additional growth stimulus by sequentially expanding recommendations on seasonal influenza vaccination to include more than 85% of the country's population by 2009 (REF. 2). This combination of 'push' and 'pull' incentives transformed the sector's commercial potential, attracting numerous vaccine developers to build and expand their influenza portfolios in the United States. Following the market entry of GlaxoSmithKline (GSK) in 2005 and CSL in 2007, the number of vaccine suppliers for the US market has increased to five in 2009, with Sanofi Pasteur as the market leader (FIG. 1).

However, as the demand for seasonal influenza vaccination in the general population has failed to meet the expectations of suppliers, oversupply of these vaccines in the United States has become a growing problem during the past influenza seasons (FIG. 2).

This has triggered a growing commoditization of influenza vaccines. Prices, which increased from below $2 per dose in the late 1990s to $12 per dose at the peak of the business in 2007, have fallen over the past 2 years to reach a new low of $8.60 on average in 2009 (REF. 3). To reverse this price decline, reduce the commodity nature of influenza immunizations and improve their market shares, vaccine developers are turning to new technologies that could offer product differentiation.

Developments in adjuvant technology

One key area of interest is an enhancement of vaccine immunogenicity through adjuvants. The key advantage in the influenza sector is ▸

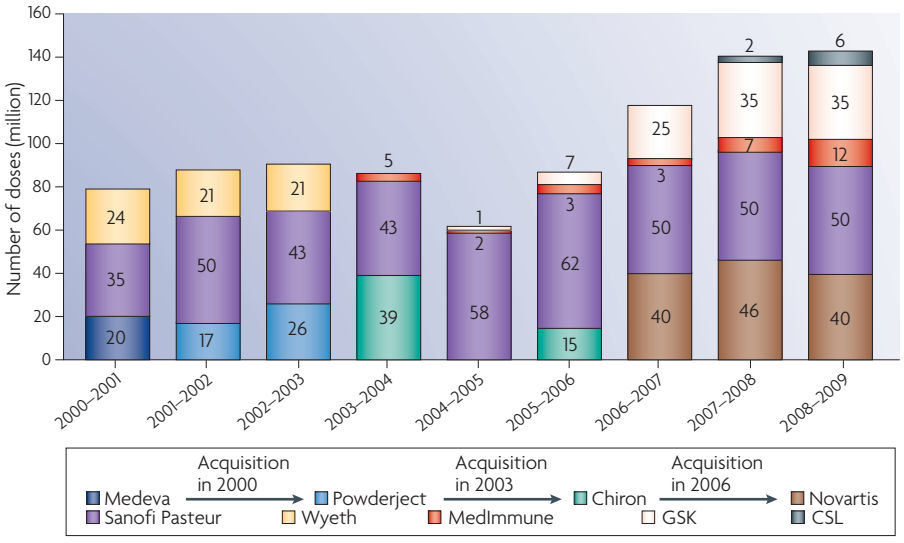

Figure 1 | **Vaccine providers for the US market for the influenza seasons 2000/2001–2008/2009.** GSK, GlaxoSmithKline. Data from REFS 1,5–7.

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INFLUENZA VACCINE MARKET DYNAMICS

a reduction in the amount of antigen required for protective immunization. This so-called dose-sparing effect helps to increase the number of available vaccine doses. This is particularly important in a pandemic, when the supply, limited by manufacturing capacity, cannot meet the demand. Another advantage of adjuvanted vaccines is their potential for improved immunogenicity in the elderly, which is a key unmet need. Novartis and GSK are currently furthest advanced in developing these technologies for influenza. Both companies have already received European approval to make products using their oil-in-water-based emulsions MF59 and AS03, respectively. By contrast, gaining US approval for adjuvanted vaccines has proven difficult, with the FDA adopting a conservative position, presumably owing to a lack of data on the long-term safety profile of novel adjuvants. The current influenza A (H1N1) pandemic has rejuvenated interest in adjuvanted influenza vaccines, with several governments investing into large adjuvant stockpiles. Clinical studies investigating potential benefits of various adjuvanted pandemic influenza A (H1N1) vaccines were initiated. However, clinical trials of non-adjuvanted H1N1 vaccines have now demonstrated sufficient immune responses, indicating that at least in the early stages of vaccination against H1N1, adjuvants will not play a part in the US.

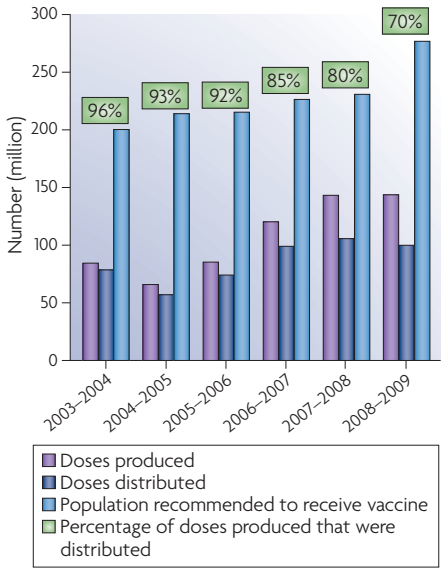

Figure 2 | **US influenza vaccine supply versus demand for the influenza seasons 2003/2004–2008/2009.** Data from REFS 1,8.

Improving manufacturing techniques

A further opportunity for product differentiation is the influenza vaccine manufacturing process. With the exception of Novartis's Madin–Darby canine kidney (MDCK) cell-based vaccine Optaflu, which gained European Union approval in 2007, all marketed seasonal influenza vaccines are still manufactured in chicken eggs. This process is not only lengthy and inflexible, but would also be unsuitable in the event of an avian influenza pandemic. To provide faster and more flexible alternatives, numerous companies are developing alternative production systems. Besides Novartis, Baxter is the only other player to have gained European approval for a cell-based influenza vaccine — its mock-up pandemic vaccine Celvapan, which is manufactured in Vero cells (a kidney epithelial cell line derived from African green monkeys). During the current pandemic, both companies are set to gain substantial commercial windfalls from using this faster production technology for H1N1 vaccine production. Smaller players, including Protein Sciences and Novavax, are developing production systems in insect cells based on the baculovirus system. Other strategies in earlier stages of development include the use of bacterial and plant expression systems.

Outlook

The current influenza A (H1N1) pandemic has boosted vaccine stockpiling contracts. Established manufacturers, particularly Novartis and GSK, are likely to draw the largest commercial benefit. Besides its direct impact on pandemic vaccine sales, H1N1 will also influence the future development of the seasonal influenza vaccines market. We think that the most likely outcome for future sales development will be a transient boost triggered by the current pandemic. Seasonal influenza vaccine uptake will increase considerably over the next two influenza seasons, with sales figures rising to $4 billion by 2010–2011 across the seven major markets. Once the pandemic has passed, however, we expect a period of stagnation caused by declining seasonal vaccination coverage in most population groups (FIG. 3). By 2018–2019, the seasonal influenza vaccine market size could reach $5 billion across the seven major markets, driven by further extensions of vaccination recommendations[1]. Sanofi Pasteur, which was market leader in 2008 with global influenza vaccine sales exceeding $1 billion[5], will maintain its top position; however, we think that GSK and Novartis will increase their share owing to their competitiveness in new technologies such as adjuvants and cell-based manufacturing.

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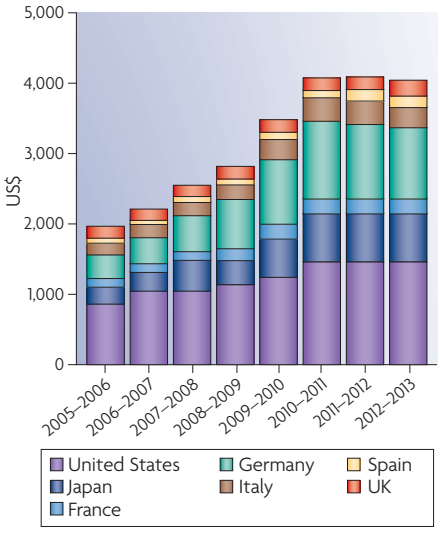

Figure 3 | **Seasonal influenza vaccine market size and forecast.** Data for the seven major markets for the influenza seasons 2005/2006–2018/2019. Data from REF. 1.

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