# MARKETSPACE

# Growth drivers and resistors of the influenza market: The importance of cell culture flu

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## Abstract

Following flu vaccine manufacturing and supply issues in the USA and the global threat of an avian flu pandemic, the flu market is attracting considerable interest. This market was worth approximately US$1.1bn in 2004, and it is expected to grow to US$3.1bn by 2010: a compound annual growth rate of 17.1 per cent. To capitalise on this explosive growth rate, flu vaccine manufacturers should position their products towards combating the avian flu pandemic threat. However, there are a number of challenges associated with producing avian flu vaccines using egg-based manufacture systems: currently the dominant vaccine production technique. In the current paper, Datamonitor's infectious disease analysis team argues the case for the potential transformation of the flu market by governmental initiatives, and specifically on the role of these initiatives in driving cell culture flu manufacture as part of pandemic preparedness plans.

## INTRODUCTION

Influenza (flu) is a contagious viral infection that primarily affects the upper respiratory tract. More than 20 per cent of the population get infected every year,[1] with the elderly or very young most affected. It is estimated that there are between 3 and 5 million annual cases of severe flu, which result in 250,000–500,000 deaths per year globally.[2] The cost of a flu pandemic to the US economy alone is placed at US$71–167bn annually.[3]

The most effective way to minimise the impact of flu on society, and the most cost-effective option, is through the use of vaccination programmes.[1] Additionally, antivirals such as Roche/Gilead's Tamiflu (oseltamivir) and GSK's Relenza (zanamivir) can be used for treating flu, although there may be resistance-related issues associated with the over-use of antiviral products.[4] For example, a recent study indicated that neuraminase mutations resulting in Tamiflu resistance were found in 18 per cent of patients.[5]

There are two main types of flu vaccine: (i) TIVs (trivalent inactivated vaccines) composed of two A strains (H1N1 and H3N2) and one B virus (surface or split virion);[6] and (ii) LAIV (live attenuated vaccine).[7] The effectiveness of a vaccine depends on the age and immunocompetence of the vaccine recipient, together with the ability to match protection by the yearly vaccine with the most prevalent circulating viral strain.

## KEY PLAYERS IN THE FLU VACCINE MARKET

There are approximately 18 flu vaccine manufacturers, of which 14 produce 90 per cent of the supply (Center for Disease Control; CDC). Key flu vaccine products are reviewed in Table 1 and include Sanofi-Aventis's Fluzone, Chiron's flu vaccine franchise (including Fluvirin, Fluad, Agrippal and Begrivac), GlaxoSmithKline's Fluarix, Berna Biotech's Inflexal, MedImmune's Flumist and Solvay's Influvac. Although many of these products are poorly differentiated from each other, Fluzone is the market leader, owing to the strong market presence of Sanofi-Aventis and the

**Table 1:** Key marketed flu vaccines

| Product | Company | Launch year | Approved age groups | Method of production | Global 2004 sales in US$m (2003 sales) |
|---|---|---|---|---|---|
| Fluzone | Aventis Pasteur | 1970 | >6 months | Egg-based | 613 (461) |
| Flu vaccine franchise (including Fluvirin, Fluad, Agrippal and Begrivac) | Chiron | 1977* | >4 years* | Egg-based | 153*** (332) |
| Fluarix | GSK | 1996 | >36 months | Egg-based | 137 (99) |
| Inflexal | Berna Biotech | 1997 | >2 years | Egg-based | 40 (28) |
| Flumist | MedImmune (formerly with Wyeth) | 2003 | 5-49 years | Egg-based | 48 (0) |
| Influvac | Solvay | 1983** | >6 months | Egg-based | 89 (79) |

*: these details refer to Fluvirin; **: Influvac was first launched in the 1950s as a whole virus vaccine, and was switched to a subunit vaccine in 1983; ***: of these total sales, Fluvirin generated only US$2m in 2004
Source: Datamonitor, company-reported data, vaccine product labels

product's approval for a wide range of patient age-groups, with Chiron's Fluvirin in second place in the valuable US market. Both products dominate the US market, facing little competition because of the perception that the flu vaccine market was low value. However, Chiron's inability to supply the USA with flu vaccine, resulting from the UK's suspension of the company's flu vaccine licence in October 2004, highlighted the fragility of the US vaccine supply system. As a result, a number of vaccines are now targeting US approval, including GSK's Fluarix, which was recently approved by the FDA in August 2005, although only for adults aged 18 or over.

FluMist is differentiated by its intranasal mode of delivery: a characteristic that was at one stage predicted to change the dynamics of the flu vaccine market. However, the product's high price, the necessity for it to be stored frozen, and its restriction to use on healthy individuals contributed to weak first-year sales, and resulted in the loss of MedImmune's co-development partner, Wyeth, in April 2004. Meanwhile, vaccines such as Fluarix and Inflexal have historically suffered from a lack of supply and/or presence in the dominant US market and owing to their poor differentiation from other vaccines, rely on competing on price to drive sales.

## DRIVERS AND RESISTORS OF FLU VACCINE MARKET GROWTH

As shown in Figure 1, the flu vaccine market is expected to rise from US$1.1bn in 2004 to US$3.1bn by 2010: a strong compound annual growth rate of 17.1 per cent.

A number of public sector-related factors are set to continue to drive this strong growth of the flu vaccine market, including health priorities established by governmental policy. Examples of these priorities include the recommendations to widen the age range of people receiving the vaccine, such as the recommendation made by the Advisory Committee on Immunization Practices to immunise children of 6–23 months, for the 2002–2003 flu season.[8] Also driving growth is the CDC's goal to achieve 90 per cent influenza and pneumoccal vaccination rates for the US population aged 65 and older by 2010. Geographically, the US market is considered attractive because vaccines normally command higher prices, and this market has the greatest scope for price growth. However, with a current contribution of only 15 per cent of the total flu market, the Japanese

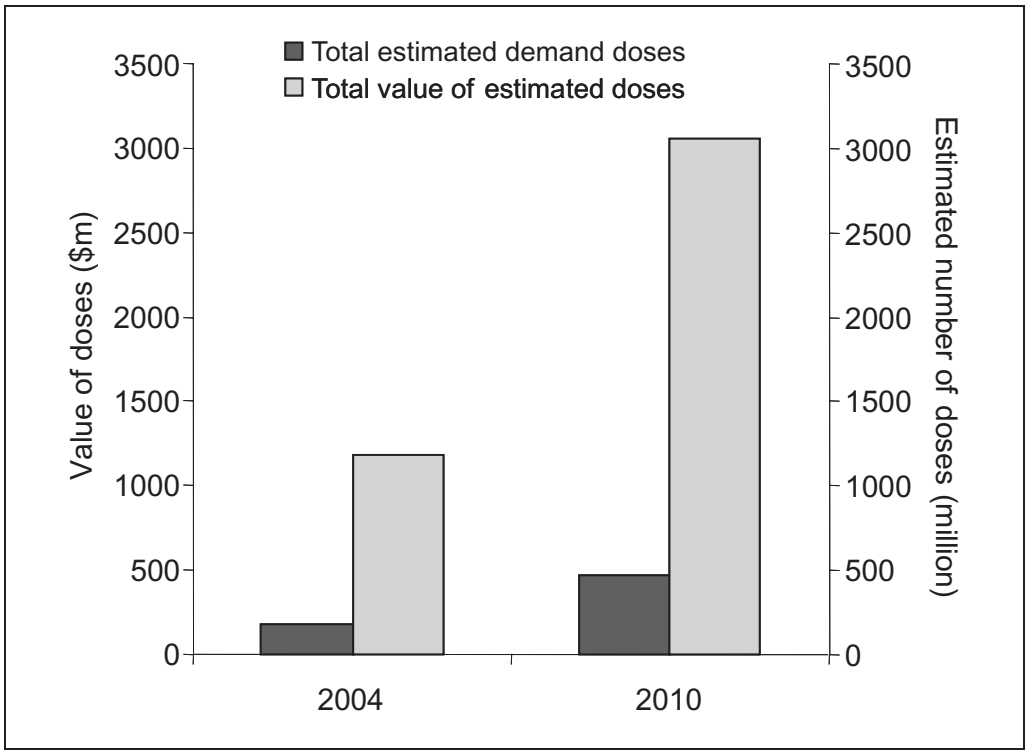


**Figure 1:** Estimated number of doses and their value in the seven major markets (USA, Japan, Germany, UK, France, Italy, Spain), 2004–2010. Note: total estimated value of doses is based on a cost of US$6.50 per dose
Source: Datamonitor

market represents a key growth opportunity.

## VACCINE PRODUCTION: EGG-BASED VERSUS CELL CULTURE FLU

Flu pandemics are characterised by their unpredictability of emergence, the degree of severity, and the effectiveness of influenza epidemic interventions.[9] The biggest concern with a pandemic is inadequate product supply capacity, owing to the inflexibility and poor responsiveness of current egg-based vaccine manufacture systems. The logistics of egg preparation means that approximately a year is needed for production, and there is concern over the availability of a sufficient quantity of eggs outside the planned period.[9] The potential impact of this inflexibility was recently highlighted when contamination issues forced British regulators to revoke Chiron's licence to manufacture flu vaccines in 2004, which halved the USA's supply of vaccines. Furthermore, provisions for the annual influenza epidemics cannot necessarily be extrapolated to a pandemic. The low adaptability of egg-based production process heightens risk of vaccine mismatch with circulating strain. If there is an avian influenza pandemic, then there will be significant issues relating to sourcing the chickens that supply the eggs. Furthermore, H5N1, the most likely pandemic strain, cannot be grown in embryonated eggs.[10] For these reasons, pandemic plans formulated by the UK and USA mention cell culture flu as a key component of future strategy, owing to the scope for catering for surge capacity,[11,12] and the WHO indicates that the use of cell culture is a key solution to longer-term vaccine manufacture.[13]

Restricting the development of cell culture flu is the high level of investment associated with establishing facilities and running clinical trials, and the low level of corporate funding for flu vaccines. Egg-based vaccines are familiar, have a good safety profile, and are cheap (at around US$6–7 per dose). The introduction of a higher price product, even if it is differentiated by an improved delivery

profile or efficacy, may struggle to gain market share. Indeed, the weak first-year sales of FluMist (which had a high price point) highlight the importance of cost in this market. Therefore, existing vaccine manufacturers who develop cell culture vaccines will have to depend on generating a profit by sales volume, rather than profit margin resulting from positioning the product at a high price point: a risky strategy without strong distribution channels in the USA. Therefore, existing vaccine manufacturers without a strong US presence may see little incentive to invest in cell culture vaccines. However, new entrants into the flu vaccine market are more likely to choose the cell culture approach (particularly if they have access to fermentation facilities) given that building an egg-based system is a significant impediment to market entrance.

Another factor likely to restrict cell culture vaccine sales is the concern that a downstream process similar to the egg-based process will be used to create a method based on cell culture, resulting in cellular contaminants in the final product. Therefore, there is significant regulatory concern, since some cell lines linked with tumorigenicity are currently being used in the development and manufacture of cell culture flu vaccines. There are alternatives to transitioning towards cell culture. These strategies include the construction of new plants, adjuvantation of existing vaccines, candidate libraries of vaccine prototypes and wider use of antivirals. Such strategies are likely to play an increasingly significant role over the short to medium term.

## CELL CULTURE FLU: KEY PLAYERS AND MARKET DYNAMICS

Influenza viruses can replicate in a variety of primary, diploid and continuous cell cultures; however, the susceptibility of most cell lines to flu virus infection is low.[14] A range of companies are developing cell culture vaccines, including Chiron, Crucell, Baxter, ID Biomedical, MedImmune and Solvay. These companies are basing their production process on three main cell lines: Madin Darby Canine Kidney (MDCK) cells, Vero (African green monkey kidney cells) and PER.C6 (human embryonic retinal cells). Of these, viral yield is believed to be considerably lower in Vero cells[15] and only the MDCK cell line is thought to produce the virus at levels comparable with eggs. MDCK cells are the WHO's preferred host for influenza;[16] however, there is regulatory concern related to the risk of tumorigenicity with this cell line. The Vero cell line has a good safety profile in the vaccine market, because it has already been used in the development of a number of vaccines, including West Nile virus, polio and rabies. However, there is a concern that the yield from Vero cells is so low that the vaccine is not as purified as much as would be normal for an egg-grown vaccine. Crucell's PER.C6 is a relatively late entrant into the cell culture vaccine market, and viral yield is believed to be lower in these cells than MDCK. However, it does have a powerful sponsor in the form of Sanofi-Aventis, who received a series of significant funding rounds from the HHS (eg US$97m in April 2005) to develop flu vaccines using this cell line during 2005.

## SUMMARY

The potential impact of a flu pandemic is critical in shaping the future growth of the flu vaccine market. Issues with inflexibility and poor responsiveness will compromise the production of vaccines using egg-based systems during a flu pandemic, particularly if it is avian in origin. There are a number of advantages with cell culture flu vaccines, as reviewed in Figure 2. However, the low level of corporate funding, the high costs associated with establishing facilities and the highly cost-conscious nature of the flu vaccine market will restrict the growth of

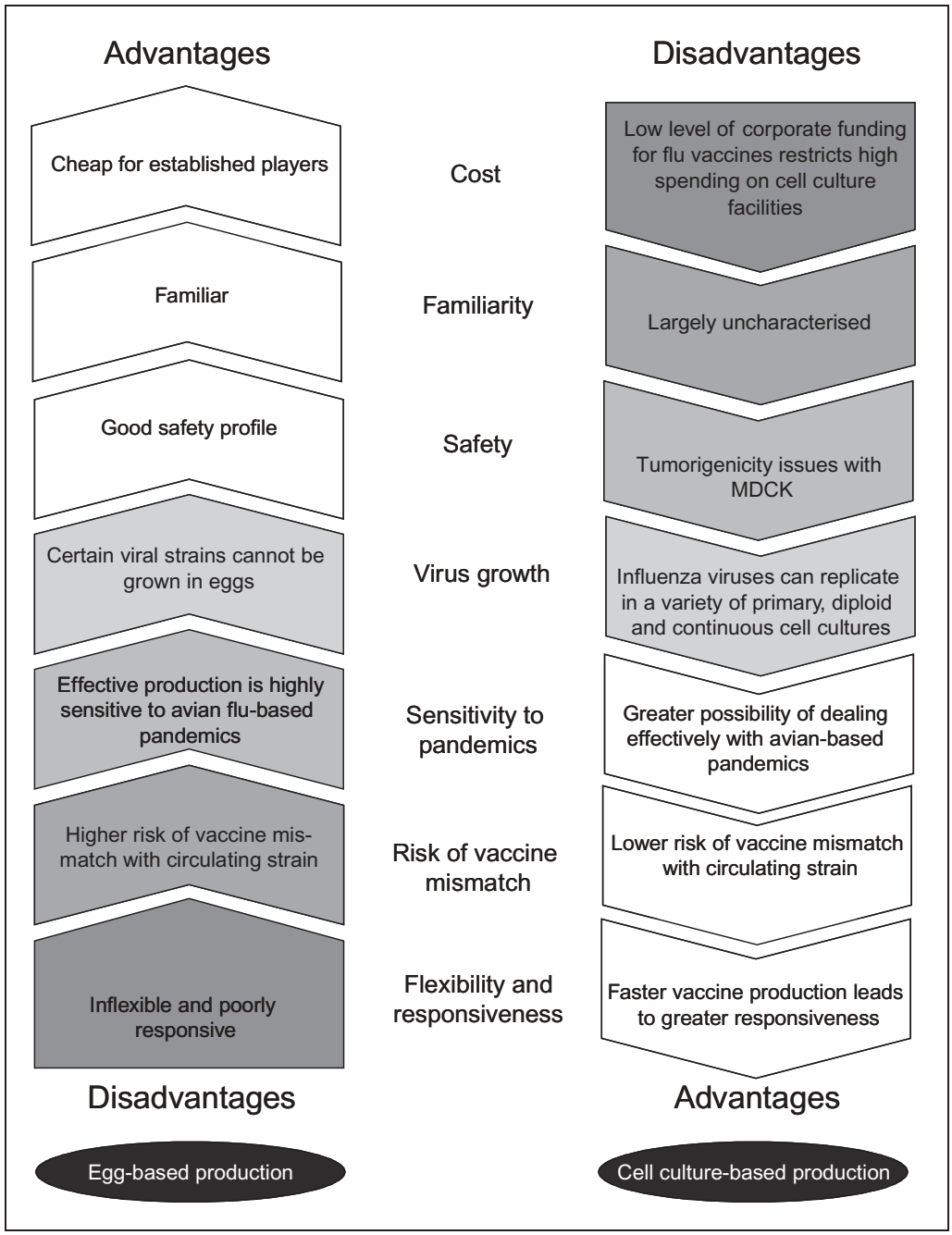


**Figure 2:** Egg-based vaccine production versus cell culture-based production
Source: Datamonitor

cell culture flu vaccines until a pandemic strikes. Indeed, it is estimated that only 20 million doses of cell culture-based flu vaccine will be ready by 2010. This is unlikely to be of much use, given that 500 million doses in the seven major markets (USA, Japan, Germany, UK, France, Italy, Spain) are likely to be required by then. It therefore seems likely that alternative strategies detailed above (eg the adjuvantation of existing vaccines) will play an increasingly important role over the short to medium term, until a pandemic takes place, after which governmental initiatives will power strong market growth of cell culture flu vaccines.



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