Acambis and ChimeriVax-JE™: increased confidence at Sanofi

LONDON, UK----25 March 2008----ExpertREACT. UK/US based vaccine player Acambis announced last week that it had extended its licensing agreement of ChimeriVax-JE™ with Sanofi Pasteur. The new deal allows Sanofi the marketing rights to the one-shot Japanese Encephalitis vaccine in India. **VacZine Analytics** believes the move signals increased Sanofi confidence in the Acambis product and now an overall lower risk as both sides to push for a stronger presence in the important SE Asia region.

ChimeriVax-JE™ is a one-shot "live" vaccine in Phase III clinical testing designed to prevent a potentially fatal infection caused by the mosquito bourne *flavivirus* Japanese Encephalitis (JEV). Approximately 3 billion people live in areas where JEV is endemic with an estimated 10,000 deaths from the infection and 30-50,000 people contracting the disease each year (CDC figures). There is no specific treatment for JE and children under 15 yrs are principally affected. Because many clinically similar diseases are endemic in rural Asia, it is widely believed that the true extent of the JE is underestimated due to significant underreporting.

Vaccines to prevent JE infection have been shown to dramatically lessen disease morbidity/mortality and for many years have been a healthcare priority in SE Asia. Numerous nations operate routine vaccination with children normally vaccinated after the age of one with two doses around 4 weeks apart and boosters thereafter until age 15. JE vaccines are normally composed of "killed" inactivated JE virus propagated in murine tissue similar to the vaccine first produced by the Research Institute of Osaka University (Biken) first licensed in Japan in the early 1950s and approved by the WHO. China also has a domestic supply of JE vaccines such as the cell culture produced live-attenuated vaccine produced by the Chengdu Institute (SA-14-14-2) (1).

After early investigational use, the Biken vaccine first became available in the US after licensure in 1982. The product known as JE VAX, was distributed by Sanofi Pasteur and established itself as low volume niche vaccine for primarily military and travel use. It is estimated that approximately 120,000 doses of JE VAX at peak were being used each year for the US market with the majority of doses (~75%) being reserved for the US military (2) who had a contract with Sanofi Pasteur to build a strategic vaccine stockpile ensuring troops were protected in endemic regions. In Europe, JE VAX was not approved but available to travellers on a named patient basis. JE VAX is composed of 3 doses (0, 7 and 30 days) and in the private travellers market commanded a relatively high price of US$200-300 per course.

In recent years there has been a drive to produce second-generation JE vaccines. The drive has been due to two main reasons. The first is that in 2005 Japan based Biken stopped producing JE VAX for the export market leaving Sanofi with a stockpile (est 5 million doses peak) to continue to meet worldwide demand (shelf life permitting). Biken, like many other producers envisaged a switch to cell-culture produced JE vaccines and currently have a Phase III candidate targetting the domestic pediatric market (predicted launch 2009). Because of dwindling supply, other companies such as Acambis and Novartis Vaccines (Ixiaro) also recognized the importance in meeting global demand. Novartis Vaccines accessed the marketing rights to Ixiaro from Austrian-based Intercell AG in 2006.

The other key driver for newer JE vaccines has been the perceived need for a fasting acting product with an enhanced safety profile. Although JE VAX is effective, its three-dose profile is not optimum for compliance neither in the travellers market nor in emergency campaigns during outbreak situations. In clinical studies to date the Acambis candidate achieved non-inferior JEV antibody seroconversion rates in comparison to JE VAX after 1 dose (3).

JE VAX also has a high-perceived level of reactogenicity, mainly due to residual matter left over from its manufacturing method. For example, JEV vaccinees are recommended to remain within access of healthcare personnel around 10 days after vaccination (JE VAX package insert). Moreover, in 2005, the Japanese healthcare authorities withdrew JE mandatory vaccination after concerning adverse events in the pediatric population.

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In commercial terms, a large number of people are potentially targets for JEV vaccination. It is estimated that 1 billion people live in endemic countries below the age of 15 yrs and each year around 14 million visits are made to JE endemic areas (WTO Figures). Within years to come many more Western travellers are expected to visit the region (est 25 million, 2017) potentially increasing the current market.

Despite the large target population numbers and withdrawal of JE VAX, it is widely believed that a new JE vaccine is not a blockbuster opportunity. Indeed, its remains difficult to accurately predict the true commercial value of the Acambis/Sanofi and Novartis candidates. **VacZine Analytics** in line with other estimates foresees revenue figures ranging from $100-300m per annum. In the Western travellers market, key limitations are the low penetration rate of JE vaccines (est 1-3% of travellers) due to low perceived risk, high price and low physician awareness. Most travellers meeting the CDC "at-risk" criteria for staying in rural areas longer than one-month are budget conscious back-packers who might preferentially reserve funds for other vaccines such as Hepatitis A and Hepatitis B. In endemic countries, although potential volumes are high, the price per dose of JEV vaccines in the public sector is very low (~$1 per dose or less). Although there is an emerging private market willing to pay a premium for a Western product, JE pricing thresholds are far below US/EU levels.

Looking at the current situation it is emerging that Sanofi/Acambis are prioritizing the endemic market(s) for their product leaving the Western travellers market to Novartis who have already filed in the US and EU (4). Sanofi have not yet exercised the US option to the Acambis product probably due to the cost of building an appropriate safety database required for FDA licensure. Novartis is expected to also target the endemic regions after initiating a Phase II pediatric trial in India but are behind Sanofi/Acambis. Many believe ChimeriVax-JE™ is more suitable to endemic regions because it is a single dose, likely to require less boosting and may have a lower production cost.

In summary the switch from Bharat Biotech to Sanofi for commercialization of ChimeriVax-JE™ in India is a well-deserved vote of confidence in the Acambis product. It could also highlight undisclosed issues with the Bharat relationship. **VaZine Analytics** believes further down the line there is foreseeable synergy with the ChimeriVax-Dengue™ product also being developed by the partnership. However, unlike Dengue for which no vaccine is available, in both the West and the endemic markets both Sanofi and Novartis are likely to spend big on promotion to convince everybody there is demand for a new higher priced JE vaccine.

References:

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(3) Press release: Acambis' JE vaccine meets and exceeds primary endpoint in pivotal Phase 3 efficacy trial. Available at http://www.acambis.co.uk/default.asp?id=1839. Accessed March 2008.

(4) Press release: Intercell finalizes submission of US BLA to FDA For Licensure of Japanese Encephalitis Vaccine. Available at: http://www.intercell.com/ShowArticle.wa?seIDM=5a5ed97f-d9f2-4b35-b7b6-97fe496e987d&seIDD=98347B08-477E-4BEC-8379-082629E47A8A. Accessed March 2008.

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