GSK and Cervarix - is AS04 a double-edged sword?

LONDON, UK----19 December 2007----Earlier this week it was announced that Cervarix, GlaxoSmithKline's HPV bivalent vaccine, would be delayed in reaching the key US market due to issuance of an FDA complete response letter. The news gives a lengthy first-mover advantage to rival Merck's Gardasil (quadrivalent vaccine), which was FDA approved in June 2006 and has already recorded sales of over $1bn by the end of Q3 2007. Looking forward **VacZine Analytics** discusses this event and how it may form an important case study with regard to the caution of US regulators to new vaccine adjuvant systems.

On the 17th December the US FDA issued a complete response letter to GSK regarding its submission of Cervarix, a recombinant vaccine containing human papillomavirus vaccine types 16 and 18. The vaccine also contains the novel adjuvant AS04 which is a combination of standard aluminium hydroxide and the new component, monophospholipid A (MPL). MPL is a derivative of the lipid A molecule found in gram-negative bacteria and is considered one of the most potent immune system stimulants known. GSK fully acquired the MPL adjuvant from Corixa in April 2005 after previously collaborating with the Seattle based company on Bexxar (Tositumomab) – the monoclonal antibody for non-Hodgkin's lymphoma and other cancer vaccine immunotherapy programs.

A significant number of programs within GSK's vaccine R&D pipeline now contain the MPL adjuvant (estimated >15). In some cases MPL is coupled with QS21 another novel adjuvant derived from a variety of tree bark and developed by Massachusetts based Antigenics. Notable programs containing MPL in the late stages of development are Mosquarix and Simplirix – the candidate vaccines for malaria and herpes simplex virus (HSV) respectively. In previous research **VacZine Analytics** has drawn attention to the enthusiasm of the vaccine industry to acquire and then commercialize new adjuvant systems **(ExpertREACT – 19 November 2007).**

Although GSK has not given exact details regarding the FDA feedback on Cervarix, it is widely believed that one major concern of the FDA might be the novel AS04 adjuvant system. AS04 has never been approved in the US but has previously been available in another GSK product, Fendrix (HBV vaccine) that was approved in the EU in 2005. The FDA's decision is a setback because GSK won EU approval of Cervarix in September of this year, is testing the product for the Japanese market and applying for WHO prequalification status. During the clinical development of Cervarix, no significant safety signals were observed although it is noteworthy that a far higher number (est 13 million doses) of Merck's Gardasil have already been administered to young females forming a large "real use" safety database.

Because GSK lag behind Merck & Co in the US market for HPV vaccines the company has made great efforts to communicate the advantages of AS04 in Cervarix, which to many has a less favourable profile because of its bivalent rather than quadrivalent antigen format. In company presentations GSK has put forward the "stronger and longer" message when describing the antibody response induced by the vaccine. This response may lessen the need for boosting later in life and allow the company to further develop a cost-saving argument. Moreover, according to preliminary data in the HPV-008 study, GSK state that AS04 might also enhance cross-protection of Cervarix against other oncogenic HPV types namely, HPV-31, 45 and 52. Cross-protection might be another potential avenue of product differentiation, again provided to some extent by AS04.

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With hindsight it is easy to put forward the argument that the first significant US launch with AS04 should have been an elderly vaccine (>65yrs) where long-term safety concerns are not as critical as those in young adolescent women prior to childbearing. Furthermore, adolescents are increasingly targetted to receiving more vaccinations such as those for meningitis and pertussis boosters. This dynamic might draw attention to the lack of significant concomitant administration data provided so far with GSK's Cervarix.

Aside from the potential concerns regarding the adjuvant system in Cervarix, other observers have drawn attention to the interim analysis of the pivotal Phase III PATRICIA study. With Gardisil Merck & Co have demonstrated vaccine efficacy against HPV 16 and 18 individually whereas GSK did not show statistical significance of Cervarix against HPV 18 alone due to a low event number (CIN lesions) in the study to date.

Regardless of the FDA's exact reasons for delaying Cervarix, this event is not only an issue for GSK but also a signal to all manufacturers. Testing novel adjuvant systems for the US market will require a safe and steady approach.

For more information about this research please visit www.vacZine-analytics.com
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About VacZine Analytics:
VacZine Analytics is a new strategic research agency based in the United Kingdom. Its aim is to provide disease and commercial analysis for the vaccine industry and help build the case for developing new vaccines.