Briefing Document

Vaccines and Related Biologicals Advisory Committee
Meeting of February 18-19, 2008

Novartis Vaccine and Diagnostics, Inc.
350 Massachusetts Ave.
Cambridge, MA 02139

Novartis Vaccines and Diagnostics, Inc. will present information at the Vaccines and Related Biologicals Advisory Committee meeting on vaccine policy issues and the development of pandemic and pre-pandemic avian influenza vaccines for the pediatric population.

As a global industry leader in pandemic influenza research, development and production, Novartis Vaccines and Diagnostics, Inc. supports influenza vaccine development in support of national governments global influenza pandemic preparedness strategies to minimize morbidity, mortality, health-system burden, economic losses, and other impacts of an influenza pandemic. Specific vaccine-based pandemic strategies that we aim to support with our research and development programs include:

- stockpiling of candidate pandemic vaccines for immunizations following the declaration of a pandemic
- making pre-pandemic vaccine available to governments and supranational organizations prior to any declaration of a pandemic for use in targeted populations, as aligned with their pandemic preparedness plans
- continued enhancement of vaccine surge production capacity

These policies are consistent with the concept of priming individuals in targeted populations with a dose of the pre-pandemic vaccine, to be followed with a booster dose of a vaccine that matches the pandemic strain after a pandemic is declared. Novartis also supports the concept of licensing a pre-pandemic vaccine for public use, thereby providing individuals with an option to obtain priming and booster doses of pre-pandemic vaccine if they voluntarily elect to receive the vaccine as a preventative measure in a pre-pandemic setting.

Vaccine safety and immunogenicity will need to be established with a pre-pandemic vaccine, but vaccine effectiveness and more extensive safety data can only be established once the vaccine is used widely, in a pandemic setting. Novartis acknowledges that there will be challenges in acquiring safety and effectiveness data during a pandemic. We will work with the FDA and other national health authorities to devise methodology for effectiveness and safety data collection in advance of a pandemic.

Experts question the timely availability of influenza vaccines during a pandemic. Therefore, Novartis believes that pandemic preparedness should also include pre-

pandemic vaccine solutions. Novartis' candidate pre-pandemic vaccine contains the commercially used adjuvant MF59™, and has demonstrated immunogenicity in children through elderly, elicits broad cross reactivity, the ability to induce rapid cross reactive immune response up to 6 years post-priming, and a demonstrated safely profile in adults and children. This candidate pre-pandemic vaccine with MF59™ provides an opportunity to prepare for an influenza pandemic by proactively immunizing individuals.

All age groups have been affected by death and disease during the past pandemics. Any pre-pandemic or pandemic influenza vaccine development program has to generate sufficient data that will enable health authorities to flexibly focusing their immunization campaigns on their most important population segment. This will require a step-wise development program that generates data beginning with healthy adults through elderly to the most vulnerable age groups (adolescent, children, toddlers). Adjuvants are required to increase immunogenicity of inactivated influenza vaccines and thus reduce antigen needs. This is especially important because of the limited production capacity relative to immunization needs for potentially the entire US population.

Although Novartis Vaccines and Diagnostics already markets an MF59™ adjuvanted seasonal influenza vaccine in Europe (Fluad®, more than 40 million doses distributed for use in the elderly since 1997), we have nonetheless adopted a careful age group approach with our candidate pre-pandemic avian influenza vaccine, Aflunov™. We first initiated extensive safety trials in healthy adults and elderly, after which we conducted safety and immunogenicity studies in adolescents and children down to 6 months of age. The evaluation of Aflunov™ in children was conducted in line with the EU guideline for development of pandemic vaccines. These studies were successfully concluded in Finland and the data are being prepared for rapid publication. It is noteworthy that Aflunov studies in adults evaluated different strains with pandemic potential, including H5N3, H9N2, and H5N1 Clades 1 and 2.

The design of the Aflunov™ program took into account several key existing datasets:

- the extensive post-marketing safety data from more than 10 years commercial use of the Novartis adjuvant MF59™ in its EU licensed seasonal influenza vaccine Fluad® (in elderly ≥65 years of age),
- the comprehensive databank from clinical studies with the MF59™ adjuvant in more than 33,000 subjects from all age groups of which almost 26,000 subjects were exposed to MF59™, and with various antigens in addition to influenza (such as HIV, Hepatitis B, Hepatitis C, cytomegalovirus),
- and specific results from the recent testing of MF59™ with seasonal influenza antigens in children 6 months to 18 years of age.

The pharmacovigilance data from commercial use of MF59™ in Fluad® since 1997 and data from subjects enrolled in clinical trials that utilized the MF59™ adjuvant (influenza and all other antigens) were compiled into a Biologics Master File that was recently submitted to FDA for their review.

Novartis is committed to the development and licensure of pandemic and pre-pandemic vaccines for all populations, including children. The candidate vaccine that was developed, Aflunov™, will be submitted for approval in the US. The MF59™ adjuvant contained in Aflunov™ was evaluated in extensive clinical studies with multiple antigens and in multiple age groups, including children. The inclusion of MF59™ adjuvant in a pandemic and pre-pandemic vaccine allows for use of lower antigen doses, elicits broad cross reactivity against different avian influenza viruses, and induces a rapid cross reactive immune response up to 6 years post-priming.