



**Written Testimony Submitted to
Congress of the United States
House of Representatives
Committee on Energy and Commerce
Subcommittee on Health and
Subcommittee on Oversight and Investigations**

Joint Hearing Regarding Vaccine Availability, Production and Distribution

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Submitted by:

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on behalf of

NOVARTIS VACCINES AND DIAGNOSTICS, INC.

Mr. Chairman, Members of the Committee, thank you for the opportunity to participate in today's joint hearing to examine the current state of H1N1 vaccine availability and the next steps in production and distribution efforts. I am Dr. Vas Narasimhan, President of Novartis Vaccines USA, and Head of Novartis Vaccines North America.

Novartis Vaccines welcomes the opportunity to provide perspective on our efforts to address the public health challenges posed by H1N1, our scientific contributions to vaccine development and pandemic preparedness and our long-standing partnership with the U.S. Government to help protect the public health of the United States. From the outset of this year's pandemic we and the U.S. Government have worked together toward the common goal of producing as many safe and effective vaccine doses as soon as possible, despite the challenge of a rapidly evolving and uncertain situation. We appreciate the impact that this pandemic is having on our population, including children, pregnant women, and high risk groups throughout the country. To address the public health challenges of H1N1, we have dedicated a large portion of our organization's resources since May to supporting the global response.

Novartis Vaccines continues to do everything possible to maximize supply of safe and effective vaccine as soon as possible based on the direction of the U.S. Government. I am pleased to report to you that Novartis Vaccines is currently on track with our H1N1 supply to the United States, despite the many challenges we have encountered along the way. We understand that the American people expected more vaccine earlier. However, we believe that when taken into full context this historic public-private partnership to produce, test, and deliver a safe and effective H1N1 vaccine to the U.S. has been a remarkable success given all the challenges and compressed timelines we have faced. Novartis Vaccines is committed to working together with HHS to ensure today and in the future we achieve our shared goal of preventing every possible case of influenza in the United States.

I would like to begin today by providing some background on Novartis Vaccines and our pandemic preparedness efforts. I will focus my remarks on our efforts to support the U.S. Government's pandemic response and potential areas for future investment and improvement.

I. Overview of Novartis Vaccines

Novartis Vaccines and Diagnostics was created in 2006 through the acquisition of Chiron Corporation. We have over 5,300 employees globally, including almost 1,300 in the United States. Since 2006, Novartis Vaccines has invested and committed over \$1 billion to upgrade our vaccines business infrastructure and for pandemic vaccine research and development. Our global headquarters is located in Cambridge Massachusetts, where Novartis Vaccines has a significant administration presence and a newly established research center dedicated to advancing innovative vaccines research in virology. The company also has a significant presence in Emeryville, California, the site of our global Diagnostics headquarters. In addition to our U.S. sites, we have manufacturing, research and clinical sites in England, Germany, Netherlands, Italy and India. Construction of our U.S.-based flu cell culture manufacturing site, the first of its kind in the U.S., was initiated in 2007 in Holly Springs, North Carolina and is currently nearing completion. By the end of November, this site will employ approximately 200

people and once fully-operational, it will employ approximately 350-400 people. A recent photo of this facility is attached as an Annex to this Testimony.

Novartis Vaccines is dedicated to preventing disease and addressing global public health needs. The company has a broad portfolio of approved vaccines globally and seventy percent of the vaccines we manufacture are supplied to the developing world. Novartis Vaccines continues to work towards introducing new important vaccine products to address unmet needs, with 17 new vaccines currently under development.

II. Novartis Influenza Vaccines and Pandemic Preparedness

Overview of Influenza Market

Since the circulating influenza strains change from year to year, influenza vaccine is the only FDA-approved drug or vaccine which is made anew from start to finish every year. Manufacturers commence vaccine manufacturing at risk prior to the Food and Drug Administration's (FDA) selection of the virus strains, in February, for the following fall's immunization season. Manufacturers receive the seed strains from the regulatory authorities so that there is consistency across manufacturers of the product provided to the market. From February-September each year, manufacturers manage the complex biological manufacturing process and work closely with regulatory authorities to successfully bring influenza vaccines through clinical development, manufacturing and regulatory approval.

Over the past three years, seasonal influenza vaccine manufacturers have faced an oversupplied and challenging marketplace. Immunization rates of the American public only rose 1% from 2007 to what is anticipated in 2009, from approximately 107 million to 110 million vaccinations. This immunization rate falls far short of the U.S. Public Health Service recommended level of 220 million Americans. As a result, the market has been oversupplied and prices have dropped by 30-40% creating a strong disincentive for manufacturers to maximize or even maintain current production capacity for the U.S. market.

Novartis Influenza Vaccines

Novartis Vaccines and its predecessor companies have been manufacturing influenza vaccines for the U.S. and the rest of the world for over 25 years. We are a leading innovator in the development of improved influenza vaccines through new technologies and novel adjuvants. Globally Novartis Vaccines has five approved seasonal vaccines, including adjuvanted and cell culture vaccines in Europe. We also have three approved H1N1 vaccines, including adjuvanted egg and cell culture based vaccines in Europe. We have over five large ongoing influenza development programs for the U.S. market.

Despite the trends in seasonal vaccine supply and demand, since 2006 Novartis Vaccines has established or improved our influenza manufacturing sites, in large part to address the challenge of global pandemic preparation. There are two investments that address U.S. influenza vaccines: our \$200 million recently approved Site 4 bulk manufacturing facility in Liverpool, England and

our investment in our flu cell culture (“FCC”) facility being constructed in Holly Springs, North Carolina with the support of HHS.

Proprietary MF59 Adjuvant

Novartis Vaccines has pioneered the study and use of influenza adjuvants over the past decade. MF59 is Novartis Vaccines' proprietary and patented adjuvant that is added to influenza vaccines to help stimulate the human body's immune response. In over 10 years of licensed use in Europe and experience in over 200,000 clinical trial subjects Novartis Vaccines has demonstrated the following benefits of adjuvantation:

- **Immunogenicity.** Adjuvanted vaccines produce higher immune response than unadjuvanted vaccines particularly in the elderly and young children;
- **Antigen Sparing.** Adjuvanted vaccines require a lower dose of antigen and have demonstrated the potential for a 2-4 fold expansion of vaccine supplies;
- **Cross-Protection.** Influenza viruses are constantly changing. Adjuvanted vaccines have show a higher likelihood of protecting against “drifted” and “heterotypic” changes in influenza strains;
- **Safety.** The safety of adjuvanted vaccines is comparable to unadjuvanted vaccines; and
- **Cross-Priming.** Adjuvanted vaccines have been shown to more broadly prime patients immune response (up to 7 years later) requiring fewer vaccinations to the newly circulating strain.

Outside of the U.S., in addition to adjuvanted seasonal flu vaccine, Novartis Vaccines is exclusively providing adjuvanted H1N1 vaccine. Our clinical data to date indicates that a single dose of adjuvanted vaccine with as low as 3.75ug of antigen meets the relevant regulatory criteria, compared to the 15ug dosage that we have manufactured for the American public to comply with regulatory requirements. We have been in discussions with the FDA since 2007 to license our MF59 adjuvanted prepandemic vaccine in the U.S. and in 2008 filed a Biologics Master File on MF59 to support this effort. However, currently no adjuvanted influenza vaccine is licensed in the U.S.

Cell Culture Vaccines

Novartis Vaccines has been a leader in developing and manufacturing influenza vaccine in cell cultures, and our flu cell culture product Optaflu was approved for use in Europe in 2007. Pioneered by Novartis Vaccines, flu cell culture manufacturing represents the first innovation in inactivated influenza vaccine production in over 50 years. It offers flexibility in the manufacturing process as the vaccine product is incubated using the tools of biotechnology rather than eggs. Cell culture-based vaccines provide three principle benefits: faster production, better matched vaccines, and no reliance on eggs. Our adjuvanted cell culture H1N1 vaccine was first produced in early June of this year, met all relevant regulatory criteria after extensive

clinical testing, and has been approved for use in Germany with other country approvals expected shortly.

We are presently working in partnership with the U.S. Government as part of its pandemic preparedness effort to develop this technology for the United States. Novartis Vaccines submitted a BLA to FDA for our cell based influenza vaccine in February 2009 and this submission contained all the required data for pivotal trials required by FDA guidelines. We withdrew the BLA at the request of FDA to incorporate data from an efficacy trial that agency officials were aware had been recently completed. Novartis Vaccines plans to resubmit this BLA once this data and data from other recently completed studies have been incorporated into the BLA. Prior to the 2009 H1N1 pandemic, Novartis Vaccines had prioritized this but we interrupted our efforts to dedicate critical personnel to H1N1 activities and, for this reason, we plan to re-focus on this BLA once these employees' H1N1 responsibilities permit.

III. HHS-Novartis Vaccines Pandemic Vaccine Partnership

Novartis Vaccines has been at the forefront of pandemic vaccine research, developing one of the first vaccines for H5N1 (commonly called avian flu) shortly after the strain was identified in 1997. For the past 8-9 years, pandemic preparedness has become a public health priority and the U.S. Government has provided global leadership in this effort.

In 2005, the United States Congress and the Administration took an unprecedented step to protect public health through the pandemic preparedness program which is now firmly established under the Biomedical Advanced Research and Development Authority (BARDA) located within the Department of Health and Human Services (HHS). Since 2005, Novartis Vaccines has established an extensive and highly productive collaboration with BARDA on pandemic preparedness, and we place the highest possible priority on working in partnership with the U.S. Government to address the United States' public health challenges.

Through this partnership, Novartis Vaccines is collaborating with HHS-BARDA on four major efforts: clinical development of flu cell culture technology, clinical development of antigen sparing (adjuvant) technology, production for pre-pandemic stockpile supply, and design, construction and operation of a flu cell culture production facility in the United States.

In January 2009, more than two years after beginning construction at our own expense, Novartis Vaccines was awarded a cost sharing contract for the construction of our U.S. flu cell culture facility in Holly Springs, North Carolina. At present, construction at the Holly Springs facility is near completion and Novartis Vaccines expects that the bulk facility will be licensed to provide cell culture-based vaccine for the 2013-2014 flu season. When fully operational, this facility will have the capacity to produce up to 50 million doses of seasonal flu vaccine and up to 150 million doses of adjuvanted pandemic vaccine for the United States within 6 months of the declaration of a pandemic.

IV. Novartis Vaccines 2009 US H1N1 Pandemic Response

With the above history as context, I would like to now turn to our current effort to respond to the 2009 H1N1 pandemic. As noted, over our 4 year partnership with the U.S. Government, Novartis Vaccines has worked closely with HHS on all aspects pandemic preparedness. As stated earlier, from the outset of this pandemic we have shared the common goal of producing as many safe and effective vaccine doses as soon as possible.

Novartis Investments in Vaccine Development and Production

This year, Novartis Vaccines undertook an unprecedented manufacturing effort to meet extraordinary demands created by the need for both seasonal and H1N1 pandemic vaccine in the United States. Novartis Vaccines has undertaken a number of these steps “at risk” to ensure no loss of time in development or supply. Novartis Vaccines is proud of what it has accomplished in responding to the challenges of the H1N1 pandemic. Some of these accomplishments are highlighted below:

- **U.S. H1N1 Clinical Development.** Novartis Vaccines developed both pilot and pivotal clinical trials for our H1N1 adjuvanted and unadjuvanted vaccine in almost 9,000 children, adults and elderly, ranging from 6 months to the elderly, including multiple trials being conducted under an FDA Treatment IND. The first clinical results were reported to HHS officials on September 4th and data on these trials is reported to HHS officials on an ongoing basis. These results helped inform government officials that a single 15ug dose was sufficient for most patients rather than two doses as previously thought. The FDA licensed our H1N1 vaccine for the U.S. market on September 15th. Novartis Vaccines also conducted clinical trials on an MF59 adjuvanted version of our U.S. H1N1 vaccine in anticipation of possible use of adjuvants in the U.S., which we had been preparing for though September.
- **H1N1 Vaccine Production.** H1N1 vaccine production in our Liverpool, England facility, which is dedicated exclusively to the U.S., was initiated in late July. We are currently operating our production facility with a very high level of quality and efficiency.
- **Opening of New Manufacturing Facilities.** Novartis Vaccines has expedited the completion of our new production facility in Liverpool, England, Site 4. This site was scheduled for opening at the end of second quarter of 2010, but we were able to accelerate validation of the facility by approximately 8 months to meet the volume of vaccine required by the U.S. Government. On October 9th, the FDA approved Site 4 and we are now manufacturing vaccine for the U.S. in this facility as well. Novartis Vaccines hired and trained 300 new employees in vaccine manufacturing and GMP so that the facility could be operational upon FDA approval.
- **Global Vaccine Development and Supply.** Novartis Vaccines has also successfully registered an adjuvanted egg based H1N1 vaccine (Focetria) and adjuvanted flu cell culture vaccine (Celtura) to supply countries across the globe. Clinical trials of our FCC

H1N1 vaccine, Celtura, were among the first clinical trials data available to government officials to determine formulation and dosage requirements of H1N1 vaccines.

- **Seasonal Vaccine Supply.** Novartis Vaccines delivered to the U.S. 27.1 million doses of seasonal influenza vaccine this season, only 400,000 doses less than we sold in the 2008-2009 influenza season. As of October 6th, we had completed our entire shipment of seasonal influenza vaccine to the United States, thereby providing more seasonal influenza vaccine earlier than at any other time in our history.

Voluntary Commitment of Liverpool Facility

Shortly after the declaration of the H1N1 pandemic, Novartis Vaccines worked closely with HHS to enter into an amendment to our pre-existing H5N1 supply agreement, entered into in September 2008, which provides a framework under which BARDA can purchase bulk antigen and adjuvant, as well as order storage and fill-finish of final vaccine to be delivered within 12 months of the order date.

At the same time we were agreeing to modify our pre-existing supply contracts, Novartis Vaccines faced the difficult decision of how to best utilize our Liverpool-based production facility. On the one hand, the U.S. Government had made clear that it would like the option to acquire all doses produced at the facility, but was not able at that time to commit to purchasing all doses produced in Liverpool nor to use adjuvanted vaccine. On the other hand, there was substantial global demand for vaccine and anticipated worldwide shortages, and Novartis Vaccines could likely quadruple our Liverpool dose output for global customers through adjuvantation. After consideration of our long-term partnership with the U.S. Government, Novartis Vaccines agreed to dedicate our entire Liverpool facility commercial production to U.S. vaccine needs. It is important to point out to the Committee that at the time Novartis Vaccines made this decision we had been in communication with more than 30 global governments to provide H1N1 vaccine. It would have been to our substantial business advantage to adjuvant our Liverpool supply to maximize global supply for an H1N1 vaccine (as another major manufacturer elected to do).

Seasonal flu production typically has a high degree of uncertainty due to many changing production variables. This uncertainty has been more extreme in this year's pandemic given the condensed production timeframe. At the time the U.S. Government ordered H1N1 vaccine, there were a number of uncertainties that Novartis Vaccines believed could impact production, including virus strain yield data, potency standards and formulation requirements to be utilized in H1N1 production. In light of these uncertainties, our contract with the U.S. Government included no fixed delivery dates by which any number of doses must be delivered. Instead, each task order includes conditional delivery dates that were based on certain stated assumptions and then current estimates applicable at the time of the order, and further, specific language was included regarding delivery timing that takes into account the unpredictable nature of vaccine manufacturing with a new and untested strain.

Accelerated H1N1 Production and Delivery

Novartis Vaccines has confronted multiple challenges and uncertainties in connection with our H1N1 pandemic efforts. To keep the government regularly informed, beginning in April, Novartis Vaccines has held weekly teleconference meetings with officials from four HHS agencies – Centers for Disease Control and Prevention (CDC), BARDA, FDA/CBER, and the National Institutes of Health (NIH) -- to review our supply forecasts and revised forecasts, clinical trial development, regulatory framework for approval of our H1N1 vaccine, production experiences with seed strains, reagent potency testing and shipping and distribution of vaccine. Novartis Vaccines has had to create and revise supply forecasts based on the most current information available to us, which have evolved over time. We have provided our forecasts to HHS on a weekly basis during these regular meetings, and they have reflected the impact on H1N1 vaccine supply of a number of issues unique to this year's pandemic, as described below:

- **Production Yields.** The initial seed virus supplied by government authorities resulted in extraordinarily low yields industry-wide in July when it was first used to produce H1N1 vaccine. For this reason, the initial government order for the vaccine assumed the 5 year average seasonal average yield and provides flexibility in delivery dates to account for the significant uncertainty that existed at the time. Yields did improve when a different seed virus was used but final yields were not known until FDA reagents and calibration values were available in August and then re-calculated in September. This led to changes in supply forecasts and stoppages in vaccine filling and ultimately affected the timetable for supply. In particular, the September re-calibration completed by regulators required Novartis Vaccines to stop fill-finishing activities for 8 days.
- **Egg Supply.** Orders for hens and eggs are generally placed 4-5 months prior to vaccine production to ensure healthy and appropriate sized flocks. Chicken farmers plan for this growth in farm size each Fall when contracts are engaged for egg supply for the following seasonal influenza season. For the H1N1 pandemic, egg supply for our Liverpool manufacturing site needed to be procured “out of season” in the late Spring and early Summer and contract farms needed to make unexpected adjustment in their flocks to provide eggs for 90 million doses of unplanned production, as well as to make adjustments in their planning to secure hens later in the Fall to assure an egg supply for the seasonal vaccine production required for the 2010-2011 influenza season.
- **Seasonal Production.** HHS prioritized seasonal influenza production, and at its request Novartis Vaccines completed seasonal vaccine production before switching to pandemic production. While this request helped to ensure that adequate supplies of seasonal vaccine were available early in the season, it left us less than 3 months to produce H1N1 vaccine prior to requested delivery.
- **Vaccine Formulation Decision.** Final direction on vaccine formulation became available in mid-August and final labeling in early September, delaying planning for executing fill and finish formulation and affecting the printing of the package inserts that accompany fill-finished vaccine.

- **Pre-Filled Syringes.** Although Novartis Vaccines indicated that we had limited pre-filled syringe formulation capacity, and therefore proposed to supply doses in multi-dose vials, the government ultimately requested a substantial part of our vaccine in pre-filled syringes. This affected our fill-finishing activities and the early availability of doses to the U.S public. Subsequently, based on HHS guidance, Novartis Vaccines prioritized multi-dose vials to accelerate the availability of finished vaccine.
- **Adjuvantation.** Although the government ordered bulk doses of our proprietary adjuvant MF59, which based on recently-available data could have quadrupled the number of doses supplied, it ultimately determined that use of the adjuvant was not warranted. Novartis Vaccines is currently providing only adjuvanted vaccine to all other regions of the world and believes that adjuvantation could have provided significant benefits to the U.S. in terms of supply volume for this year's pandemic.

As of November 16th, Novartis Vaccines has manufactured for the U.S. over 57 million doses of bulk antigen and over 61 million doses of bulk adjuvant and has shipped approximately 19 million fill-finished doses of H1N1 vaccine to the United States, of which almost 18 million doses are quality-released and available to supply HHS orders.

Given the totality of circumstances, the successful development, clinical testing, and large scale production of an H1N1 vaccine in such a short amount of time, despite all the challenges and uncertainties that were overcome, was a significant accomplishment for the U.S. Government and Novartis Vaccines partnership.

VI. Areas for the Future

We also believe, based on the experience this year, there are important opportunities to improve pandemic preparedness and response in the future, including the items described below:

- **Continued investment in new production technologies and manufacturing capacity including cell culture production.** Specifically, these investments should ensure production technologies and capacities enable the production of a wide range of influenza viruses and also ensure that these capacities can be brought on line quickly in the case of an influenza pandemic. Investment in technologies that support the rapid availability of vaccine candidate strains is also needed. During this pandemic there was a significant delay between the isolation of pandemic virus and the availability of vaccine candidate strains and too few laboratories were leveraged through the WHO Collaborating Centers to develop these seed strain candidates.
- **Acceleration of regulatory pathways for novel influenza adjuvants.** Novel adjuvants for influenza, such as oil in water emulsions like MF59, have been successfully used in Europe since 1997 both to provide dose sparing effects (and so allow the production of more doses in a limited amount of time) and improved cross protection (protection against drifted strains over a longer period). The licensure for these vaccines in the U.S. has not progressed due to the absence of a clear regulatory pathway.

- **Implementation of new methodologies for vaccine potency and sterility testing.** The analytical methods used to test vaccine potency and sterility are time consuming and often the rate limiting step to vaccine supply. The vaccine potency method, which involved the use of sheep antisera, often requires 8 weeks to develop for each new vaccine strain. During the current pandemic, Novartis Vaccines used a number of more modern methods to estimate vaccine potency which proved to be accurate. These methods are not currently accepted by regulatory authorities for vaccine batch release.
- **Streamlined regulatory approvals for pandemic vaccines including the use of mock-up filings.** The registration (before a pandemic occurs) of pandemic vaccines which requires only the submission of a strain change supplement after pandemic strain identification has streamlined the approval of pandemic vaccines in Europe.
- **Continued maintenance of the strategic national stockpile for rapid deployment.** Even the fastest and most efficient vaccine manufacturing technologies cannot produce vaccines within the first months of a pandemic outbreak and so are of little use when trying to contain the spread of pandemic virus. The establishment of a national stockpile of likely pandemic strains, along with adjuvant required to provide the protection against drifted strains, provides an opportunity to make vaccine available very quickly. To be most effective this vaccine needs to be held as filled, ready to use product.

In addition to the above areas, it is critical that the U.S. Government support seasonal influenza vaccination demand to ensure that suppliers are not forced out of the market if an oversupply situation arises as has happened repeatedly in the past.

Despite expanded recommendations in recent years, oversupply of seasonal influenza vaccines has led to a downward trend in pricing. U.S. seasonal influenza manufacturing at 2008/2009 pricing levels was not profitable. This situation, combined with ever increasing regulatory requirements and additional data requirements for the licensure of new and improved influenza vaccine products, means that many improvements that could be made to ensure increased availability of vaccines in the event of a pandemic and to improve the efficacy of influenza vaccines in the U.S. are not being pursued.

VII. Conclusion

Novartis Vaccines continues to do everything possible, in close collaboration with HHS, to maximize supply of safe and effective vaccine as soon as possible. We believe that when taken into full context the productive public-private partnership to produce, test, and deliver a safe and effective H1N1 vaccine to the U.S. has been a remarkable success. We are fully committed together with HHS to ensure we achieve our shared goal of preventing every possible case of influenza in the United States.

Thank you for the opportunity to present these views to the Committee. I will be happy to answer any questions that you may have for me.

Annex

Holly Springs Facility Photo

