

STATEMENT OF BEN MACHIELSE, DRS.
EXECUTIVE VICE PRESIDENT, OPERATIONS
MEDIMMUNE

BEFORE THE HOUSE ENERGY AND COMMERCE
SUBCOMMITTEE ON OVRSIGHT AND INVESTIGATIONS AND
SUBCOMMITTEE ON HEALTH

“CURRENT STATE OF VACCINE AVAILABILITY AND
THE NEXT STEPS IN PRODUCTION AND DISTRIBUTION
EFFORTS”

NOVEMBER 18, 2009

Joint Hearing of the Subcommittee for Health and the Subcommittee for Oversight & Investigations of the House of Representatives Energy & Commerce Committee

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Chairmen Stupak and Pallone, Ranking Members Walden and Deal, Members of the Committee, thank you for the opportunity to address this joint hearing of the Subcommittees of Health and Oversight and Investigations.

Overview

My name is Ben Machielse, and I am executive vice president of operations for MedImmune and also the chair of MedImmune's H1N1 response team. By way of introduction, MedImmune is a biotechnology company wholly owned by AstraZeneca, PLC. MedImmune is headquartered in nearby Gaithersburg, Maryland, and is committed to delivering life-changing products and improvements in patient health. As part of that mission, we pioneered the first major innovation in influenza vaccine development in almost 60 years with the 2003 launch of the intranasally delivered seasonal FluMist®, the first (and still the only) live, attenuated influenza vaccine approved by the FDA.

We are now in our seventh season as a licensed manufacturer of a commercially available influenza vaccine. This season has been unlike any other we have been through with the outbreak of the 2009 novel influenza A/H1N1 virus. As you well know, President Obama has declared a national State of Emergency and the World Health Organization has declared a global pandemic. Influenza pandemics are not new, having occurred every few decades during the 20th century.

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What is new is that, for the first time, we have advancements in place to protect ourselves against a pandemic, thanks in large part to a successful collaboration between the private sector and the U.S. Department of Health and Human Services (HHS).

Since 2006, MedImmune has been working with the Biomedical Advanced Research and Development Authority (BARDA) in the Office of the Assistant Secretary for Preparedness and Response within HHS on pandemic preparedness efforts. This year MedImmune contracted to deliver nearly 42 million doses of our intranasal live, attenuated H1N1 vaccine to HHS/BARDA for delivery to the U.S. public between September 2009 and February 2010.

Today I am pleased to share that we are on schedule to fulfill the terms of this contract to provide pandemic vaccine to the American population. The FDA released over 13 million doses of our finished sprayer-filled H1N1 vaccine as of Friday, November 13, 2009, and our schedule for delivery of finished product through the end of February remains on track and consistent with BARDA's expectations. We have finished the bulk manufacturing of all 42 million doses of the vaccine ahead of the schedule agreed upon with BARDA. All of the vaccine material is here on U.S. soil, and we are now in the process of filling the vaccine into the specialized single-dose nasal sprayers we use for delivery of our vaccine. I am also pleased to report that MedImmune was the first of the five influenza vaccine manufacturers contracted by HHS to deliver an H1N1 vaccine this year. We did so three days ahead of schedule on September 22, 2009. As a result, our vaccine was the first available for the U.S. public and has been used in the H1N1 vaccination campaign to help protect priority populations including health care workers, first responders and eligible children and young adults between the ages of 2 and 24. Our product remains a significant proportion of the vaccine supply available to date.

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I believe it is also important for the Members of the Subcommittees to be aware that there was no disruption of our seasonal influenza vaccine manufacturing or delivery due to our work on the H1N1 vaccine. When we began work on the H1N1 vaccine, we also accelerated our manufacturing processes to ensure that our commitment to make approximately 10 million doses of seasonal vaccine was met.

Manufacturing

I understand that the Members of the Subcommittees have questions about our manufacturing process, so I will provide a brief overview. As the manufacturer of the only live, attenuated influenza vaccine in the U.S. as well as the only influenza vaccine administered by nasal spray rather than a shot, our manufacturing process differs from that of the inactivated, injectable vaccine in several important respects.

First, we have a highly specialized and dedicated vaccines research and development team that every year develops a special “master virus seed” for every strain to be included in the vaccine for the upcoming influenza season. I understand the other influenza vaccine manufacturers rely on the CDC or other reference laboratories around the world to generate the necessary master virus seed, which makes our team in Mountain View, California, one-of-a-kind in the industry. This year, our team had completed their work for the 2009-2010 seasonal FluMist vaccine and was working on other projects when the H1N1 outbreak was first identified at the end of April. We immediately invested our own resources and reassigned this expert team of influenza vaccine scientists to begin work on an H1N1 vaccine seed due to the emerging and unpredictable public health threat.

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Our team uses a patented process known as “reverse genetics” or “plasmid rescue” to first select those parts of the H1N1 virus that will stimulate an immune response and then harness them to a special, proprietary vaccine strain. This specialized strain is “live” when it is administered, in that it has been adapted to grow in the cooler temperatures of the nose (which allows for generation of an immune response), but “attenuated” and “temperature sensitive” which means it cannot survive in the warmer body temperature of the lungs (so it cannot cause influenza). This reverse genetics process allowed our team to quickly make 23 different candidate master virus seed variants before identifying that one which exhibited the best attributes, including good growth in chicken eggs necessary for vaccine production. This master virus seed was sent to our egg-based bulk vaccine manufacturing plant in the United Kingdom at the end of June. In parallel to this H1N1 development activity, we accelerated and completed the production of the seasonal bulk vaccine to allow for the start of bulk H1N1 vaccine manufacturing on July 3, 2009.

Like the inactivated vaccine of our competitors, our vaccine is grown in eggs. However, unlike the inactivated vaccine, which typically generates only one to seven doses per egg, we find that live, attenuated vaccine strains can generate between 60-100 doses of vaccine per egg. This year the live, attenuated H1N1 master virus seed has been no exception, allowing us to generate approximately 90 doses of vaccine per egg. The high yields of the live, attenuated vaccine are a direct result of MedImmune’s ability to prepare multiple candidate seeds using reverse genetics and then selecting the seed that has optimal performance properties in our manufacturing process. Because MedImmune’s vaccine is live and grows in the nose where it activates an immune response, much less virus is required to be given in comparison to the

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injectable vaccine. In the height of the seasonal vaccine production cycle we normally manufacture two bulk vaccine lots per week, but given the public health emergency, we have added over 40 people to our bulk vaccine manufacturing labor force, and stretched manufacturing capacity by running three lots per week on average.

Finally, all the bulk vaccine is shipped from our UK facility to our facility in Pennsylvania where we fill the vaccine into sprayers and finish the packaging process. We have also augmented staff at this site to fill and finish product on a 24/7 basis and have suspended manufacturing activities at our primary non-vaccine manufacturing facility to focus on our H1N1 efforts.

I would also like to highlight that in 2007, MedImmune contracted with BARDA to retrofit existing facilities to prepare for a surge in case of a pandemic. Part of that effort included development of a second high-speed, FDA-approved fill line in our Pennsylvania facility that was scheduled to be completed by June 2010. Fortunately, this project was far enough along that we were able to accelerate its development by seven months. Obtaining early licensure for this second high-speed fill line in service has been critical for us to continue to deliver H1N1 vaccine on the schedule agreed upon with BARDA. We received extraordinary support from the FDA to accelerate the process and I am pleased to announce that this fill line was officially licensed Friday, November 13, 2009.

I would also like to recognize the efforts of the team in our distribution facility outside Louisville, Kentucky. This site is generally used for storage and distribution of our products. However, last-minute changes required by the FDA for the package insert for the H1N1 vaccine meant that approximately 40 staff members at the Louisville facility worked in double shifts for

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six weeks in the minus 40 degree Celsius temperature freezers in which the product is stored to ensure that the correct package insert was included with the vaccine.

The men and women of MedImmune are honored by the trust placed in us by the U.S. Government and humbled by our responsibility to the U.S. public. I am proud of the dedication and commitment shown by the MedImmune team that has allowed us to continue to deliver vaccine as contracted. That is not to say that there have not been challenges, but in each case, the team has been able to find a way to minimize the impact of any disruptions to our delivery schedule. We are on pace to deliver nearly 42 million doses of H1N1 vaccine this season in addition to the 10 million doses of seasonal vaccine we have already distributed. Combined, this means we are on track to complete a 700% increase over the seven million doses of seasonal vaccine we delivered for the 2008-2009 flu season. We believe this to be a tremendous accomplishment and speaks to the company's commitment and ability to respond intelligently and quickly to a public health emergency. Yet, we also recognize that while we are meeting our commitments to BARDA, that fact is of little comfort to those members of the public who have not yet obtained vaccine. It is with this in mind that we have continued to push our teams to see if there are any parts of the process we can further accelerate to deliver product even sooner. Given the overall vaccine supply shortage, we have also been working with BARDA to determine if there are other steps we can take to safeguard public health both for the remainder of this season and the future. I would like to take a few minutes to inform the Subcommittees of our latest thinking in that regard.

New Approaches

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Multi-Dose Vials with Disposable Nasal Droppers

MedImmune's capacity for bulk production of live, attenuated vaccine significantly exceeds our ability to acquire the specialized sprayers and fill them, particularly in the context of a pandemic when a rapid surge of vaccine supply is quickly needed. When we realized in late July and August that we had the capability to produce more than enough bulk vaccine to meet our commitments to HHS, we began discussing with BARDA and the FDA the possibility of filling our vaccine into vials that would contain multiple doses of vaccine and distributing them with single-use disposable nasal droppers. At that time, we proposed an aggressive schedule to deliver 30 to 50 million more doses in October in this multi-dose presentation. However, we slowed our development efforts in September when BARDA believed there would be enough injectable vaccine forthcoming, particularly in light of clinical data showing one dose of injectable vaccine would be sufficient for most Americans over nine years of age.

Although it would likely be the end of January or early February 2010, before we could have doses available in this multi-dose presentation, we believe it is important to pursue this development program with renewed vigor for two reasons. First, while no two pandemics have been the same, history has shown that there can be multiple waves of infection and the length of each wave can vary. If the current wave continues for a prolonged period or another wave occurs early next year, this approach would provide additional quantities of vaccine to augment the sprayer-filled doses we are currently providing, particularly if the delays with injectable vaccine delivery continue. Second, historically, the influenza virus has shown a remarkable ability to mutate, but we have no way of predicting how and when it might. If it mutates enough in 2010 that current H1N1 vaccines do not provide sufficient protection, it may be necessary to

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rapidly create a novel vaccine against the mutated strain. In such a circumstance, MedImmune believes we could use the same technology used this year to rapidly create a high-yielding vaccine strain. However, the limited supply of sprayers could delay ability to deliver vaccine. The multi-dose vial and disposable dropper solution we are proposing, however, would alleviate sprayer supply constraints, allowing for a significant surge in 2010 or in future pandemics. For these reasons, we believe this solution holds strategic importance for pandemic preparedness both in the near-term and in the long-term.

A key factor for this approach will be determining if the FDA has the resources to evaluate and grant regulatory approval for the multi-dose vials and disposable droppers in time to release product in January or February. Fortunately, several of the early clinical trials of seasonal FluMist used droppers rather than sprayers, providing us with existing clinical data showing that nasal drops are an equivalent alternative. One existing procedural hurdle is that current regulations constrain the FDA's ability to evaluate the safety and efficacy of multi-dose vials of vaccines that do not contain preservatives. MedImmune's vaccine is preservative-free. It is our scientific opinion that this regulation was intended to cover injectable vaccines and is not as critical for vaccine administered into the nose, which is not itself sterile. This position is supported by the United States Pharmacopeia guidance for intranasally administered pharmaceutical products. Without modernizing FDA's evaluation process, we are concerned that introducing preservatives could affect a live, attenuated intranasal vaccine in unanticipated ways. Initial studies have indicated that a preservative is not necessary. In addition, the time required to test the product with a preservative would significantly delay the timeline for availability of vaccine in the multi-dose vial presentation. These same FDA regulations also

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contain an exception to the preservative requirement for yellow fever vaccine, providing a precedent for producing vaccine in multi-dose vials without preservatives, but the standard procedure required for FDA rulemaking would also delay delivery of vaccine, even if the agency concurs with our scientific position and supportive data.

As previously stated, we have been in an on-going dialogue with the FDA and BARDA regarding this approach and are hopeful that our approach can be added to the pandemic preparedness arsenal.

Cell Culture-Based Vaccine

While licensure of seasonal FluMist by the FDA was a significant milestone in influenza vaccine innovation, we view this as not the culmination of our work, but rather a step along the evolution of this important vaccine. MedImmune continues to seek out and develop improvements that will help more people get access to this vaccine well in advance of the first waves of influenza disease. While not a possibility for the current H1N1 pandemic, replacing dated technologies with a modern cell culture manufacturing system would be a key improvement for the development of this vaccine. Cell culture manufacturing offers many advantages compared to egg production. Among these advantages are the protection of the vaccine from external contaminants, and the scalability of production. A typical production run of our live, attenuated vaccine uses 30,000 eggs, each of which must be individually handled to extract the vaccine from it, yielding approximately two to three million doses of bulk vaccine. In contrast, two moderately sized bioreactors could yield more than one hundred times that amount of bulk vaccine and require significantly less handling. Cell culture production, therefore, is less

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labor intensive and produces more vaccine per unit of time. Conversely, increasing the scale of egg-based production requires a coordinated increase in both the number of eggs as well as the number of hens to lay the eggs. This egg-based system is inflexible, could take more than a year and result in a substantial increase in the number of eggs. The egg-based system is also susceptible to viruses that affect the hens or the eggs such as the H5N1 “avian flu” virus that was identified a few years ago. Such a virus could significantly deplete the number of hens and eggs, reducing the supply of eggs required to create the vaccine. In contrast, cell culture production is limited only by the number of available bioreactors, standard equipment throughout the biotech industry. Current estimates predict that MedImmune could produce hundreds of millions of doses of bulk vaccine within six months with only two mid-sized bioreactors. Increasing this output would require only modest investments in equipment and facilities compared to an egg-based approach.

MedImmune understands the importance of protecting the U.S. population from influenza and, as a result, there is a clear and compelling need to advance beyond egg-based manufacturing to cell culture production technology. The company currently has a research and development program focused on developing a cell culture-manufactured live, attenuated vaccine and has performed this work under a contract with BARDA since 2006. Key components of successfully incorporating changes for any product are identifying, characterizing and managing potential risks associated with the changes. MedImmune’s initial contract for cell culture-produced live, attenuated vaccine examined the key risks of the program and set forth a series of studies to evaluate the magnitude of these risks. The genetic elements of the vaccine are identical between the cell-produced and egg-manufactured products, and we therefore determined that there was

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little risk that the effectiveness of the vaccine would be different. We proposed to directly assess this by evaluating the immunogenicity of the two products side-by-side in human studies.

In September 2008, the Vaccines and Related Biological Products Advisory Committee, a body of scientific experts convened by the FDA, supported initiation of human clinical studies. However, the FDA determined that additional studies would be required which substantially increased the cost and duration of the development program by several years. In light of these changes, the program remains at a late preclinical stage and would unlikely be licensed in a similar population as indicated for FluMist within the next five years. The program no longer fit the original expectations of the contract and is currently on hold while MedImmune and HHS discuss an appropriate path forward. Our egg-based live, attenuated technology has proven to be a very important asset in the pandemic preparedness program in terms of its yield and speed to market. These advantages translate directly to the cell culture technology presenting a clear and urgent need to define an efficient approval process.

Manufacturers urgently need a way to discuss end-to-end product development plans with the FDA or its advisory boards early in the product development process. We must work together towards efficient, meaningful science-based outcomes that move medicines forward. In the current environment, the hurdles to bringing forward innovative products like cell culture-produced live, attenuated influenza vaccines are likely to take many years and cost a great deal. Measurement of infrequent events is better managed by improved post-marketing tools. It would be unfortunate to not have available, technology with large-scale production capabilities in place in advance of the next pandemic. Cell culture-produced live, attenuated vaccine can and should be a cost-effective, fast and reliable part of the U.S. pandemic preparedness program.

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The events of 2009 have reinforced the need for a strong public-private partnership to advance influenza vaccine manufacturing and development. For cell culture manufacturing to become a reality for pandemic and seasonal influenza vaccine, manufacturers, regulatory agencies and public health agencies of the U.S. government must work in concert to make these important advancements a reality.

Blow-Fill-Seal Technology

While we are on track to increase our vaccine production by 700% this year, it is clear that availability of the sprayers and the speed at which they can be filled can be rate-limiting when a significant surge in production is required. Accordingly, MedImmune has also been developing a new method of delivering our live, attenuated vaccine in a more cost and time-efficient manner. Such a method would eliminate our current dependence on sprayers. This technology, referred to as “blow-fill-seal,” would allow for rapid mass filling of the bulk vaccine into plastic bulbs and is currently being studied in clinical trials at MedImmune. Based on the feedback we have received from the FDA to-date, we believe that vaccine in this presentation may be available in three to five years.

Looking Ahead

While our strong collaborative efforts with the U.S. Government have allowed us to respond well to this public health challenge, we have already explored what we can do better the next time a pandemic threat emerges. There are many opportunities to continue to develop the

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science and capacity needed to enhance our pandemic vaccine preparedness for potentially even more serious outbreaks.

First, there is a very strong correlation between a manufacturer's seasonal influenza vaccine capacity and the ability to produce an adequate supply of pandemic vaccine. As demand for seasonal vaccine increases, manufacturers respond with more supply and are more prepared to meet the demands of a pandemic. In order to ensure that manufacturers have the capacity to produce an adequate supply of pandemic vaccine, it is critical that HHS and CDC continue to encourage increased seasonal vaccination in all recommended populations. Influenza vaccines are safe, effective and among the most cost-effective medical interventions available. By significantly increasing the annual use of seasonal vaccines we could improve health, reduce health care costs, diminish the impact on the economy from missed days of work and establish the manufacturing capacity and distribution systems necessary to respond adequately to protect all Americans when the next pandemic strikes.

Second, there are many misconceptions about the risks of vaccination, including a lack of understanding of its benefits and of the scientific and medical data supporting the vaccine. For example, the safety of our live, attenuated vaccine has been demonstrated in numerous human clinical studies and reconfirmed annually by testing one dose per patient in approximately 300 adults before that year's vaccine is approved by the FDA. For this year's H1N1 vaccine, at the FDA's request, we went even further and tested two doses per patient in approximately 300 adults and 300 children. We would strongly encourage a substantial investment in education campaigns that would provide the public with the appropriate scientific information on influenza vaccines. With our focus on innovation, we would be particularly interested in making sure that

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any such public awareness and education campaigns, particularly those that are government-sponsored, go beyond the “flu shot” language that is currently used to instead discuss the “flu vaccine” more generally so they are inclusive of the live, attenuated vaccine, as well as address the ease and simplicity of nasal delivery and other technological enhancements that have come to the forefront.

As stated before, while there are delays in injectable vaccine availability, this is the first pandemic in history in which vaccine manufacturers have been able to develop and mass-produce a vaccine within the same season that the pandemic strain first circulated. BARDA has done a remarkable job of establishing a plan to vaccinate the American public and coordinating related efforts of public health agencies and private industry. While the decision-making process and speed of response have been much faster than usual, we do believe that rapid responses to emergency situations would benefit from collaborative advance scenario planning. Both manufacturers and regulatory decision makers can learn lessons from this pandemic to minimize the risk of future vaccine supply delays and disruption.

Finally, we believe it is important that Congress continue to fund pandemic preparedness efforts not just at BARDA, but also to ensure that other key agencies, such as the FDA and CDC have the necessary resources.

Conclusion

MedImmune is fully committed to and engaged in assisting the U.S. government in its efforts to protect public health during this challenging time. We have, to date, successfully executed against an aggressive schedule and believe we can continue to so. We believe we have

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an exceptional team in place to handle this H1N1 influenza pandemic and continue to benefit from excellent input and collaboration with HHS. It is our continuing honor and privilege to be able to serve the country during this national emergency.

I would like to again express thanks to the Subcommittees on behalf of MedImmune and our parent company, AstraZeneca for the opportunity to testify today. I hope this information has been useful and I am pleased to answer any questions from Members of the Committees.