An Affordable Pandemic Influenza Vaccine Solution for Developing Countries (and Developed Countries Too)

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New Cells for New Vaccines III
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The Current State of Pandemic Influenza Readiness

Progress is being made due to good government/industry collaboration

- Stockpiles of anti-viral drugs have been built and rotation plans are in place
- Some countries have stockpiled H5N1 vaccines and plan the use of adjuvants to cover antigenic drift within H5N1 clades
- Additional countermeasures are being planned
- Personal preparedness is being emphasized

More needs to be done

- No country has a timely solution for a novel strain
- No country has sufficient capacity/supply of vaccine without the use of adjuvants
- New capacity by traditional manufacturing approaches is expensive
- Many developing countries are at a higher risk of a local pandemic outbreak, and are less prepared to address the problem
An Affordable Pandemic Influenza Vaccine Solution for Developing Countries (and Developed Countries Too)

Agenda
- Influenza Vaccine Overview
- Influenza Virus-Like-Particle (VLP) Vaccines in Insect Cells
- Phase II Clinical results for Pandemic Influenza VLP Vaccine (A/Indonesia/2005)
- Manufacturing VLPs in Insect Cells
- Unique Economics of Manufacturing Approach at Novavax
- Building the Prototype Facility
- Creating access to In-border Influenza Vaccine Supply
Influenza Vaccine Overview

Licensed
- Inactivated influenza vaccines
  - Whole virion
  - Split virion
- Live-attenuated vaccines

Approaching Licensure
- Adjuvanted inactivated vaccines*
- Recombinant HA vaccine

In Development
- Virus-Like Particles
- DNA Vaccines
- Universal Flu Vaccines

*some licensed in EU
Influenza Vaccine Overview

Targeted Influenza Vaccine Solution

Seasonal Product
• Safe and well tolerated for all age groups
• Cross-protective product for antigenic drift
• Improved protection in older adults

Process
• Cell culture-based production
• High yielding process supporting a robust supply / response
• Fast response to an emerging influenza strain
• Flexible facility that supports other products when not producing for a pandemic threat

Pandemic Product (all of the above +)
• Available during 1st pandemic wave
• Sufficient supply for entire population
• Available regionally
Influenza Virus-Like-Particle (VLP) Vaccines in Insect Cells

Novavax, Inc. is developing an Influenza Virus-Like Particle (VLP) Vaccine as an alternative to traditional influenza vaccines

- The process uses recombinant baculovirus to infect an insect cell culture and express VLPs that contain Hemagglutinin (HA), Neuraminidase (NA), and Matrix (M1) Protein

- The proteins self-assemble as they are secreted from the insect cells as particles that resemble influenza virus, but do not contain flu RNA
Influenza Virus-Like-Particle (VLP) Vaccines in Insect Cells

Novavax H5N1 (Indonesia) VLPs

Contain 3 immunologically important proteins
- Current flu vaccines consist almost entirely of HA
- Genetic match to wild-type strains causing influenza in humans

- HA – neutralizing ab prevents infection
- NA – neutralizing ab reduces disease severity
- M1 – cell mediated responses reduce disease severity
- Avoid changes in HA protein that may occur with egg or mammalian cell culture adaptation

Influenza virus pleiomorphy characterized by cryoelectron tomography

Novavax

Laboratory of Structural Biology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, and Department of Microbiology, University of Virginia, Charlottesville, VA 22908.
Phase II Clinical results for Pandemic Influenza VLP Vaccine

Does it work?
Phase II Clinical results for Pandemic Influenza VLP Vaccine

Virus Neutralizing Antibody (VN) Responses Against the A/Indonesia Strain After 2 Doses of the H5N1 VLP Vaccine

<table>
<thead>
<tr>
<th>Percentage of subjects (n = 160) with VN titer ≥1:20 (≥4-fold rise in titer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 mcg – 72%</td>
</tr>
<tr>
<td>45 mcg – 73%</td>
</tr>
<tr>
<td>90 mcg – 94%</td>
</tr>
<tr>
<td>Placebo – 0%</td>
</tr>
</tbody>
</table>

- Product does not contain an adjuvant
- Seeking partnerships (Commercial, Government, Non-government) for advanced clinical development
- Results from this study of the H5N1 pandemic influenza VLP vaccine candidate support the VLP platform for development of vaccines against seasonal influenza and other diseases
- Phase 2 studies of the seasonal influenza VLP vaccine candidate are underway
Manufacturing VLPs in Insect Cells

Process Attributes:
• Controlled cell culture process (Serum-free, Protein-free, Suspension Culture)
• No eggs
• No pathogenic virus in manufacturing (BL-1 Facility)
• Yields are higher than egg-based production; potential for additional increase in yield
• The use of this approach has allowed Novavax, Inc to develop a process that uses disposable equipment and closed systems for product processing

Beneficial to Pandemic Influenza Vaccine Need:
• Speed from strain selection to product release is 10 - 12 weeks
• Exact genetic match to circulating virus (HA, NA, M1)
Faster Delivery of First Dose of Pandemic Vaccine

In 2008, Three new seasonal strains were added to the formula.
Novavax produced VLP’s for all three strains within 6 weeks of the availability of the viruses from CDC.

First doses released in week 10 - 12
Manufacturing VLPs in Insect Cells

Relative Influenza Process Yield (H5N1)

Yield based on lots of H5N1 produced with WAVE reactor technology

Higher yields expected with enhanced aeration and process control

Seasonal yields > Pandemic yields
Traditional Influenza Vaccine Production

Traditional Flu Vaccine Production:

- Cell Substrate Preparation
- Infect & Incubate
- Remove Cells, Purify Virus
- Inactivate Virus

Mammalian Cell Culture Vaccine Production:
Manufacturing VLPs in Insect Cells

Insect Cell Culture-Based Flu Vaccine Production in Disposable Mfg Systems:
# Manufacturing VLPs in Insect Cells

## Process Equipment Comparison

<table>
<thead>
<tr>
<th>Process</th>
<th>Egg Based</th>
<th>Insect Cell Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Upstream</strong></td>
<td>Custom Inoculators</td>
<td>Single Use Bioreactors</td>
</tr>
<tr>
<td></td>
<td>Large Incubators</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Candling Stations</td>
<td></td>
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<tr>
<td></td>
<td>Custom Harvesters</td>
<td></td>
</tr>
<tr>
<td><strong>Purification</strong></td>
<td>Large Fixed Tanks</td>
<td>Single Use Bags</td>
</tr>
<tr>
<td></td>
<td>Low Speed Centrifuges</td>
<td>Single Use Microfiltration</td>
</tr>
<tr>
<td></td>
<td>Filtration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ultrafiltration Skids</td>
<td>Single Use Ultrafiltration</td>
</tr>
<tr>
<td></td>
<td>Ultra Centrifuges</td>
<td></td>
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<tr>
<td></td>
<td>Chromatography</td>
<td>Chromatography</td>
</tr>
<tr>
<td></td>
<td>Buffer Prep</td>
<td>Single Use Buffer Prep</td>
</tr>
<tr>
<td></td>
<td>Buffer Storage</td>
<td>Buffer Bags</td>
</tr>
<tr>
<td></td>
<td>Sub-micron Filtration</td>
<td>Single Use Sub-micron Filters</td>
</tr>
</tbody>
</table>
## Manufacturing VLPs in Insect Cells

### Support Equipment Comparison

<table>
<thead>
<tr>
<th>Support</th>
<th>Egg Based</th>
<th>Insect Cell Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Process</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large WFI System</td>
<td></td>
<td>Small WFI System</td>
</tr>
<tr>
<td>CIP Skids (Multiple)</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Clean Steam/SIP Systems</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Egg Disposal System</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Autoclaves</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Parts Washers</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Containment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decon Autoclave</td>
<td></td>
<td>Decon Autoclave</td>
</tr>
<tr>
<td>Large Liquid Waste Kill System</td>
<td></td>
<td>Small Liquid Waste Kill System</td>
</tr>
<tr>
<td>BL2+ Facility Design</td>
<td></td>
<td>GLSP Facility Design</td>
</tr>
<tr>
<td>Class B HVAC Systems</td>
<td></td>
<td>Class C HVAC Systems</td>
</tr>
</tbody>
</table>
Unique Economics of Manufacturing Approach at Novavax

Traditional Flu Vaccine Production Capital Costs:

- **egg-based facility**
  - sanofi pasteur, USA
  - 100M doses/year (600K eggs/day)
  - 140K square feet
  - $150M
  - (on existing site/infrastructure)

- **mammalian cell culture facility**
  - Novartis, USA
  - 50M doses/year
  - 140K square feet
  - $600M
  - (new site/infrastructure)

Insect Cell Culture-Based Flu Vaccine Production Capital Costs:

- **Novavax, Inc Insect Cell Culture Disposable Approach**
  - 75M doses/year
  - 55K square feet
  - $40M
  - (new site/infrastructure)

All projects fully-integrated manufacturing and designed/estimated by the same US-based Engineering & Construction Firm in 2004 - 2007
Unique Economics of Manufacturing Approach at Novavax

Comparison of Project Duration

Egg-Based Process
- Design
- Construction
- Commissioning
- Qualification
- Validation

Time Saved

Insect Cell Culture
- Design
- Construction
- Commissioning
- Qualification
- Validation

Time, yrs

0 1 2 3 4
Traditional Flu Vaccine Production Unit Costs:

- Relative Variable costs
  - Egg-based: materials, labor
  - Mammalian cell culture: materials, labor

- Relative Fixed costs
  - Egg-based: depreciation, utilities
  - Mammalian cell culture: depreciation, utilities

Insect Cell Culture-Based Flu Vaccine Production Unit Costs:

- Cost of Goods Sold (COGS)
  - equivalent to egg-based

- COGS expected to drop with yield increase or lower dose

COGS = unit variable costs + \[ \frac{\text{fixed costs}}{\text{units produced}} \]
Traditional Flu Vaccine Production:

- Large, central manufacturing facilities
- Located in developed countries
- Supported by complex site infrastructure
- ~100M doses
- $150 – $600M

Insect Cell Culture-Based Flu Vaccine Production:

- Facilities Distributed Globally
- Located where vaccine is needed
- Requiring little local infrastructure
- 10 – 50 M doses

Egg/Mammalian Cell Based
- 50 – 100M doses
- Facility $150 – 600M
- Sq ft 145,000

NVAX VLPs
- 75M doses
- Facility $40,000,000
- Sq ft 55,000
Building the Prototype Facility

Novavax’s Pilot Plant and Commercial Launch Facility
Rockville, MD

-~10,000 ft² (1,000 m²)
-Class C HVAC System
-(Class B for Seed Prep)
-1000L Cell Culture Reactor
-Capacity: 25 – 30 M doses in 6 mo.*
-120 days to construct

Prototype Facility to be Fully Operational at 1000L in 12/08

Total Cost ~6M USD#

*Assumes 15 mcg dose of H5N1 & current yields
# Media, Buffer, Form & Fill are outsourced
# Costs/space does not include QC
Building the Prototype Facility
Building the Prototype Facility

Cost Breakdown:

- Design: 38%
- Permitting: 46%
- Demolition
- General Construction
- HVAC
- External Validation (est’d)
- Process Equipment
Building the Prototype Facility

Belward Facility Capacity at 1,000L/batch
(H5N1 VLP vaccine availability in 6 months)

<table>
<thead>
<tr>
<th>Dose (mcg HA)</th>
<th>15 mg HA/L*</th>
<th>30 mg HA/L#</th>
<th>45 mg HA/L#</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>26</td>
<td>52</td>
<td>78</td>
</tr>
<tr>
<td>45</td>
<td>8.7</td>
<td>17</td>
<td>26</td>
</tr>
<tr>
<td>90</td>
<td>4.3</td>
<td>8.7</td>
<td>13</td>
</tr>
</tbody>
</table>

*15 mg HA/L (recovered yield) demonstrated in Wave Production System

#2 – 3x yield increase projected with enhanced aeration and control
Creating access to In-border Influenza Vaccine Supply

- No country has adequate supply of pandemic vaccine or the ability to respond to a novel strain
- Borders will close to reduce disease transmission during a pandemic
- An in-border solution is difficult to justify with a traditional manufacturing approach.
- The disposable manufacturing of insect cell-produced VLPs is a lower-cost approach to providing protection
Creating access to In-border Influenza Vaccine Supply

Additional opportunities with a regional or in-border supply:

- Customized vaccine
  - Match to local circulating strains
    - Different Strains for East and West, North and South
    - Prevent a pandemic at the source
  - Added strain (second B-strain, pre-pandemic strain)

- Vaccine for a “late breaking strain”

- Platform process supports multiple products
  - Seasonal Influenza (warm base operations)
  - Alternate Pandemic Strains (1918 H1N1, H9… H7, H2)
  - SARS and HIV VLPs
  - Potential for other regional vaccines
How can Novavax provide vaccine to the world?
Collaboration signed with GE Healthcare in Dec 2007

- General Electric serves foreign governments with construction of hospitals and utility plants.
- Within the collaboration, GE provides engineering, project management and government access.
- GE Healthcare has a wide range of disposable manufacturing systems and process expertise.

Novavax and GE Healthcare will jointly offer governments the opportunity to create an in-border solution for pandemic influenza using GEHC Systems, Project Management and Engineering and the Novavax VLP vaccine process.