Novartis Vaccines and Diagnostics: Advanced Technology

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Novartis Cell Culture Vaccine

- Novartis vaccines description
- Cell culture-derived influenza vaccine technology
- Synthetic seeds
- Business model
- Conclusion

MDCK Cells

in vitro
Novartis Vaccines at-a-glance

- World’s fifth-largest vaccines business
- Second largest manufacturer of influenza vaccines
- Globally produce over 500 million doses of vaccine, 70% to developing countries
- Invested over $2 bn in vaccine production since 2006
- Innovation leader with adjuvantation with the established MF59® adjuvant
- A leading position in cell culture production technology for influenza vaccines
- Significant investments in R&D focused on meningitis, influenza (including H5N1) and other vaccines for preventable diseases

<table>
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<tr>
<th>Key facts</th>
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<tbody>
<tr>
<td>Net sales 2011</td>
<td>USD 2.0 Billion</td>
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<tr>
<td>CEO</td>
<td>Andrin Oswald, M.D.</td>
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<td>Headquarters</td>
<td>Cambridge, MA</td>
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<td>Employees*</td>
<td>5,500</td>
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<td>Research Centers</td>
<td>Cambridge (Virology) Siena (Bacteriology) Emeryville (Diagnostics)</td>
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Advanced Technologies – Key Features of Cell Culture for Influenza Vaccine Production

- Large volume of cells can be grown rapidly, increasing the number of doses produced\(^1,2\) (5.0 \times 10^6 \text{ to } 2.3 \times 10^{12} \text{ cells}) in 3 weeks.

- Production can be accelerated and scaled up to meet unexpected changes in demand i.e. emerging pandemic strains\(^1,2\).

- Critical redundancy for pandemic response i.e. “Plan B”

- Production with sterile, closed-system bioreactors reduces contamination and allows production under higher containment – was critical in 2009 pandemic\(^3\)
  - Final vaccine is antibiotic free\(^4\)*

- Influenza A viruses grown in MDCK cells were shown to have fewer genetic changes in the HA antigens compared to egg-grown viruses = improved genetic fidelity (clinical significance uncertain)\(^5\)

- Vaccine production method uses no egg protein

*Not all egg-based vaccines contain antibiotics.
MDCK: Madin-Darby canine kidney cells.
Vaccine production time *may* be shortened relative to egg-based production time and can begin at any time of year.²

Summary – Cell Culture Vaccine Production

- Flucelvax, the first US cell culture-based flu vaccine licensed in November, 2012!

- Novartis, in partnership with US Government, has been successful in getting the cell culture production process up to multimillion dose scale

- Cell culture vaccine production eliminates dependence on eggs, allows for rapid scale-up, quick response and results in egg- and antibiotic-free vaccine production process (after seed generation). Provides vital back up to eggs in face of poor growth or zoonotics.

- In three randomized controlled clinical trials evaluating CCIV versus TIV:
  - CCIV was safe and well tolerated in adults
  - Immunogenicity of CCIV in adults was comparable to that of egg-derived TIV
  - CCIV efficacy in adults (based on culture-confirmed influenza) was demonstrated
Advanced Technologies - Synthetic Seeds
Future Process Flow from Isolate to Vaccine
Synthetic Seeds - Summary of accomplishments to date

- Research process to generate synthetic seeds established
  - Synthetic viruses are **quickly** generated from sequence data – as fast as 4 days and 4 hours
  - Synthetic viruses are **accurately** generated – 100% of viruses generated have expected sequence
  - Synthetic viruses are **reliably** generated – 29/30 strains successfully generated (H1N1, H3N2, B Yamagata, B Victoria, H5N1, H7N9, H3N2v)
  - Synthetic viruses created with new backbones produce **more HA** in MDCK cells and eggs - typically 1.25-15x the yield of conventional seeds

- Improved computational methods to select the strains to synthesize developed

- Process has moved from research to development
The emerging system

More rapid and reliable protection of the public from flu

How the system will work

- Continuous computational monitoring of sequences on the web combined with human intelligence identifies strains of interest as soon as they are posted
- Selected strains synthesized on high-growth backbones within days of sequence posting
- Rapid testing for growth, identity, antigenicity, HA production
- Based on triaging protocol, manufacturing optimization for new strains started at risk
- By the time a seasonal strain has been selected or a pandemic threat has been declared, the manufacturer already has a high growth vaccine seed that produces more HA than any conventional seed, and vaccine production can begin (if not already underway)

System advantages

- Primary synthesis by the manufacturer from posted sequences with no need for reassortment allows faster pandemic responses and earlier seasonal production
- Greater selection of seeds allows better strain match and more reliable production
- The “electronic filter” decreases adventitious agent risk
- Higher yields with new backbones allow more vaccine to reach the population sooner
Synthetic vaccinology holds promise for seed improvement

Synthetic process can create a completely egg-free influenza vaccine

RG can be applied to rapidly produce influenza viruses suitable for vaccine manufacture and has been used to create backbone combinations that improve yield

Synthetic process allows better strain match (no egg-adaptive mutations) and potential for optimization of HA and NA gene segments for vaccine uses

Combining rapid synthesis with RG should increase speed of obtaining useful seeds

Further realization of speed advantages from synthetic seeds requires development of an alternative potency release assay that does not require strain specific antiserum

Further application of synthetic biology to manufacture of influenza vaccines in cell culture should allow for earlier generation of seeds that can be used to more efficiently produce vaccines
Support for Advanced Technologies in a Challenging Environment

- Influenza vaccine environment is highly volatile:
  - Seasonal flu needs to be a viable business, pandemic manufacturing can not stand alone
  - Strains change every year and yields vary
  - Length and intensity of season varies from year to year
  - Rapidly changing regulatory and policy environments
  - Cost of vaccine is being driven down
  - Cost of clinical trials runs into hundreds of millions of dollars

- Public/private partnerships are critical in supporting advanced technologies:
  - Research collaborations
  - Support for development, manufacturing and commercialization of products
Novartis / HHS-BARDA Partnership
Pre-Pandemic Preparedness

Holly Springs, North Carolina

- Collaboration between US Department of Health and Human Services (USHHS) and Biomedical Advanced Research and Development Authority (BARDA)
- Collaboration via sharing of initial capital investment and US commitment to annual pre-pandemic stockpile purchases
- Site will have seasonal, pre-pandemic, and pandemic vaccine capability (150m doses within 6 month of declaration of influenza pandemic)
- Construction of US-based flu cell-culture site began in 2007
  - Ribbon cutting was on November 25, 2009
  - Ready to respond to pandemic as early as 2011
  - Full-scale commercial production by 2013
- Construction of the facility represents a financial commitment of nearly USD 1 billion for Novartis and HHS
Conclusions

- Influenza environment is extremely volatile
- Exciting progress is being made in advanced technologies which will provide manufacturers with more options for both pandemic response and seasonal manufacturing
- Combination of high development costs and decreasing price for vaccine is a major deterrent for investment
- Public/private partnerships are crucial in sustaining advancements in technology