Sustainable Pandemic Influenza Vaccine Manufacturing in Developing Countries

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Conclusions So Far

• Long term sustainability:
  – Egg based production may offer limited future expansion capabilities to new vaccine markets
    • Adapting to new technologies will be challenging
  – Microbial production has an expanding set of possible ‘sustaining’ products

• Pandemic influenza preparedness
  – Microbial production has higher technology risks for pandemic influenza vaccines
  – Greenfield facility construction is not necessary where
    • Egg based products are currently manufactured
    • High risk and long time-lines to pandemic preparedness are acceptable (e.g. non-egg based systems)
  – Near term preparedness requires greenfield or significant facility retrofitting where egg-based products are not currently manufactured.

• Any decision requires a careful assessment of needs, risks and resources.
Barriers to Sustainable Pandemic Influenza Vaccine Manufacturing in Developing Countries

• Ideally local/domestic seasonal influenza vaccine market supports pandemic preparedness

• Small market for seasonal influenza vaccines in developing countries
  — Limited demonstration of relevance to immediate health priorities of developing countries
  — Developing country public health policies rarely address influenza vaccination for the general population

• Resource limitations
  — Facility construction costs
  — Facility maintenance costs

• Training opportunities for personnel in biological manufacturing are limited and requires a specialized skill-set.
Outline of Survey Approach to Identify Sustainable Solution

1. Assess technical feasibility of multiproduct facilities in developing country settings
   - Pandemic Influenza vaccine and what… Seasonal influenza? Yellow fever? HiB? Crossover product depends on existing manufacturing capabilities as well as domestic requirements.
   - Single-use technology maturity/adoption trends

2. Mixture of dedicated buildings and multiproduct approaches
   - Adoption occurs in large pharma where clear benefits exist
   - Are there examples of multiproduct facilities in developing countries?

3. High level production scenarios including
   - Possible influenza vaccine alternatives
   - Egg vs Cell vs Bacterial
Single Product Facilities (if no seasonal)
• Purpose built pandemic response manufacturing facility is not self-sustaining
• Possible dedicated workforce

Multi-product Facilities
• Primarily employed by CMOs, although some adoption by ‘large pharma’
• Share resources
  – Workforce
  – WFI, HVAC, Utilities, Quality, Facility
What Companion Products Should be Paired with Influenza Vaccine:

• Satisfy a regional market requirement
• Coincide with current and planned manufacturing capabilities
• Have previously accessed technology transfer pathways
• Sufficiently advanced development to increase probability of successful insertion into market
• Capture risk and risk tolerance of organization
• Marry correct influenza vaccine technology to the best alternative product
  – Influenza vaccine technology options include
    • Production options: egg-based, cell (mammalian, insect) or bacterial
    • Vaccine technologies: LAIV, IIV or recombinant SUV
## Influenza Vaccine Landscape and Risk

### Market Approval

<table>
<thead>
<tr>
<th>Phase 3</th>
<th>Phase 2</th>
<th>Phase 1</th>
<th>Pre Clinical</th>
</tr>
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<td>CSL Biotherapies</td>
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<td>Sanofi Pasteur</td>
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<td>MVA Based</td>
<td>H1N1 Inactivated</td>
<td>H1N1 Inactivated</td>
</tr>
<tr>
<td>DNA / Vaxfectin</td>
<td>DNA / Vaxfectin</td>
<td>WIV</td>
<td>WIV</td>
</tr>
</tbody>
</table>

### Egg-based inactivated

- **Egg-based inactivated**
  - H1N1 post DNA vaccine
  - H1N1 split w/ APO4
  - H1N1 split w/ APO4
  - H1N1 split w/ APO4
  - H1N1 split w/ APO4
  - H1N1 split w/ APO4
  - H1N1 split w/ APO4
  - H1N1 split w/ APO4
  - H1N1 split w/ APO4
  - H1N1 split w/ APO4

### Cell-culture inactivated

- **Cell-culture inactivated**
  - Cell-culture & split
  - Cell-culture & split
  - Cell-culture & split
  - Cell-culture & split
  - Cell-culture & split
  - Cell-culture & split
  - Cell-culture & split
  - Cell-culture & split
  - Cell-culture & split

### LAIV

- **LAIV**
  - LAIV
  - LAIV
  - LAIV
  - LAIV
  - LAIV
  - LAIV
  - LAIV
  - LAIV
  - LAIV

### Recombinant (VLPs)

- **Recombinant (VLPs)**
  - VLP / HA
  - VLP / HA
  - VLP / HA
  - VLP / HA
  - VLP / HA
  - VLP / HA
  - VLP / HA
  - VLP / HA
  - VLP / HA

### Universal

- **Universal**
  - NYU / MSSM
  - NYU / MSSM
  - NYU / MSSM
  - NYU / MSSM
  - NYU / MSSM
  - NYU / MSSM
  - NYU / MSSM
  - NYU / MSSM
  - NYU / MSSM

### Vectors

- **Vectors**
  - MVA Based
  - MVA Based
  - MVA Based
  - MVA Based
  - MVA Based
  - MVA Based
  - MVA Based
  - MVA Based
  - MVA Based

### DNA

- **DNA**
  - DNA
  - DNA
  - DNA
  - DNA
  - DNA
  - DNA
  - DNA
  - DNA
  - DNA

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Updated: 03/13/2011
Advanced Development Pipeline

Balance risk and time requirements

<table>
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<th>TIME</th>
<th>3-7 yr</th>
<th>0.5-2 yr</th>
<th>1-2 yr</th>
<th>2-3.5 yr</th>
<th>2.5-4 yr</th>
<th>1-2 yrs</th>
</tr>
</thead>
</table>

**PHASES**

- **Discovery**
- **Preclinical Development**
- **Phase I**
- **Phase II**
- **Phase III**
- **Licensure**
- **Production & Delivery**

**TRLs**

- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9

**PRODUCT PIPELINE**

<table>
<thead>
<tr>
<th>1-3%</th>
<th>5-17%</th>
<th>10-25%</th>
<th>18-35%</th>
<th>45-70%</th>
<th>90%</th>
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</thead>
</table>

Risk mitigation strategies are required to manage the inherently risky drug development process

* Source: PRTM & Industry Data
Risk mitigation strategies are required to manage the inherently risky drug development process.

* Source: PRTM & Industry Data

Hypothetical Scenario Starting Points

Influenza vaccine capability starting point

• Egg based inactivated influenza vaccine production:
  — Technology transfer partners and path clear
  — Alternative products include endemic diseases in many developing countries – e.g. yellow fever, measles, rabies

Non-influenza vaccine capability starting point

• Microbial based vaccine production:
  — Few advanced microbial influenza candidates
  — Licensing agreements uncertain
No Influenza Vaccine
Microbial Based Starting Point

1. Monitor development of microbial-based influenza vaccine technology and evaluate public health priorities
2. Develop a contingency plans for long development timelines for microbial-based influenza vaccine candidates

1. Monitor development of insect cell, VLP-based influenza vaccine technology and evaluate public health priorities
2. Contract A&E firm to develop conceptual designs for retrofitting fermentation suite
3. Conduct resource requirements assessment
4. Identify technology transfer opportunities and commence discussions

1. Contract A&E firm to develop conceptual designs for green-field construction of egg-based facility
2. Conduct resource requirements assessment
3. Explore opportunities for leveraging egg-based capabilities

1. Identify technology transfer opportunities and commence discussions
2. Contract A&E firm to develop conceptual designs for retrofitting fermentation suite
3. Conduct resource requirements assessment
Potential Multiproduct Vaccine Manufacturing Scenarios for Microbial Starting Point

Manufacturing Scenarios are developed based on:
1. Hypothetical planned (and potential) capabilities*
   - “Planned” refers to vaccines intended to produce
   - “Potential” refers to vaccines which Case Study #1 has interest in producing
2. The regional vaccines of interest
3. Vaccines compatible with current (and planned) platforms and vaccines of interest (based on 1 and 2 above)

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**Planned (and Potential) Capabilities***

**Typical Developing Country Immunization Schedule**
- BCG
- DTaP-Hib-IPV
- HepB
- Influenza (high risk pop.)
- Measles
- OPV
- Pneumococcal
- Rotavirus
- Td
- TT

**Vaccines of Interest**
- GAVI
  - DTP-Hib-HepB
  - Hib
  - HepB
  - Measles
  - Meningitis A
  - Pneumococcal
  - Rotavirus
  - Yellow Fever
- GAVI (planned rollout)
  - HPV
  - JE
  - Rubella
  - Typhim Vi

**Vaccines for Multiproduct Manufacturing Consideration**
- Diphtheria
- HepB
- Measles
- Meningitis A
- Pertussis
- Pneumococcal
- Rubella
- TB
- Td
- Typhim Vi

**Notes:**
1. technology platform to manufacture influenza vaccine to be determined
2. Top six most demanded vaccines

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**Scenario 1**
Mammalian Cell LAIV + Mammalian Cell sIPV

**Scenario 2**
Mammalian Cell IIV + Mammalian Cell sIPV

**Scenario 3**
New product + Microbial-based (rProtein) Influenza

**Scenario 4**
Egg-based IIV + YF + Measles

**Scenario 5**
Influenza Insect-Cell VLP + HPV Insect-cell VLP
Egg-based Influenza Vaccine Starting Point

**Egg-based Strategy**

1. Characterize in-country / in-region market demands for non-influenza vaccines
2. Identify technology transfer opportunities and commence discussions
3. Conduct resource requirements assessment

**As-Is**

- **Egg-based Capability**
  - Pilot Scale
  - Commercial Scale
  - Emerging Technology Strategy
    - Insect
    - VLP, rHA
    - HPV

**Egg Supplier**

**Emerging Technology Strategy**

- **Egg-based Strategy**
  - IIV/LAIV
  - YF
  - Measles

**Egg-based Strategy**

1. Characterize in-country / in-region market demands for non-influenza vaccines
2. Identify technology transfer opportunities and commence discussions
3. Conduct resource requirements assessment
4. Contract A&E firm to develop conceptual designs for facility expansion to house additional eggs
5. Conduct regional market analysis for eggs for influenza vaccine manufacture

**Emerging Technology Strategy**

1. Characterize in-country / in-region market demands for non-influenza vaccines
2. Identify technology transfer opportunities and commence discussions
3. Contract A&E firm to develop conceptual designs for retrofitting inoculation suite
4. Conduct resource requirements assessment
Potential Multiproduct Vaccine Manufacturing Scenarios for Egg-based Influenza Vaccine Facility

Manufacturing Scenarios are developed based on:
1. Hypothetical current (and potential) capabilities*
2. The vaccines of regional interest
3. Vaccines compatible with current (and planned) platforms and vaccines of interest (based on 1 and 2 above)

*Top 6 demanded vaccines

Creative Sustainability Opportunities for Egg-based Operations: Beyond Vaccine Products

Egg-based Influenza Vx Operations

- Secondary egg-base products
  - Phospholipid (purified from egg yolk) as carriers for lipophilic drugs
  - Liposomes for drug delivery
- Supplier of Eggs
- Other Vaccines
  - Measles
  - Mumps
  - MVA / MVA Vectors
  - Yellow Fever
- Veterinary Vx’s

• Veterinary vaccines are out of scope for the current project

Source:
1http://www.phospholipid.jp/phospholipid_2-1.html
Ongoing Areas of Assessment

Other Key Considerations for Sustainability

This technology feasibility study provides a foundation for a comprehensive sustainability analysis with a long-term perspective. Additional considerations should be given to other key elements:

- Economics and resource requirements
- Market demand
- Public health and industrial policies
- IP / tech transfer

Assessment of sustainability feasibility should also explore alternative operating models (e.g., ‘hub-and-spoke’, partnerships with large pharma) that may offer more efficient and effective access for developing countries to influenza vaccines.
Conclusions

• Long term sustainability:
  – Egg based production may offer limited future expansion capabilities to new vaccine markets
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