Assessment of Influenza Vaccine Production Compatibilities

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The findings and conclusions in this presentation are those of the author(s) and do not necessarily represent the views of the Department of Health and Human Services or its components.
WHO Global Action Plan to increase pandemic influenza vaccine manufacturing capacity in developing countries suggested an assessment of a multiproduct approach as a means to advance manufacturer sustainability.

HHS commissioned an assessment of the feasibility of multiproduct facilities, where one product is influenza.

Critical Elements of the Assessment

• Manufacturing compatibility
  — Platform technology (egg, mammalian, etc)
  — Current capability

• Case Study Multiproduct scenarios
Study Approach

• **“As-Is” Research:**
  – Characterize the current capabilities and capacities of Case Study facilities
  – Update licensed influenza vaccine products and vaccine candidate landscape
  – Identify higher priority in-market vaccines that may be of interest for Case Study facilities to manufacture
  – Characterize industry adoption of multiproduct manufacturing operations

• **“To-Be” Technical Scenarios:**
  – Develop illustrative hypothetical operational scenarios
  – Examine potential cost implications, operational models, staffing requirements and potential risks

• **Recommendations & Roadmaps:**
  – Develop implementation recommendations and roadmaps to achieve sustainable multiproduct manufacturing capability and capacity in developing countries that could support production of influenza vaccines
Included in the technology assessment:

- Egg based manufacturing
- Mammalian cell culture
- Microbial fermentation
- Insect cell
- Phase 2+ products
Toward Multiproduct Influenza Vaccine Facilities

Technology Drivers
• Increased diversity of influenza vaccine manufacturing technologies
• Smaller-scale facility footprints
• Single use equipment adoption
• Shared resources

Challenges/Opportunities
• Human capital
• Scalability and supply chain
• Costs
• Influenza vaccine candidate development risks
• Operational complexity
• Risk of contamination
# Influenza Vaccine Landscape

## Pre Clinical
- Egg-based inactivated
- Cell-culture inactivated
- Recombinant (VLPs)
- Universal
- Vectors/Adjuvant
- DNA

## Phase 1
- sanofi pasteur
- GPO
- Vical

## Phase 2
- sanofi pasteur
- Biogen Vaccines
- Vical

## Phase 3
- sanofi pasteur
- CSL Biotherapies
- Sanofi Pasteur

## Market Approval
- CSL Biotherapies
- Sanofi Pasteur

## Cell-culture inactivated
- MedImmune
- Vivalis

## LAIV
- MedImmune

## Recombinant (VLPs)
- TechnoVax
- GLOBEImmune
- GLOBEImmune

## Universal
- NYU / MSSM
- Emergent

## Vectors/Adjuvant
- MVA Based
- Adenovirus
- Mucosia

## DNA
- Vical

Updated: 10 JAN 2013
# Influenza Vaccine Manufacturing Technology Compatibility?

<table>
<thead>
<tr>
<th>Manufacturing Platform</th>
<th>Influenza vaccine candidate/ products</th>
<th>Non-influenza vaccine candidate/ products</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Embryonated Chick Egg</strong></td>
<td>Licensed: 21</td>
<td>Yellow Fever&lt;br&gt;Mumps&lt;br&gt;Measles (CEF)</td>
</tr>
<tr>
<td></td>
<td>Phase 3: 5</td>
<td>Rabies&lt;br&gt;</td>
</tr>
<tr>
<td></td>
<td>Phase 2: 8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phase 1: 5</td>
<td></td>
</tr>
<tr>
<td><strong>Mammalian Cell Culture</strong></td>
<td>Licensed: 2</td>
<td>Yellow Fever&lt;br&gt;Yellow Fever&lt;br&gt;HepA&lt;br&gt;Japanese&lt;br&gt;Encephalitis&lt;br&gt;Measles&lt;br&gt;Rotaviral&lt;br&gt;Rubella</td>
</tr>
<tr>
<td></td>
<td>Phase 3: 0</td>
<td>Rabies&lt;br&gt;</td>
</tr>
<tr>
<td></td>
<td>Phase 2: 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phase 1: 2</td>
<td></td>
</tr>
<tr>
<td><strong>Microbial Fermentation</strong></td>
<td>Licensed: 0</td>
<td>BCG&lt;br&gt;Diphtheria&lt;br&gt;DTP&lt;br&gt;HepB&lt;br&gt;Hib&lt;br&gt;Meningitis A/C&lt;br&gt;Pneumococcal&lt;br&gt;Pertussis&lt;br&gt;Rubella&lt;br&gt;Td&lt;br&gt;TT&lt;br&gt;Typhoid</td>
</tr>
<tr>
<td></td>
<td>Phase 3: 0</td>
<td>Rabies&lt;br&gt;</td>
</tr>
<tr>
<td></td>
<td>Phase 2: 5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phase 1: 6</td>
<td></td>
</tr>
<tr>
<td><strong>Insect Cell Expression</strong></td>
<td>Licensed: 0</td>
<td>HPV</td>
</tr>
<tr>
<td></td>
<td>Phase 3: 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phase 2: 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phase 1: 3</td>
<td></td>
</tr>
</tbody>
</table>
Scenarios Presented

- Maintain existing manufacturing infrastructure and capabilities
- Improve sustainability by adding a compatible product(s) to the facility’s manufacturing portfolio, with minimal investment
Risks that are Independent of the Scenario

- Limited manufacturing expertise and experience
- Timelines to new vaccine development
- Facility Design challenges
- Technology transfer
- Intellectual property costs
- Regulatory compliance
- Supply chain
- Financial sustainability
### Example Multiproduct Scenario 1

<table>
<thead>
<tr>
<th>Capability: Microbial Fermentation</th>
<th>Campaign 1</th>
<th>Campaign 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbial, Hib vaccine</td>
<td>Microbial, recombinant influenza vaccine</td>
<td></td>
</tr>
<tr>
<td>Output (doses)</td>
<td>3.8M</td>
<td>0.35M TIV</td>
</tr>
<tr>
<td>Mfg Time (wks)</td>
<td>7-13 (3-6 runs)</td>
<td>27 (9 runs)</td>
</tr>
<tr>
<td>CapEx (US$)</td>
<td>None</td>
<td>Minimal</td>
</tr>
<tr>
<td>OpEx (US$)</td>
<td>1.6-3.1M</td>
<td>10-11M</td>
</tr>
<tr>
<td>Risk: Cross-contamination</td>
<td></td>
<td>Risks:</td>
</tr>
</tbody>
</table>

- Unproven microbial based influenza vaccine product
- Long development/ approval timelines
- Scale of production does not meet projected demand
- Cost per dose may be prohibitive

**Location:** South Africa
## Example Multiproduct Scenario 2

<table>
<thead>
<tr>
<th>Capability: Egg based</th>
<th>Campaign 1</th>
<th>Campaign 2</th>
<th>Campaign 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location: Vietnam</td>
<td>Egg-based IIV</td>
<td>Egg-based Yellow Fever, live attenuated</td>
<td>CEF Cells, measles live attenuated</td>
</tr>
<tr>
<td>Capacity: 5k Eggs/wk</td>
<td>Output (doses) 27-33K TIV</td>
<td>Output (doses) 5M</td>
<td>Output (doses) 10-12.3M</td>
</tr>
<tr>
<td></td>
<td>Mfg Time (weeks) 20</td>
<td>Mfg Time (weeks) 2</td>
<td>Mfg Time (wks) 14</td>
</tr>
<tr>
<td></td>
<td>CapEx (US$) N/A</td>
<td>CapEx (US$) Live viral lab: $300-400k</td>
<td>CapEx (US$) Minimal</td>
</tr>
<tr>
<td></td>
<td>OpEx (US$) 100k</td>
<td>OpEx (US$) 1-2M</td>
<td>OpEx (US$) 7-7.5M</td>
</tr>
</tbody>
</table>

**Risks:**
- Local utility infrastructure
- Yield may not meet market demand
- Egg supply

**Risks:**
- Difficulty recruiting qualified staff
- Isolated location may create supply chain risks
- No prior experience manufacturing YF vaccine
- No regional market
- Cross-contamination potential

**Risks:**
- No prior experience with CEF cell culture
- Cross-contamination potential
“Crawl – Walk – Run”

- Continue to develop capability though partnership with existing seasonal influenza manufacturers
- Strengthen core competencies – quality, regulatory, process control
- Progressively implement more complex processes with higher risk

**Assessment Outlook**

<table>
<thead>
<tr>
<th>Phases</th>
<th>Discovery</th>
<th>Preclinical Development</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Licensure</th>
<th>Production &amp; Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>3-7 yr</td>
<td>0.5-2 yr</td>
<td>1-2 yr</td>
<td>2-3.5 yr</td>
<td>2.5-4 yr</td>
<td>1-2 yrs</td>
<td></td>
</tr>
<tr>
<td>Pipeline</td>
<td>$100M-130M</td>
<td>$60-70M</td>
<td>$70M-100M</td>
<td>$130M-160M</td>
<td>$190M-220M</td>
<td>$18M-20M</td>
<td></td>
</tr>
<tr>
<td>Phase Cost</td>
<td>$100M-130M</td>
<td>$60-70M</td>
<td>$70M-100M</td>
<td>$130M-160M</td>
<td>$190M-220M</td>
<td>$18M-20M</td>
<td></td>
</tr>
<tr>
<td>Post to Licensure</td>
<td>1-3%</td>
<td>5 - 17%</td>
<td>10 - 25%</td>
<td>18 - 35%</td>
<td>45 – 70%</td>
<td>90%</td>
<td></td>
</tr>
</tbody>
</table>

*Total out of pocket costs from Discovery through Licensure to develop a single successful product (includes attrition).

Sources:
Assessment Conclusions

• It is technically feasible to implement a multiproduct manufacturing facility
  – BARDA CIADM investment is an experiment in multiproduct facilities
  – VABIOTECH, MedImmune multiproduct cell based facilities
• However, in the near term (10 years) when considering the existing capabilities, complexities of implementation and training requirements, a multiproduct approach may not appear practical for all settings
  – Not surprising – multiproduct facility design and implementation is difficult for any organization
• Adoption of new technologies in single use, manufacturing quality or regulatory may dramatically change this assessment
Thank You for Your Attention

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