Challenges of Making Vaccines for Trans-boundary Diseases:

An Industry Perspective

September 2012

Robert M Nordgren
Global Head of Biologics R&D
Merial Ltd
“It is time to close the book on infectious diseases and shift all national attention (and dollars) to … chronic diseases.”

- US Surgeon General, 1967

“Prophecy is very difficult, especially as it relates to the future”

- Mark Twain, Niels Bohrs, Casey Stengel and I predict many more in the future
The reality is…it’s a jungle out there.
The consequences of urbanization, global travel, climate changes and demands of expansive commercial agriculture:

- **Zoonosis**
  - The three most devastating pandemics in history were zoonotic.
  - 75% of the recent emerging pathogens are zoonotic (WNV, SARS, AIV, Nipah/Hendra, ...)

- Newly Discovered Commercial Animal Pathogens
  - IBDV, PRRS, PCV2, SBV

- Emerging and Remerging Animal Pathogens
  - FMD, CSF, BTV, ASF

Not to mention food safety…
The question then becomes:

How do you make a vaccine you hope to never have to use?
The question then becomes:

How do you make a vaccine you hope to never have to use?

Or worse yet:

That no one wants to pay for?
The question then becomes:

How do you make a vaccine you hope to never have to use?

Or worse yet:

That no one wants to pay for?

One way “industry” addresses this…
Net Present Value

- NPV is one of the standard financial methods used to appraise the interest of long-term projects.
- Is one indicator of the amount of value an investment or project adds to the firm.
- Is a risk-adjusted calculation, taking into account outgoing and incoming cash flows over time.

**Simply;**
- **NPV > 0**: the investment would add value to the firm and the project may be accepted.
- **NPV < 0**: the investment would subtract value from the firm and the project should be rejected.
- **NPV = 0**: the investment would neither gain nor lose value for the firm but may be interesting for other reasons.
## NPV Evaluation

<table>
<thead>
<tr>
<th>Market Potential</th>
<th>Geographical Areas and Countries</th>
<th>Populations Concerned</th>
<th>Persistence of the Problem</th>
<th>Achievable Market Share</th>
</tr>
</thead>
<tbody>
<tr>
<td>Return on Investment</td>
<td>R&amp;D Costs</td>
<td>Capital Expenditures</td>
<td>Revenues</td>
<td>Operating Expenses</td>
</tr>
<tr>
<td>Environmental Risks</td>
<td>Vaccine Need</td>
<td>Control Policies</td>
<td>Veterinary Capacities</td>
<td>Budget</td>
</tr>
</tbody>
</table>
The Desired Model i.e. PCV2, iPod

- Disease well known and the need and product profile are clearly defined.
- Market potential exists and likely to persist for at least 5 years and beyond.
- R&D facility and capabilities in place (red) without major resource constraints.
- Minor adjustment to production and storage facility (orange).
- Technical feasibility confirmed and regulatory pathway typical
- Investments relatively limited and clearly linked to time needed for development.

NPV > 0: the investment would add value to the firm and the project would be accepted
What happens when…..?

- Disease not well understood or no confirmed need for a vaccine.
- Sudden need for a vaccine, but disease is either self-limiting, rapidly controlled, only few animals are vaccinated, leading to a very short product lifecycle.
- Technical feasibility confirmed and some short cuts in regulatory pathway negotiated to assure short to medium time to market.
- R&D costs and time to market are limited but investment into production and storage facility (orange) are high.

NPV < 0: the investment would subtract value from the firm and the project should be rejected.
Ways to Address the Challenge

1. Use simple proven or platform technology.

NPV < 0: the investment would subtract value from the firm and the project should be rejected.
Ways to Address the Challenge

1. Use simple proven or platform technology.
2. Strictly limit claims to short term defined needs.

NPV < 0: the investment would subtract value from the firm and the project should be rejected.
Ways to Address the Challenge

1. Use simple proven or platform technology.
2. Strictly limit claims to short term defined needs.
3. Collaborate early and often with Regulatory Agencies to refine requirements.

NPV < 0: the investment would subtract value from the firm and the project should be rejected.
Platform Technology – Regulatory Cooperation

- Early Regulatory timelines often exceed technical timelines (103.3, SIF FONSI, review times...).
- Growing recognition of well established platforms like Alvac:
  - Specific rules for emergency situations.
  - Specific exemptions for well established platforms.

**West Nile Virus Timeline**

- **2/00** - 9/00
  - Marketing Request for Support of WNV Vaccine

- **2/2000**
  - Requested Import to Athens
  - Denied

- **3/01 - 6/01**
  - Aventis Pasteur Vet Team
  - Master Seed Virus
  - MS Made
  - Back-passage Study Complete
  - Efficacy Testing Initiated
  - 6/20/2001

- **7/2001**
  - MS Made
  - Efficacy Testing Completed
  - 4/02

- **8/2002**
  - FONSI Reports Submitted to USDA
  - 5/20/2002

- **9/2002**
  - FONSI Reports Submitted to USDA
  - 4/02

- **10/2002**
  - PLS Scheduled Off Test
  - 7/20/2002

- **11/2002**
  - PLS Scheduled

- **10/03**
  - Complete Field Study Trial

**Virogenetics**
- Access genes & start R&D program (Nov 00)
- Constructs ready for shipment to Athens (Mar 01)
- Import permit granted (Jun 01)

**Master Seed Virus**
- MSV Production (Jun 01)
- MSV Testing Complete (1 02)
- Transfer MSV to Production (2 02)

**Manufacturing**
- Transfer Lyon Process (3 02)
- Transfer Carbomer Production (Ongoing)
- Production PLS (Jun 02 Start)

**Milestones to Achieve**
- Duration of Immunity Feasibility (Oct 02)
- Submit efficacy report (Sep 02)
- Repeat Efficacy Study (Jan 03)
- Complete Field Trial Testing (4Q 03)

Ways to Address the Challenge

1. Use simple proven or platform technology.
2. Strictly limit claims to short term defined needs.
3. Collaborate early and often with Regulatory Agencies to refine requirements.
4. Gain external financial to lessen risk.

NPV < 0: the investment would subtract value from the firm and the project should be rejected.
opportunities are expanding:

- CRADA’s with USDA
- Department of Homeland Security
- FAZD, CEEZAD
- BMGF, others (BAUC)
- Shared resources with other agencies (CDC)
- GalvMed
- EU Funding (Horizon 2020)
- Others…
Ways to Address the Challenge

1. Use simple proven or platform technology.
2. Strictly limit claims to short term defined needs.
3. Collaborate early and often with Regulatory Agencies to refine requirements.
4. Gain external financial to lessen risk.
5. Ensure funding by way of banks or supported markets.

NPV < 0: the investment would subtract value from the firm and the project should be rejected.
Banks etc...

How big is the pie, and how many slices do you have

Decisions about how to use it

Korea FMD 2011

Size and who is willing to share...

Small private banks?
Ways to Address the Challenge

1. Use simple proven or platform technology.
2. Strictly limit claims to short term defined needs.
3. Collaborate early and often with Regulatory Agencies to refine requirements.
4. Gain external financial to lessen risk.
5. Ensure funding by way of banks or supported markets.
6. Vaccination becomes common place - disease becomes endemic.

NPV < 0: the investment would subtract value from the firm and the project should be rejected.
West Nile 1999

Incidences per million:
- .01-9.99
- 10-99.99
- >=100
- Any WNV Activity

West Nile Virus Transmission Cycle

1. Mosquito vector
2. West Nile virus
3. Bird reservoir hosts
4. Incidental infection
WNV Activity from 2000-2003

2000

2001

2002

2003
Ways to Address the Challenge

1. Use simple proven, or platform technology.
2. Strictly limit claims to short term defined needs.
3. Collaborate early and often with Regulatory Agencies to refine requirements.
4. Gain external financial to lessen risk.
5. Ensure funding by way of banks or supported markets.
6. Vaccination becomes common place - disease becomes endemic.
7. Expand markets to the include source countries.

NPV < 0: the investment would subtract value from the firm and the project should be rejected.
Going Back to the Home Country…

West Nile has been recorded in the south of France for 20+ years…

Vaccines were developed in the US 6-8 years earlier that EU spread to the north..
Ways to Address the Challenge

1. Use simple proven or platform technology.
2. Strictly limit claims to short term defined needs.
3. Collaborate early and often with Regulatory Agencies to refine requirements.
4. Gain external financial to lessen risk.
5. Ensure funding by way of banks or supported markets.
6. Expand markets to the include source countries.
7. Vaccination becomes common place - disease becomes endemic.
8. It becomes part of your Corporate Strategy.

NPV < 0: the investment would subtract value from the firm and the project should be rejected.
Industry overview

- A complex sector due to a large variety of species

Animal Health...

...is a public health concern:
Food safety, response to epidemics, fight against emerging and zoonotic diseases (rabies, avian influenza, etc.)

...contributes to human welfare:
Companion animals become family members

...has important economic implications:
The livestock industry supports a country’s economic health and trade (foot and mouth disease, Bluetongue, etc.)
Ideal State?

- Vaccine Development program is streamlined with well known, platform technologies.
- Conditional - ATU registrations are employed to reduce regulatory times.
- Cooperation with State/Fed/Private fundings allow for resources to be deployed.
- Vaccination is used as a coordinated effort to control spread of the disease.
- Vaccine stacks are available for future outbreak or extensions into new markets.

NPV > 0: the investment could gain nor lose value for the firm but is interesting because the risks can be mitigated through a close collaboration between all major stakeholders.
A Tale of 2 Diseases

“They were the best of vaccines, they were the worst of vaccines.”

- Hendra and Nipah viruses are newly discovered zoonotic viruses first isolated from outbreaks in Australia (1994) and Malaysia (1998).
- The viruses are closely related and member of the paramyxoviridae family, genus Henipavirus.
- The viruses cause severe disease in a variety of animal species, including humans, horses, pigs, dogs and cats.
- **Both viruses are classified as BSL-4 pathogens and Nipah is on the list of select agents by the USDA.**

Hendra Outbreaks

In September 1994, an outbreak of acute respiratory disease occurred in a group of horses outside Brisbane.

20 horses affected: 14 died (6 euthanized).

Two people caring for the index case became infected, 1 died.

Cases (including fatalities) have continued to appear sporadically through this year with impact on equine practice and horse industry.

- Cairns 1999: 1 horse 2004: 1 horse, 1 human
- Mackay 1994: 1 horse, 1 human
- Rockhampton 2009: 3 horses, 1 human
- Townsville 2004: 1 horse
- Cannonvale 2008: 1 horse
- Peachester 2006: 1 horse 2007: 1 horse
- Brisbane 1994: 20 horses, 2 humans
- Brisbane 2008: 5 horses, 2 humans
- Murwillumbah 2006: 1 horse

Adapted from Heil & Richards (2000)
Nipah Outbreak

Nipah emerged in 1998 in Malaysia and caused widespread panic because of the high mortality rate (40%) in people and the inability to control the disease initially.

The Malaysian outbreak caused considerable social disruptions and tremendous economic loss to an important pig industry.

- Nearly 1 million pigs culled (58 M$)
- Loss of the capital infrastructure on farms
- Loss of employment - 36,000 jobs
- Loss of export income - 120 M$
ALVAC – the example of Hendra

- Recombinant ALVAC constructs expressing G and F of Hendra were made and tested for immunogenicity in horses (MS). A vaccination/challenge experiment in horses funded by CSIRO, Australia is scheduled for 4Q2012.
- Registration program aggressively underway (by at least 2 companies).
## ALVAC – The Example of Nipah

### Challenge control pigs

<table>
<thead>
<tr>
<th>dpi</th>
<th>1+2</th>
<th>3+4</th>
<th>6+7</th>
</tr>
</thead>
<tbody>
<tr>
<td>#39</td>
<td>NW</td>
<td></td>
<td>480</td>
</tr>
<tr>
<td>PS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#40</td>
<td>NW</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>PS</td>
<td>10</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>#41</td>
<td>NW</td>
<td>100</td>
<td>10</td>
</tr>
<tr>
<td>PS</td>
<td></td>
<td></td>
<td>60</td>
</tr>
<tr>
<td>#42</td>
<td>NW</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### ALVAC – F vaccinates

<table>
<thead>
<tr>
<th>dpi</th>
<th>1+2</th>
<th>3+4</th>
<th>6+7</th>
</tr>
</thead>
<tbody>
<tr>
<td>#31</td>
<td>NW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#32</td>
<td>NW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#33</td>
<td>NW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#34</td>
<td>NW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### ALVAC – G vaccinates

<table>
<thead>
<tr>
<th>dpi</th>
<th>1+2</th>
<th>3+4</th>
<th>6+7</th>
</tr>
</thead>
<tbody>
<tr>
<td>#35</td>
<td>NW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#36</td>
<td>NW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#37</td>
<td>NW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#38</td>
<td>NW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### ALVAC-F + ALVAC-G vaccinates

<table>
<thead>
<tr>
<th>dpi</th>
<th>1+2</th>
<th>3+4</th>
<th>6+7</th>
</tr>
</thead>
<tbody>
<tr>
<td>#43</td>
<td>NW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#44</td>
<td>NW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#45</td>
<td>NW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#46</td>
<td>NW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Results: Vaccination prevented virus shedding

ALVAC – The Example of Nipah

ALVAC – F vaccinates

ALVAC – G vaccinates

ALVAC-F + ALVAC-G vaccinates

Results: Vaccination prevented virus shedding
Recombinant Nipah Virus Vaccines Protect Pigs against Challenge

Hana M. Weingartl,¹,²* Yohannes Berhane,¹ Jeff L. Caswell,³ Sheena Loosmore,⁴ Jean-Christophe Audonnet,⁵ James A. Roth,⁶ and Markus Czub²,⁷

NCFAD, CFIA, Winnipeg, Canada¹; NML, PHAC, Winnipeg, Canada⁷; Department of Medical Microbiology, University of Manitoba, Winnipeg, Canada²; Department of Pathobiology, University of Guelph, Guelph, Canada³; College of Veterinary Medicine, Iowa State University, Ames, Iowa⁶; Sanofi Pasteur, Toronto, Canada⁴; and Merial SAS, Lyon, France⁵
ALVAC – The Example of Nipah

However.....

Recombinant Nipah Virus Vaccines Protect Pigs against Challenge

Hana M. Weingartl,1,2* Yohannes Berhane,1 Jeff L. Caswell,3 Sheena Loosmore,4 Jean-Christophe Audonnet,5 James A. Roth,6 and Markus Czub2,7

NCFAD, CFIA, Winnipeg, Canada1; NML, PHAC, Winnipeg, Canada7; Department of Medical Microbiology, University of Manitoba, Winnipeg, Canada2; Department of Pathobiology, University of Guelph, Guelph, Canada3; College of Veterinary Medicine, Iowa State University, Ames, Iowa6; Sanofi Pasteur, Toronto, Canada4; and Merial SAS, Lyon, France5
Classic example of:

- Even when the science is proven and the willingness and support of *some of the finest* scientists are present,
- Coordination, collaboration and contribution are key and required,
- Will likely only succeed with a clearly communicated business case.
Summary

Trends show that epidemiological intrusions into our status quo are not slowing and a perfect storm is likely out there…

History shows all parties can come together to address the food production and veterinary public health needs in times of crisis.

Recent evidence of new collaboration models bring promise that we are closer than ever to allowing all parties to fulfill their roles in protecting the public’s needs.
Thank you for your attention.