Biologics Industry Challenges for Developing Diagnostic Tests for the National Veterinary Stockpile

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September 17, 2012
Pfizer Animal Health Overview

FAD Threats & National Veterinary Stockpile

Product Development

Industry Challenges
Pfizer Animal Health

World leader in discovery, development, and manufacture of veterinary vaccines & medicines

5000+ colleagues worldwide including 800+ veterinary R&D scientists and specialists

Diverse portfolio of leading veterinary products & services for livestock & companion animals

Operating in 70 countries
Leadership by Regions & Species

2011 Revenue By Region

- U.S.: 39%
- EuAfME: 19%
- CLAR: 15%
- Asia: 26%

2011 Revenue By Species

- Cattle: 38%
- Poultry: 12%
- Small Animals: 30%
- Swine: 13%
- Equine: 4%

1% of revenues not accounted for through regional commercial groupings and 3% of revenues not accounted for through species groupings are considered "other"; Based on PAH 2011 revenues.
Pfizer Animal Health Overview

FAD Threats & National Veterinary Stockpile

Product Development

Industry Challenges
Foreign Animal Disease Threats

- Foreign Animal Threat Subcommittee
  - Identified R&D needs to fill product gaps
    - Models
    - Vaccines & Diagnostics
    - Decontamination
    - Basic research

- High Priority Threats
  - Highly Pathogenic Avian Influenza
  - Foot and Mouth Disease
  - Rift Valley Fever
  - Exotic Newcastle
APHIS List of 17 Most Damaging Animal Disease Threats

1. Highly Pathogenic AI (F)
2. Foot-and-Mouth Disease
3. Rift Valley fever (F)
4. Exotic Newcastle Disease
5. Nipah and Hendra virus (F)
6. Classical swine fever
7. African swine fever
8. Bovine spongiform encephalopathy
9. Rinderpest
10. Japanese encephalitis (F)
11. African horse sickness
12. Venezuelan equine (F) encephalitis
13. Contagious bovine pleuropneumonia
14. *Ehrlichia ruminantium* (Heartwater)
15. Eastern equine encephalitis (F)
16. *Coxiella burnetii* (F)
17. Akabane virus

F: Potentially fatal to humans - Zoonotic
Gold text: FBI pathogens of concern
A comprehensive diagnostic plan which addresses many of the interagency consensus, critical diagnostic gaps in FAD diagnostics would include:

- Validated single and multiplexed, high-throughput (HTP) differential diagnostics for use in surveillance, confirmation, response, and recovery
- Validated HTP diagnostics to differentiate infected vs. vaccinated animals (DIVA) during the recovery phase
- Capabilities for validation and technology transfer of these assays to NVSL and the NAHLN
- An enduring basic discovery, development, validation, and technology transfer program for continued identification and movement of new and emerging technologies to NVSL and the NAHLN
- A robust reagent production program to ensure a reliable source of reagents (produced in the U.S.) needed to proficiency test, train, validate and perform assays in the NVSL and NAHLN laboratories
Vaccine and Compatible DIVA Diagnostic ELISA

**Competitive ELISA**

- **Bovine Sera**
- **Goat Anti-bovine IgG(H+L) HRP**
- **Infected Bovine Sera**
- **Blocking mAb**
- **Goat Anti-bovine IgG(H+L) HRP**
- **Vaccinated Bovine Sera**
- **Blocking mAb**
- **Goat Anti-bovine IgG(H+L) HRP**

50% Cut-off

- **Infected**
- **Vaccine 1**
- **Vaccine 2**
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Product Development

Industry Challenges
Typical Vaccine and Diagnostic Product Progression Paths – Programmatic Synergy

**Concept Evaluation**
- Establish product profile
- Antigen selection
- Model development
- Formulation
- Safety & efficacy testing
- Preliminary assay development

**Discovery Phase**
- Scale-up manufacturing
- Analytical and in-process assays
- Formulation confirmation
- Transfer to manufacturing
- Potency assay validation
- Pre-license serials
- Pivotal safety and efficacy testing
- Labels, etc.

**Development Phase**
- US and ROW Regulatory filing
- Product launch
- Label and claim extension studies

**Vaccines**

**Diagnostics**
- Establish product profile
- Biological reagents selection
- Feasibility study
- Assay Development and Optimization
- Research Efficacy Study

- Scale-up manufacturing
- Transfer to manufacturing
- Pre-license serials
- Field trials

**Post-Launch Studies**
- US and ROW Regulatory filing
- Product launch
# Diagnostics and Decision Making

## Emotion-based decision making

<table>
<thead>
<tr>
<th>Pets</th>
<th>Horses</th>
<th>Cow/Calf</th>
<th>Feedlot</th>
<th>Dairy</th>
<th>Pigs</th>
<th>Poultry</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Dogs &amp; Cats)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

- Creating awareness
- Confirming clinical picture: infectious, parasitic, metabolic, neoplastic, congenital, degenerative diseases
- Determining immunologic status
- Monitoring & measuring compliance & control

## Economic-based decision making

### Analyzing Economic Performance:
- Feed Conversion
- Average Daily Gain
- Fecundity

### Monitoring Pathogens & Immunologic Status:
- Vaccine compliance
- Food Safety/Zoonosis
- BioSecurity/Eradication
Varying Diagnostics Intervention Points

1. Problem
2. Creating Awareness
3. Clinical Evaluation
4. Confirm Clinical Picture
5. Determine Intervention
6. Timing of Intervention
7. Intervention VAX/RX
8. Measuring Compliance & Effectiveness
RIM® Rapid Immuno Migration

Sample pad 14mm
Conjugate pad 10mm
Nitrocellulose
Adhesive Baking

Test line
Control line
Absorbant pad
RIM® Rapid Immuno Migration- Ab test

Positive sample (with Anti-\textit{Ehrlichia} \textit{Ab})

Protein A Colloidal gold

Anti-rabbit - colloidal gold goat \textit{Ab}

\textit{Ehrlichia} \textit{Ag}

Test line

Control line

Rabbit serum
Rapid Immuno Migration

Sample application (1 drop) with the calibrated pipette

Buffer solution (3 drops)

Waiting...

Résultat négatif

Negative result

Interpretation

Résultat positif

Positive result
Microwell ELISA Technology

Plate Washer

Plate Reader
Molecular Diagnostics
Expanding Role of Diagnostics

- Increased corporate ownership of intensive, integrated production systems
  - Food safety promotes systems with high biosecurity
  - Globalization of agricultural trade
  - Foreign animal diseases pose a great threat to livestock industry
  - Demands for rapid detection, diagnosis, and prevention of foreign animal diseases
  - Rapid point-of-care tests will increase
  - More synergy between diagnostics, therapeutics and vaccines with DIVA concept
Expanding Future Diagnostics Role

• Traditional clinical confirmation
• Accurate, relevant, consistence, and rapid monitoring diagnostics tests
• Provide intervention timing for successful outcome
• Herd Health Management
  – New Sophisticated lab based data management system to handheld devices for rapid dissemination of diagnostic results in a cost efficient manner
Future Veterinary Molecular Diagnostics

• Portable, point of care diagnostic devices
• Multiplex
• Quantitative
• Rapid Polymerase chain reaction assays
• Microarray testing
• Genomic analysis
• Metabolic profiling
• Isothermal-based molecular diagnostics

Putting A Laboratory In The Palm Of Your Hand

Sensitive diagnostic methods for detecting pathogens will continue to be the basis for treating, controlling, monitoring and eradicating infectious diseases of veterinary importance.
Evolving Technology

1. Collect sample, simple lysis
   - 1 - 2 mins

2. Rehydrate lyophilised RPA reagents (stabilised format)
   - 1 min

3. Reaction incubation
   - 8 - 12 mins

4. Diagnosis
   - Cheap
   - Easy-to-use
   - Results within ~15 mins
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Product Development

Industry Challenges
Industry Challenges: Process

- Process and Government interactions
  - Many AH large companies don’t check FedBizOps regularly
  - CRADA process not well understood
  - Government invoicing
  - FADT SC, DHS, USDA-CVB, & NVS alignment
  - Office of Procurement

- Select Agent Program hurdles
  - Bureaucracy
  - Paperwork
  - Expertise and clearances
  - Physical laboratory requirements
Industry Challenges: Legal

• Intellectual Property rights
• Ability to obtain isolates and/or antigens with FTO
• International shipping
• Import permits
• Liability
Industry Challenges: Fiscal

- **Fiscal:** “Valley of Death” & lack of open markets

<table>
<thead>
<tr>
<th>Disease</th>
<th>Select Agent</th>
<th>Present in US</th>
<th>Present in EU</th>
<th>US/EU Diagnostics</th>
<th>US¹/EU² Vaccines</th>
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<tbody>
<tr>
<td>Highly Pathogenic AI</td>
<td>Yes</td>
<td>No (2004)</td>
<td>No</td>
<td>No/Yes</td>
<td>Yes</td>
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<tr>
<td>Foot-and-Mouth Disease</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No/Yes</td>
<td>Yes</td>
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<tr>
<td>Rift Valley fever</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Exotic Newcastle Disease</td>
<td>Yes</td>
<td>Yes (wild)</td>
<td>Yes</td>
<td>Yes (Govt only)</td>
<td>Yes</td>
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<tr>
<td>Nipah and Hendra virus</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Classical swine fever</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>African swine fever</td>
<td>Yes</td>
<td>No</td>
<td>Yes (Sporadic)</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Bovine spongiform encephalopathy</td>
<td>Yes</td>
<td>No (2006)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Rinderpest</td>
<td>Yes</td>
<td>No</td>
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<td>No/Yes</td>
<td>No</td>
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<td>Japanese encephalitis</td>
<td>Yes</td>
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<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>African horse sickness</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Venezuelan equine encephalitis</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No (Govt only)</td>
<td>Yes</td>
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<tr>
<td>Contagious bovine pleuropneumonia</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<td><strong>Ehrlichia ruminantium</strong> (Heartwater)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Eastern equine encephalitis</td>
<td>Yes (HHS)</td>
<td>Yes (Sporadic)</td>
<td>No</td>
<td>No (Govt only)</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Coxiella burnetii</strong> (Q-Fever)</td>
<td>Yes (HHS)</td>
<td>Yes (Sporadic)</td>
<td>Yes</td>
<td>No/Yes</td>
<td>Yes</td>
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<tr>
<td>Akabane virus</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

### Industry Challenges: Technology

#### Conventional Technologies
- Traditional clinical pathology Microbiological
- Culture based confirmation
- Lab-based Conventional Serology (HI, SN, IFA, AGID)

#### Existing Technologies
- High throughput ELISA
- Ag and Ab
- POC lateral flow
- Ab and Ag
- Rt PCR

#### Evolving Technologies
- Rapid PCR (Pen side)
- Lateral Flow Detection-Isothermal PCR
- Microfluid immunoassay (1 or 2 minutes)
- Nanotechnology – Lab on the Chip
- Fluorescent polarization
- Radio-frequency-phase-shift (RFPS)
- Sensor based rapid assays
Industry Challenges: Technology

Range of Detection in a Flock/herd

- **Rapid Detect**
  - AGID (may start to decrease after 30 days)
  - rRT-PCR

- **Virus Isolation**

- **ELISA**

- **HI**

Days Post-Infection

Virus Level

0 7 14 21 28
Points to Consider

- Focus on partnerships
  - Government - Academia – Industry
- Reduce bureaucracy
- Early product profile development
- Clear IP and ownership
- Co-Development funding for Veterinary Medical Countermeasures
  - Analogous to DoD and HHS MCM Development Programs
    - Funding and Advanced Development facilities (MCM-I)
Back-up Slides
Who We Are

A Pfizer business

A leading global animal health company

Working to assure a safe, sustainable global food supply from healthy beef and dairy cattle, swine, poultry and fish

Helping dogs, cats and horses live healthier longer lives

WORKING ON VACCINES FOR CHILDREN.

AND THOSE WHO ACT LIKE THEM.

Working together for a healthier world.™
A Long History of Leadership & Growth

1952
Pfizer established Agricultural Division

1995
Acquired SmithKline Beecham Animal Health (Norden Laboratories)

2007
Acquired Embrex

2009
Acquired Wyeth/Fort Dodge Animal Health
  Acquired Vetnex

2011
Acquired King/Alpharma Animal Health

1971
Central Research Division created

1988
Agricultural Division renamed Animal Health Division

2003
Acquired Pharmacia
  Established PAH R&D HQ in Kalamazoo, MI
  Acquired CSL Animal Health

2008
Acquired Catapult and Bovigen to form Animal Genetics business
  Acquired Schering-Plough/Intervet product brands for European market

2010
Acquired Microtek
  Epitopix Global Licensing Agreement
  Acquired Synbiotics
Future FAD Veterinary Countermeasure Development – Areas of RDT&E

- Diagnostic technologies to provide tools for detection and surveillance and surge capacity during response and recovery
- Vaccines and immunomodulators needed for an effective response to an incursion of the disease
- Basic research on disease epidemiology and disease pathogenesis to provide a greater understanding of disease spread

This research would allow for the development and the implementation of next generation diagnostics at National Veterinary Services Laboratories (NVSL), the National Wildlife Health Center (NWHC), and in the National Animal Health Laboratory Network (NAHLN) [part of the Laboratory Response Network (LRN)], and provide well-characterized current generation and next generation vaccines and immunomodulators available for acquisition by the NVS.
Select Agent List

**SELECT AGENTS AND TOXINS**

The following biological agents and toxins have been determined to have the potential to pose a severe threat to both human and animal health, to plant health, or to animal and plant products. An attenuation strain of a select agent or an inactivated form of a select toxin may be excluded from the requirements of the Select Agent Regulations. This list of excluded agents and toxins can be found at [http://www.selectagents.gov/Select%20Agents%20and%20Toxins%2FExclusions.html](http://www.selectagents.gov/Select%20Agents%20and%20Toxins%2FExclusions.html).

**HHS SELECT AGENTS AND TOXINS**

- Abir prophage
- Botulinum neurotoxins
- Botulinum neurotoxins producing species of Clostridium perfringens
eulavirus
- Corynebacterium diphtheriae
- Cutaneous herpesvirus 1 (Herpes B virus)
- Clostridium tetani
- Dengue virus
- East Measles Virus
- Ebola virus
- Filoviridae
- Francisella tularensis
- Lassa fever virus
- Marburg virus
- Monkeypox virus
- Reconstructed replication competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all eight gene segments (Reconstructed 1918 influenza virus)
- Rna virus
- Rickettsia prowazekii
- Rickettsia rickettsii
- Staphylococcal ribosome inactivating proteins (Staphylococci)
- South American Hemorrhagic Fever viruses
- Francisella tularensis
- Vola
- Zoonotic agents
- Reoviridae
- Reovirus
- Sabin
- Staphylococcus aureus
- Toxoplasma gondii
- TBE virus
- Tick borne encephalitis complex (TBE) viruses
- Central European Tick-borne encephalitis
- Far Eastern Tick-borne encephalitis
- Kyasanur Forest disease
- Orf (Vesicular Exanthem of Sheep and Goats)
- Russian Spring and Summer encephalitis
- Varicella major virus
- Varicella minor virus
- Varicella zoster virus
- Yersinia pestis

**OVERLAP SELECT AGENTS AND TOXINS**

- Bacillus anthracis
- Bacillus cereus
- Bacillus licheniformis
- Bacillus subtilis
- Burkholderia mallei (formerly Pseudomonas mallei)
- Burkholderia pseudomallei (formerly Pseudomonas pseudomallei)
- Hendra virus
- Nipah virus
- Rift Valley fever virus
- Venezuelan Equine Encephalitis virus

**USDA VETERINARY SERVICES (VS) SELECT AGENTS**

- Anthrax
- Avian flu
- Avian influenza virus (highly pathogenic)
- Blue-tongued virus (exotoxins)
- Brucella spirochete encephalopathia agent
- Camel pox virus
- Classic swine fever virus
- Ehrlichia ruminantium (Rickettsia)
- Fowl-anti-mouse brain virus
- Goat pox virus
- Japanese encephalitis virus
- Leptospira spirochetes
- Malignant catarrhal fever virus
- (Alcaloide herpesvirus type 1)
- Marburg virus
- Mycoplasma capricolum sub-ossae caprine pneumoniae
- Mycoplasma mycoides sub-ossae mycoides small colony (M. s. C. colony pneumoniae)
- Pasteurella multocida
- Peste des petits ruminants virus
- Rift-yello virus
- Swine pox virus
- Swine vesicular disease virus
- Vesicular stomatitis virus (virus): Indiana subtypes
- VSIV IN3, H virus
- Virulent Newcastle disease virus

**USDA PLANT PROTECTION AND QUARANTINE (PPQ) SELECT AGENTS**

- Pectobacterium atrosepticum (P. atrosepticum sp. atrosepticum)
- Phoma exigua (formerly Pyrenopeziza exigua)
- Polycotylus sobralii
- Rhabdovirus toxins
- Sclerotinia rolfsii cotton
- Synchytrium endobioticum
- Xanthomonas oryzae
- Xylella fastidiosa (Citrus variegated chlorosis strain)

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¹ A virulent Newcastle disease virus (avian pneumovirus serotype 1) has an intranasal pathogenicity index in day-old chicks (Coltus gallus) of 2.5 or greater, or has an amino acid sequence of the fusion (F) protein gene sequence that is consistent with virulent strains of Newcastle disease virus. A failure to detect a clearance site that is consistent with virulent strains does not confirm the absence of a virulent virus.