Translating Research intoLicensed Vaccines & Validated &Licensed Diagnostic Tests

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Topics

► Vaccine, diagnostic test approval process
► “Standard” licensing process
► Considerations for emerging/emergency animal health situations
► Historical examples
► “Good Research Practices”
► Licensing Development Plan and Critical Path Agreement
► Summary
Organizational Structure

- USDA
- APHIS
- VS
- CVB

→ United States Department of Agriculture
→ Animal and Plant Health Inspection Service
→ Veterinary Services
→ Center for Veterinary Biologics
FOR HOG GOLDS

$1.50

1 BOTTLE TREATS 100 HOGS

EBY’S
MARENGO, IOWA

Safeguarding Animal Health
Virus-Serum-Toxin Act of 1913

- Worthless
- Dangerous
- Contaminated
- Harmful

- Pure
- Safe
- Potent
- Effective
Vaccine Development/Approval

▸ Vaccine/host characteristics
  • Live vs. killed, stability, duration of immunity
  • Strain specificity
  • Host response
  • Carriers, masking of infection

▸ Factors affecting decision to vaccinate
  • Trade implications, exit strategy, wildlife hosts/reservoirs, vaccination strategy (control vs. eradicate, vaccinate & slaughter), feasibility, availability, delivery, etc.
Vaccine Development/Approval

- Vaccine development (speed)
- Importation (risk)
- Vaccine banks (availability/expiration)
- Exotic disease vs. emerging disease
- Companion diagnostic products
- Economics
“Standard” Licensing Considerations
Licensing Requirements for Vaccines

- **Purity**: Master Seed, Master Cell Stock, Product must not contain extraneous agents

- **Safety**: Product must be safe (overdose studies and when used as directed) in target animals.
  - Live products may require reversion-to-virulence and shed-spread data, also safety data in non-target species.

- **Efficacy**: Product must generate a statistically significant, clinically relevant protective or therapeutic effect
  - Diagnostic test kits must be suitably specific and sensitive for their intended purpose.

- **Potency**: Must have assays to ensure adequate potency + stability of a production batch (serial)
Diagnostic Test Kit Licensing Requirements

- Must be prepared in licensed facilities following an approved Outline of Production using approved components
  - Antigen(s) must be prepared from approved Master Seed(s) or each lot must be approved
  - Antibodies must be prepared from approved Master Seed(s) (monoclonals) or well-characterized
  - Conjugates may be purchased from approved vendor
  - All ingredients must be free from contamination
  - Minimal variation within and between serials

- USDA evaluation of test kit before and after licensure
- Monitoring of field performance and investigations
Prelicense Validation of Diagnostic Tests

- Test large number of known positive + negative animal samples covering a range of reactivities, all sample types
- Determine onset of detection of disease
- Evaluate (in at least 3 laboratory settings)
  - Ruggedness, repeatability, suitability
  - Against gold standard assay
  - Adequacy of instructions
- Accuracy and precision
- Diagnostic sensitivity
  - Dynamic range
  - Analytical sensitivity
- Diagnostic specificity
Intended Diagnostic Use(s) May Impact Licensing Requirements

- Herd/population status vs. individual animal tests; screening vs. confirmatory test
- Trade implications (clearance for export)
- Vaccination status vs. susceptibility to disease vs. exposure to agent
- Matched diagnostic kits and companion vaccines
- State/Federal animal health control programs
  - Use may be controlled by APHIS
  - Positive + negative predictive values for specific disease prevalence (especially for Program Diseases)
Considerations for emerging/emergency animal health situations
Changes (???) to General Licensing Considerations

- Purity - freedom from dangerous/exotic agents??
- Safety - willingness to accept untested products??
- Potency/Efficacy – often uncertain?? Kits tested outside the U.S.
- Relevance of available data to emergency animal disease situation
Mechanisms for Product Approval

1. Standard license
2. Experimental
3. Autogenous
4. Conditional license
5. Importation
6. Vaccine Bank or Stockpile
7. USDA exemption
## 1. Standard License

Title 9 Code of Federal Regulations 101-118

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<tr>
<th>Pros</th>
<th>Cons</th>
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<tbody>
<tr>
<td>▶ Purity, safety, potency and efficacy well established</td>
<td>▶ Relatively slow process</td>
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<tr>
<td>▶ Facilities inspected and approved</td>
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<tr>
<td>▶ USDA confirmatory tested (seeds, cells, and product)</td>
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<td>▶ Closest to “ideal”</td>
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Canine Parvovirus
Canine Parvovirus

- Disease emerged in 1976-1977
- Variants CPV 2a + 2b emerged in 1979 and 1984
- Initially feline panleukopenia (FPLV) cat vaccines were used in dogs based on the limited cross protection shown
- First vaccine with CPV claim licensed in 1981
- By 1985 codified regulations were in place
- Presently both CPV and FPLV based modified live and killed vaccines are available
- CPV 2a + 2b strains are believed to cross protect
- Diagnostic test kits detect CPV in fecal material
2. **Experimental Vaccine**

**Pros**
- Quicker
- Can get new/emerging strains out for trials per 9 CFR 103.3
- Regulatory oversight, State approval required

**Cons**
- Safety, potency and efficacy still uncertain (closest to basic research)
- Labeled “for experimental use – not for sale”
- Limited distribution
Porcine Reproductive & Respiratory Syndrome Virus
Porcine Reproductive & Respiratory Syndrome Virus

- First seen in US 1987, in W. Europe in 1990
- 2 antigenic types, American + European
- Full license issued June 1994
  - MLV vaccine - patented virus - respiratory claim only
  - Protection against heterologous PRRSV
- License for reproductive & respiratory forms July 1996
- Shed in the semen of vaccinated boars (label precaution)
- Presently both modified live and killed virus products are available
Rabies

Safeguarding Animal Health
Rabies

- Oral Vaccinia Vectored Rabies Vaccine
- Licensed (conditional) for use in raccoons April 20, 1995
- Efficacy studies in coyotes and foxes in 1994 preceding field trials with experimental vaccine
- 1995 Experimental field use in Texas
- Annual use of experimental vaccine in Texas, with manufacturer submitting reports of the testing results
- Label claim for use in coyotes in 2002
- Currently, fully licensed for use in raccoons, coyotes; conditionally licensed for use in gray foxes.
Rabies

► Adenovirus Vectored Rabies Vaccine
► Experimental use in raccoons and skunks 2011-2
► Trials in Vermont, New Hampshire, New York, Ohio, and West Virginia
► Currently used in Canada to control rabies in raccoons, skunks, + foxes
► Vaccination of skunks more challenging
► Canadian experience: vaccination rate for skunks of 17-51%, for raccoons > 70%
### 3. Autogenous License (9 CFR 113.113)

<table>
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<tr>
<td>▶ Basic purity (freedom from bacteria, fungi) known</td>
<td>▶ Host animal safety, potency and efficacy not established</td>
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<tr>
<td>▶ Lab animal safety known</td>
<td>▶ Limited distribution (primarily to herd/flock of origin)</td>
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<tr>
<td>▶ Inactivated microorganisms only</td>
<td>▶ No confirmatory testing of seeds</td>
</tr>
<tr>
<td>▶ New isolates, quick</td>
<td>▶ License restrictions for exotic agents</td>
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<td>▶ Veterinarian-Client-Patient relationship</td>
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Infectious Salmon Anemia Virus
Infectious Salmon Anemia Virus

- Primarily Atlantic Salmon – other fish infected; Orthomyxovirus (Influenza) –
- First report – Norway, 1984: then Scotland, Canada, South America
- August 9, 1999 – CVB Notice announcing autogenous and other licenses considered
- February 2001 – First U.S. case - APHIS assistance, indemnity: depopulation, disinfection, fallowing
- Killed Vaccine approved October 2001
  - Canada isolate, manufacture
4. Conditional License
(9 CFR 102.6)

**Pros**
- Meets an emergency condition, limited market, etc.
- Purity, safety known
- Master Seeds tested
- Reasonable expectation of potency + efficacy
- Wider distribution
- Relatively quick
- Proceed to standard license later

**Cons**
- Time to license
- Efficacy may be uncertain
- May lack potency test for each serial
- Distribution may be limited
- Limited to domestic products (no permits)
Swine Influenza Virus
Swine Influenza Virus

- Worldwide occurrence in pigs, can also infect humans and turkeys, primarily H1N1 + H3N2 but atypical reassortants can occur
- In 1998-99, H3N2 strains were isolated from sick pigs for the 1st time in the USA
- A conditional license Jan 2000 to a Killed Virus Vaccine with 1999 and 1973 H3N2 strains
- Ongoing need for “current” SIV vaccines:
  - Now, many H1N1/H3N2/H1N2 killed vaccines available (full license), plus combination + autogenous products
  - VS Memo 800.111 for expedited strain changes
pH1N1 Master Seed Virus Vaccine

2009: four pre-tested/approved pH1N1 viruses provided to the manufacturers by USDA

- A/CA/04/09, A/MX/4108/09:
  - CDC-NADC-CVB, pig and cell passages
- X-179A (with CA/07 HA and N):
  - NYMC-CDC-CVB, egg passages

Extraneous agent testing: FA on 6 cell lines, hemadsorption and CPE testing, PCR assays, pan-human microarray assays, mouse safety

Conditional license on 12/11/09 to a monovalent pH1N1 Killed Virus Vaccine for use in swine
FMDV Live Adenovirus Vector Vaccine

- Developed at Plum Island Animal Disease Center (USDA/DHS)
- No live FMD virus
- Structural FMD capsid gene inserted into vector
- First FMD vaccine to be manufactured on U.S. mainland
- Conditional License issued in 2012 (cattle)
West Nile Virus
West Nile Virus in 2004
States with an Equine Case(s)
Total Cases 1,341


USDA
Safeguarding Animal Health
West Nile Virus

► First seen in Uganda, 1937 (human); can be fatal in horses, humans, and birds
► Discovered in New York, late summer 1999
► USDA notifications
  • Availability of Master Seed - January 2000
  • Product licenses considered - February 2001
► Conditional license for WNV Vaccine, Killed Virus, Aug 2001; full license Feb 2003
► West Nile Virus Antibody, Equine Origin, conditionally licensed August 2003
5. **Importation (existing product)**
   
   *(9 CFR 104)*

**Pros**
- Permit for experimental use (research and evaluation) or distribution and sale
- Licensing standards apply
- Risk/benefit analysis
- Purity, safety, potency and efficacy known

**Cons**
- Regulatory review, inspection, and testing outside of the U.S.
- Formal risk assessment required
- Potential for exotic agents
FMDV Vaccine, Killed Virus

► Commercial multi-fraction vaccine manufactured and used outside the U.S.

► US Vet Biological Product Permit for Distribution and Sale issued in July 2011 with restrictions:
  • Distribution and use shall be under the supervision or control of APHIS as part of an official USDA animal disease control program

► Full regulatory approval:
  • Demonstrated Purity, Safety, Potency, and Efficacy
6. Vaccine/Seed Bank & Stockpile

**Pros**
- No specific regulations (apply standard licensing guidelines)
- Purity, safety, potency and efficacy well known
- Seeds tested
- Real-time Delivery or Rotating Stocks
- Licensed and available for Immediate (widespread) use

**Cons**
- Cost
- Maintenance and storage
- Did you bank/stockpile the right strain?
- Expiration of product while in storage
Foot-and-Mouth Disease
North American FMD Vaccine Bank

- 1982 Consortium: Canada, US, Mexico
- Bank: Antigen concentrates + Master Seeds
- Antigen concentrates: killed virus preps, several subtypes, vaccine available quickly
- Master Seeds: live, frozen, many subtypes, tested and approved for use
  - New seeds added as needed/isolated
  - Vaccine available in weeks
- Activation of vaccine bank or seeds via Chief Veterinary Officers from member countries
Avian Influenza H5 & H7
Avian Influenza Vaccine Bank

- Established 2005
- Killed frozen bulk antigens
- 40 Million Doses
  - 10 million doses of each of two H5 and H7 subtypes
  - Subtypes chosen to allow for use of the DIVA (differentiating infected from vaccinated animals) strategy in the event of an a HPAI outbreak
7. USDA Exemption

Pros

- USDA oversight
  - National Program
  - Emergency Animal Disease Situation
  - USDA Experimental Use
- Quick

Cons

- Contingent on product used (all Cons in other sections may apply)
Bovine Spongiform Encephalopathy

Safeguarding Animal Health
BSE Diagnostics

- December 23, 2003; first U.S. case
  - Canadian-born cow
- January 8, 2004; USDA notification of product licenses/permits considered
- March/April 2004; Diagnostic Kit approvals
- May 2005; >300,000 samples tested
Licensing Pathways

- Multiple mechanisms to qualify products for emerging or transboundary diseases
- Domestic production possible
- Responsive to the situation (quick)
- Sound research practices can greatly facilitate the approval process
Research Practices that Facilitate Technology Transfer

- Keep the licensing pathways in mind
- Consult with manufacturers & regulators (early)
  - Determine regulatory jurisdiction
  - Obtain comments on development plan and study protocols (Critical Path Agreement)
  - Familiarity of the regulations vary (new manufacturer, academia)
- “Purity, Safety, Potency, Efficacy”
- Ensure detailed records; data to support the label claim
  - GMP or GMP-like requirements for documentation
Master Seeds & Cells

- All biologicals (vaccines and diagnostics) must be produced from a well-characterized, approved lot of seed and/or cells.
- Important to document source of seeds & cells and how they have been handled (passage history).
- Important to trace all experimental products to defined seeds/cells.
Genetically Engineered Seeds

- Additional documentation required for seeds that have been genetically engineered (basic research)
- Specialized and specific formats summary information (Summary Information Format [SIF])
- Requirements vary according to type of construct and how it will be used in the final product
- Environmental Assessment and Risk Analyses may be required for some products prior to release (human, animal, environment)
An “Outline of Production” is required to document how a product is made. Every change to the Outline must be approved.

- Document all changes, no matter how minor

All study results must be traceable to a product made in a specified manner. Without link to production process and records, data may not support licensure.

- Link each batch of experimental product to a specific production procedure
Testing Biological Products

- Document test methods in detail
- Ensure tests utilize appropriate and sufficient controls
- Emphasis on test validation; *in vitro*
- Prelicense testing by manufacturer and regulatory authority
Shipping Experimental Product

- For products that will be used in animals authorization required prior to shipment (9CFR 103.3; VS Memo 800.67)
  - Must also have State approval
  - Includes diagnostic test kits
- Authorizations for specific batches (serials) & recipients
- Responsibility of person shipping product to obtain required approvals (researcher, manufacturer)
- Turnaround time for 103.3 authorizations is ~1-7 days
- Shipments also must comply with applicable shipping regulations promulgated by U.S. Department of Commerce and requirements of individual couriers
  - Hazardous goods
  - Special regulations for select agents, high consequence pathogens
Licensing Plans and Agreements

- Conversations with regulators early in the process (Research, Regulatory Affairs, Quality Control/Assurance Production)

- Licensing Development Plan
  - Best worked out between the manufacturer and the regulator
  - Highlights new/unique areas relative to innovative products, technologies, testing strategies

- Opportunity for Critical Path Agreement(s) outlining the necessary steps to be taken towards licensure
References and Contacts

Laws and Regulations
• Title 9 Code of Federal Regulations, Parts 101-121

Guidance documents from regulatory authorities
• Veterinary Services (VS) Memoranda
• Center for Veterinary Biologics Notices

Center for Veterinary Biologics
1920 Dayton Avenue
Ames, IA 50010
• phone 515-337-6100; fax 515-337-6316
• http://www.aphis.usda.gov/animal_health/vet_biologics/
• cvb@aphis.usda.gov
Key Guidance Documents

- VS Memo 800.50: Overview of general licensing process
- VS Memo 800.101: Overview of permit process (imported products)
- VS Memo 800.200: Documentation practices
- VS Memo 800.67: Shipping experimental product
- VS Memo 800.73: Licensing considerations for diagnostic test kits
- VS Memo 800.205: How to prepare a SIF (for recombinant products)
- VS Memo 800.109: Master Seeds & Cells
- VS Memo 800.206: Outline of Production
- VS Memo 800.202: Efficacy studies
- VS Memo 800.204: Field Safety
Considerations for Biologics Regulators

- Application of the standards during an “emergency” environment
  - License/authorize product fast (but not too fast that public/animal health or environmental interests are compromised)
  - Maintain availability of domestic animal health products

- Keep pace with technology and adapt and change Standards appropriately
  - License new and innovative products Animal welfare concerns (vaccine production or use)

- Veterinary Services Request for Information – FMD Vaccine

Safeguarding Animal Health
Summary

- Foundation: Purity, Safety, Potency and Efficacy
- Regulatory review process with “emergency” considerations in mind (flexibility)
- Decisions needed quickly
- Proactive vaccine + diagnostic test development/use strategy
  - Vaccine/seed banks or Stockpiles
  - “Pre-approved” products
  - Knowledge of world-wide vaccines and diagnostics
  - Researchers, Biologics Industry, Regulators
- Licensing Plans and Agreements