The Center for Veterinary Biologics
Regulatory Update -
Equine & Swine Influenza
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Safeguarding Animal Health
Orthomyxoviridae

Virus classification

- Group: Group V (-ssRNA)
- Family: Orthomyxoviridae
- Genera:
  - Influenzavirus A
  - Influenzavirus B
  - Influenzavirus C
  - Isavirus
  - Thogotovirus
Influenza Virus

*Influenzavirus A*: serologic assays differentiate HA and NA surface proteins into 16 H and 9 N antigenic types that reassort into subtypes, e.g. H1N1, H3N2
Influenza Virus

- Subtypes undergo antigenic drift, shift
  - Random mutations
  - Reassortment

- Avian flu viruses prefer cell receptors for HA containing α2-3-linked sialic acid residues; mammalian viruses prefer HA cell receptors with α2-6-linked sialic acid residues

- Swine have both types of cell receptors for HA: dual infection allows for reassortment and development of new subtypes and new variants of subtypes
Influenza Virus Vaccines

- Humans, birds, horses, swine
- Human model: 3 killed virus strains, subvirion or subunit; also cold-adapted ts MLV given IN
- Live vaccines are a safety concern unless reversion to virulence is not possible
- Vaccines protect best vs. homologous strains
- Antigenic drift and shift require changing antigenic content periodically
- Surveillance, prediction - sometimes wrong: 40% vs. 85-95% effective
- A mechanism to replace and add strains fast is helpful
Human Influenza Vaccines effective, not perfect

- Killed vaccines are typically changed each year, based on surveillance data: H1N1, H3N2, Type B
- The live cold-adapted vaccine licensed several yrs ago is not approved for use in < age 2 or > age 50
- Comparison efficacy studies with antigenically similar and dissimilar challenges showed no statistically significant advantage for either the live or killed vaccine
  - The killed vaccine has greater efficacy against Type B
  - The live vaccine may be more effective among children
Equine Influenza Virus

- H7N7 (A1) - no confirmed case since 1980
- H3N8 (A2) – ‘Eurasian’, ‘American’ lineages

2004, Expert Surveillance Panel, vaccine strains:

- S. Africa/4/2003-like (American) or equivalent A2 strain (e.g. Ohio/2003, Wisconsin/2003)
- Newmarket/2/93-like (European) or equivalent A2 strain (e.g. Suffolk/89, Borlange/91)
Current EIV Situation

- 2007: same recommendations for vaccine strains
- All H3N8 isolates from Europe & North America characterized in 2006 were from the ‘American’ lineage
  - North American isolates since 2003 have 2 more amino acid changes in antigenic sites of HA than viruses isolated in Europe, i.e. more drift
  - 2007 Australian outbreak via Japan – H3N8 of ‘American’ lineage
- H3N8 equine flu in dogs:
  A/canine/Florida/43/2004
  w/ 4 a.a. changes in HA
Swine Influenza Virus

- **H1N1** - ‘classical’ (1930), ‘atypical’ + ‘novel’
- **H3N2** - late 1998 (hu x sw, hu x sw x av)
- **H1N2** - 2001; hu-H1 viruses - 2005
- **H2N3** - 2006 (av X sw)
  - H2 not in humans since 1968 = pandemic risk
  - European vs. American strain differences
  - Other strains detected in pigs: H1N7, H3N1, H4N6, H9N2, HPAI H5N1
Current SIV Situation

- H3N2: abortion storms, off feed, fever, mortality
- Most H3N2 isolates are triple reassortants with a similar ‘cassette’:
  - Human (HA, NA, PB1)
  - Swine (NS, NP, M)
  - Avian (PB2, PA)
- swH3N2 similar to huH3N2 (protected in part), swH1N1 not similar to huH1N1 (more susceptible)
- H1N1, H3N2, H1N2, H3N1 strains continue to evolve through drift and reassortment
To Allow for Expedited Strain Change: VS Memo No. 800.111, 9/19/07


VETERINARY SERVICES MEMORANDUM NO. 800.111

TO: VS Management Team
    Directors, Center for Veterinary Biologics
    Biologics Licensees, Permittees, and Applicants

FROM: John R. Clifford
      Deputy Administrator

SUBJECT: Viral Strain Changes in Equine Influenza and Swine Influenza Vaccines (Killed Virus)

I. PURPOSE

This memorandum gives guidance to licensees, permittees, and applicants, per Title 9, Code of Federal Regulations (9CFR) 102.5(c)(1), concerning expedited procedures for influenza virus strain changes in licensed or permitted products containing inactivated (killed) equine and swine influenza viruses.
VS Memo on Viral Strain Changes in Inactivated Equine and Swine Influenza Vaccines

• EIV and SIV vaccines on market for many years
• To replace/add strains shouldn’t result in substantial production changes
• Allow to sub/add strains w/o repeating full-scale efficacy and field safety studies
• Justification of strain replacement/selection
• No more than 3 strains of a subtype/licensed product
• Specify H and N subtypes
• Encourage dropping of H7N7, irrelevant strains
**Substitution of Strains, Same Subtype**

- Allow up to two strain substitutions within each of the subtypes present in the currently licensed vaccine
- Antigen/dose of each new strain is $\geq$ that of the original strain, unless justified by a host challenge study
- For demonstration of immunogenicity:
  - Similar immune response in host or suitable lab animal model as in the original licensing application
  - Test in $\geq 6$ seronegative host animals @ minimum age rec’d
  - Can use $\geq 10$ suitable lab animals
  - Serum Ab geometric mean titers (GMT) $>\text{GMT from original efficacy study, using the same post-vaccination interval and the same validated assay (but with the new Ag)}$
Addition of Strains, Same Subtype

• Based on adequate justification, additional strains of each subtype may be added to a licensed vaccine
• Cannot decrease the antigen/dose of the original strains, unless justified by a host challenge study
• For demonstration of immunogenicity:
  – Similar immune response in host or suitable lab animal model as in the original licensing application
  – Test in ≥ 6 seronegative host animals @ minimum age recc’d
  – Can use ≥ 10 suitable lab animals
  – Serum Ab GMT ≥ GMT from original efficacy study, using the same post-vaccination interval and the same validated assay (but with the new Ag)
Addition of Strains, New Subtype

• Based on adequate justification, strains of new subtypes may be added to a licensed vaccine
• Cannot decrease the antigen/dose of the original strains, unless justified by a host challenge study
• In this case, for demonstration of immunogenicity:
  – Host animal vaccination/challenge, using at least 10 vaccinates and 5 controls
  – The challenge virus must be a field-relevant strain
• For an entirely new product or new process, efficacy and field safety data will be required.
Licensing Elements

- Characterization of the Master Seed, H & N subtypes
- General requirements for KV vaccines met (9 CFR 113.200)
- Firms encouraged to use SRD assay as a measure of H antigen content during production (SRD not for use in the presence of adjuvant)
- EIV SRD reference reagents from NIBSC, UK
- EIV strain-specific antisera from European Pharmacopoeia
For SIV & new EIV strains, SRD reagents not available

Besides SRD, an alternative Ag quantification test acceptable to the CVB can be used

Subtype & strain designations on product labeling

Conditional licensure may be considered for an entirely new flu product or manufacturing process

- Where there’s a reasonable expectation of efficacy and adequate field safety data, efficacy studies can be pending
Conditional License

- Title 9 Code of Federal Regulations (102.6)
- Emergency condition
- Limited market
- Other special circumstances
- License expiration
- Special labeling
- Live, killed vaccines
Conditional License

**Pros**
- Purity, safety, well known
- Seeds tested
- Reasonable expectation of potency and efficacy
- Wider distribution
- Relatively quick
- Proceed to standard license

**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)
Autogenous License

- Title 9 Code of Federal Regulations (113.113)
- Inactivated products only
- Veterinarian-Client-Patient relationship
- Restricted to herd of origin (adjacent premises under certain conditions)
- Restricted to domestic agents
Autogenous License

Pros

- Basic purity known (freedom from bacteria, fungi)
- Inactivated
- Laboratory animal safety known
- New isolates
- Quick

Cons

- Host animal safety, potency and efficacy not established
- Limited distribution (primarily to herd of origin)
- No USDA confirmatory testing of seeds
- Limited to domestic
Questions???