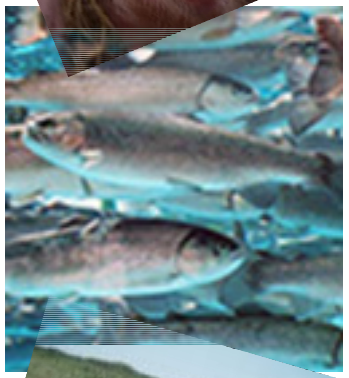
USDA

United States Department of Agriculture

Regulatory Perspective on Trends in Veterinary Biologics



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February 2019

Predominating Trends

- Increased pressure to bring products to market more quickly
- Increased interest in customized biologicals to meet regional or individual needs
- National regulatory authority and global trade

Regulating at the Speed of Commerce

- Increased pressure to bring products to market as quickly as possible:
  - Highly mutable agents
  - Emerging diseases
  - Novel technologies
  - Acceptance of other regulatory approaches

vs.

- USDA's mission to ensure licensed products are pure, safe, potent, and effective

Time to market

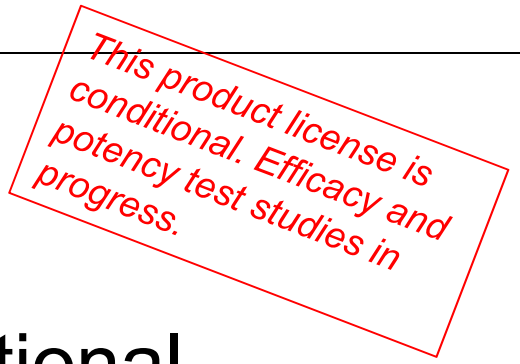
- Several approaches have been useful in the U.S. to reduce the time for a new product to gain marketing approvals

Conditional Licenses

This product license is conditional. Efficacy and potency test studies in progress.

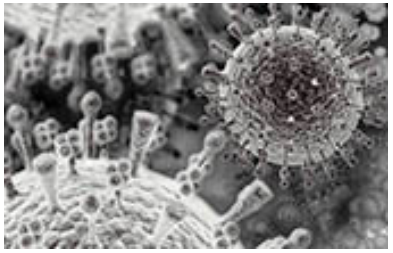
- 9 CFR 102.6
- To meet emergency conditions, limited market, local or special circumstance
- Reduced requirements for proof of efficacy ("reasonable expectation") but otherwise must meet all licensing requirements for full licensure

Conditional Licenses: Limitations



- Special labeling to disclose conditional status, no trade names
- Restricted distribution—requires permission from State or importing authorities
- Annual or biannual license renewal
- Conditionally licensed fractions cannot be mixed with fully licensed fractions
- Once a similar product has full license, no additional conditional licenses are issued

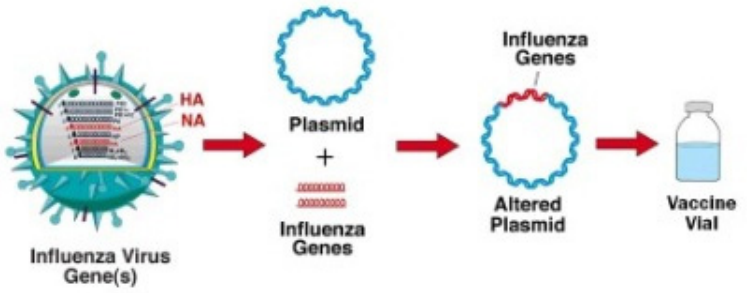
Influenza virus changes

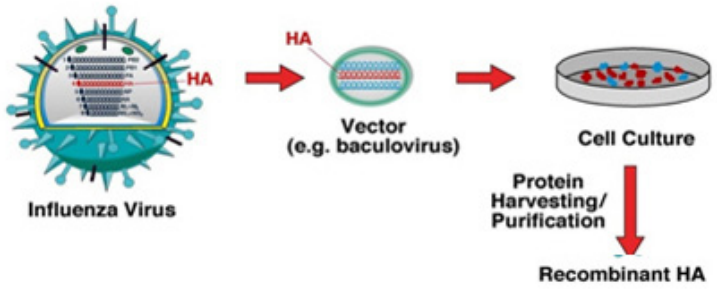


- Veterinary Services Memorandum 800.111, first published in 2007
- Arose from need to keep vaccine Seeds up to date with rapid, frequent virus shift/drift
- Once manufacturer has a full license for killed product, can add, remove, exchange Seeds of same HN type(s) in expedited manner
- Requires only similar serological response. No large-scale field safety
- Updated product receives full license

Platform Technology

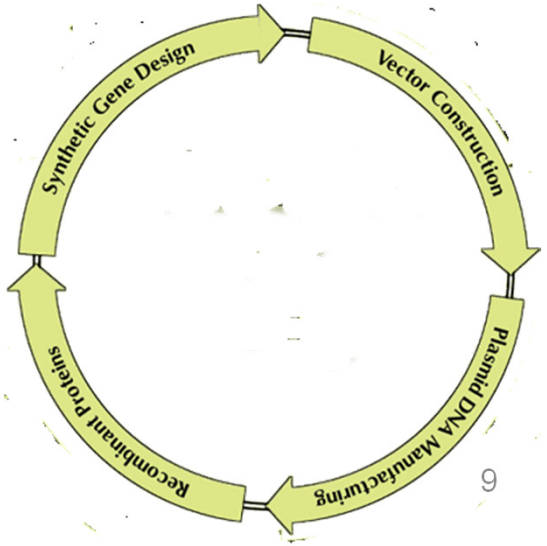
- VS Memorandum 800.213, first published 2013
- Inactivated, non-replicating protein or nucleic acid vaccines (any agent) from recombinant technology
- Unchanging part of vector construct + consistent manufacturing method = **production platform**
- Can prepare limitless vaccine constructs differing only in inserted gene sequence





Production Platforms

- First license using a defined platform--traditional requirements
- Subsequent licenses for same platform expedited
- Depending on similarity of new insert to licensed insert(s):
  - Abbreviated inactivation kinetics
  - Abbreviated field safety studies
  - Abbreviated risk assessment



Production Platforms

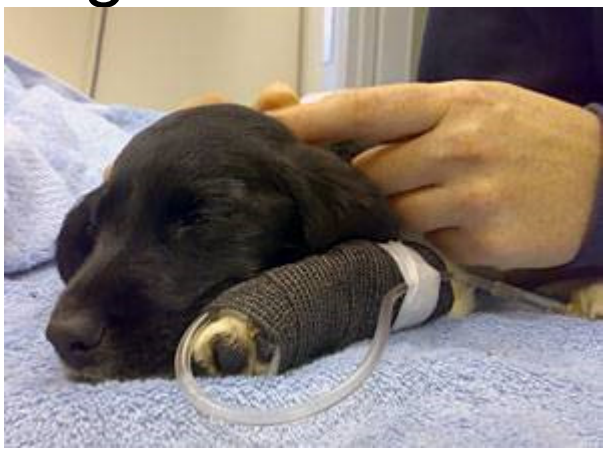
- Platform-based Seeds (vector + gene insert) that only have reasonable expectation of efficacy (“conditional” license) may be combined with fully licensed Seeds from same platform
- May be eligible for conditional license even if similar full licenses exist

Emerging Diseases

- Recent examples: Pandemic H1N1 influenza (2009), porcine epidemic diarrhea virus (2013), H3N2 canine influenza viruses (2015)
- To expedite product licensure, USDA obtained, tested Master Seeds for direct distribution to biologics manufacturers. Applicants could use these Seeds in product development with minimal or no additional testing.
- Provided challenge virus and standardized challenge protocol for PEDV

Products for Grave Diagnoses

- Niche products for diseases with grave diagnoses (e.g., cancer) may be conditionally licensed on limited efficacy *and* safety data with expectation more will be gathered
- Typically evaluated in well-controlled clinical trials with rolling enrollment

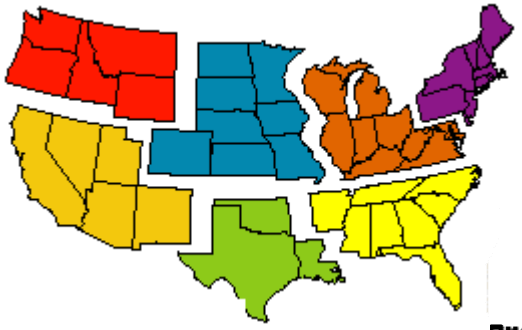


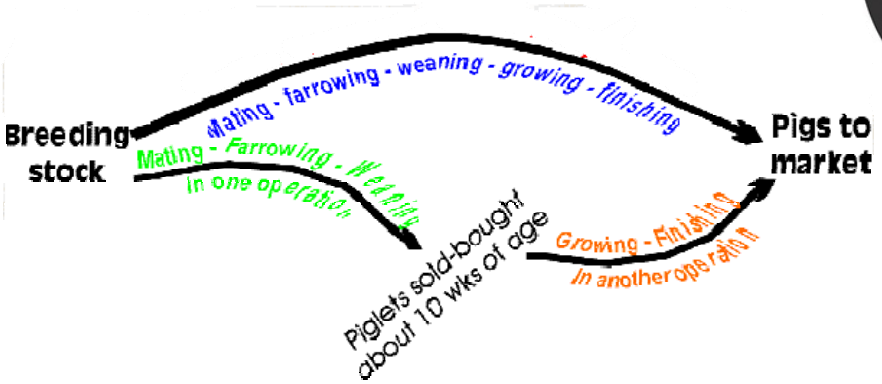
Products for Emergency USDA Use

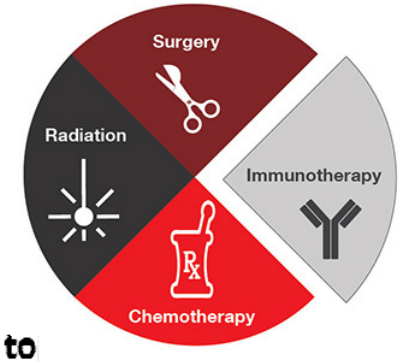
- Foreign animal diseases
- *Can* be used under exemption with no license/permit (9 CFR 106.1)
- BUT current goal is to use only licensed product in emergencies
- Increased reliance on pre-existing foreign dossiers and other streamlined processes to justify conditional licenses or restricted import permits for emergency use

Customized Biologicals

- To meet distinct needs in:
  - A geographic region
  - An integrated animal production system
  - Individual animals

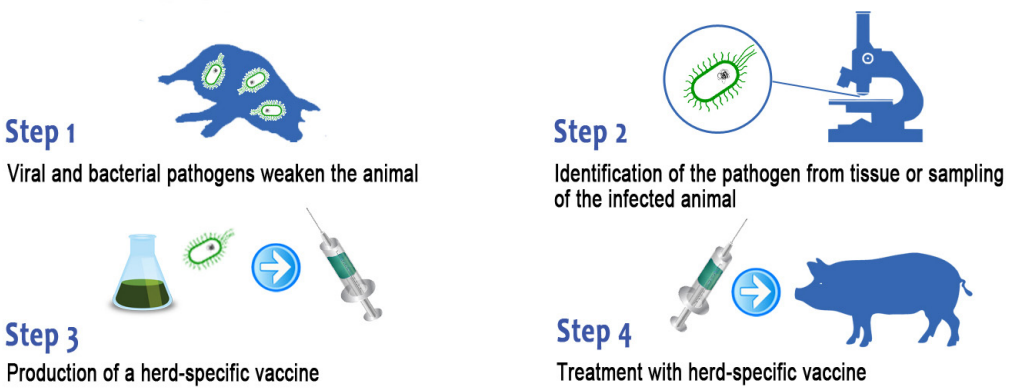






Autogenous Products

- 9CFR 113.113 and VS Memo 800.69
- Traditional Seeds
- Open-ended license to make conventional vaccine from an isolate from a source herd
- Purity tested only. No efficacy or safety testing.
- Can only be used in source herd and adjacent premises



Prescription Products

- VS Memo 800.213 (added 2015)
- Open-ended license to create custom recombinant formulations based on established production platform
- Requires prescribing veterinarian
- Serials (batches) tested for safety, purity. Vet assumes liability for efficacy.
- Gene sequence for platform Seed may be obtained from prescribing veterinarian or other epidemiological data

Prescription Products

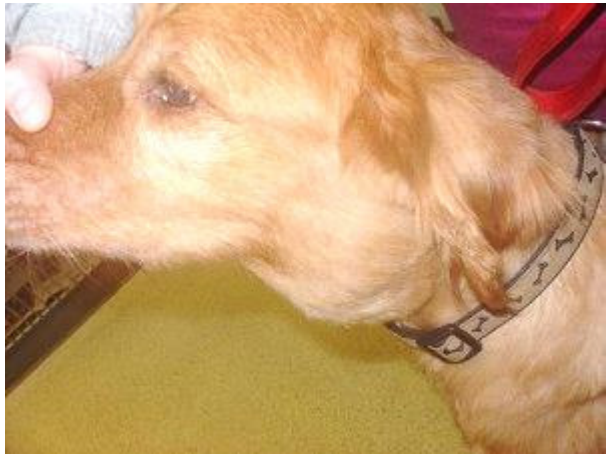
- May be used in geographically distant sites, as veterinarian deems appropriate.
- May include gene sequences animals are at risk for exposure but not yet in herd
- Prescription fraction may be combined with fractions licensed for non-prescription products

Prescription products

- Restricted labeling—similar to conditional
- Restricted distribution—only by State permission
- Individual serial (batch) release by USDA
- License issued for 2 years, subject to renewal

Autologous cancer therapeutics

- Immunotherapy as an adjunct to other cancer treatment
- Vaccines prepared from patient's tumor cells stimulate immune response against same cells
- Custom products prepared in small quantity solely for administration to the same patient are considered a laboratory service and NOT regulated as biologicals by the USDA



Accept other regulatory approaches

- Mutual recognition / regulatory convergence / harmonization
  - All requires a relationship
- National sovereignty and the VICH approach
  - Standardized data/testing vs. standardized decisions
  - Ultimately, will a result be acceptable?
  - Political consequences for failures

Summary

- **Expediting time to licensure**
  - Conditional licenses
  - Streamlined updates of influenza strains
  - Production Platforms
  - USDA provides Seeds for emerging diseases
  - Products for USDA emergency use
  - Products for grave diagnoses

- **Custom Products**
  - Autogenous products
  - Prescription products
  - Autologous cancer therapeutics
- **Regulatory approaches in a global environment**
  - It will continue to be a challenge

Questions?