Veterinary Biologics: General Licensing Requirements and Regulatory Trends

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Two main topics for today-

• Basic requirements for licensure
• Where are we going in the future
Virus-Serum-Toxin Act of 1913
Virus-Serum-Toxin Act

...it is unlawful to:

• Sell worthless, dangerous or contaminated biologics

• Ship biologics unless they are:
  – prepared in compliance with USDA regulations
  – prepared in a licensed establishment
"Biological Product" - Definition:

- all viruses, serums, toxins, or analogous products.....which are intended for the use in the treatment of animals and which act primarily through.....the immune system or immune response.
Product Jurisdiction

• To be considered a biologic, it must fit the definition
  – What’s the primary mechanism of action?
  – What is the regulatory claim for the product?
• Joint efforts (MOU & Committee)
• If it does not meet the definition of a biological product, it’s covered by the FD&C Act
• If it does, it’s exempt from FD&C Act and is covered by the VST Act of 1913
Product Types

- Vaccine
- Bacterin and Bacterial Extract
- Toxoid
- Bacterin-Toxoid
- Antitoxin
- Antiserum and Antibody
- Diagnostic
- Immunomodulator and Immunostimulant
- Allergenic Extract
Amendment to the Virus-Serum-Toxin Act
(Passed December 23, 1985)

• Provides for
  – Regulation of all veterinary biologics (intrastate)
  – Licensing for export
  – Conditional or Special Licenses
  – Detentions, seizures and condemnations and injunctions

• Exemption from licensure by regulations for certain products
Licensing Exemptions

- Official USDA Program, emergency disease situation, or USDA experimental use
- Veterinarian-client-patient relationship
- Animal owners
- Products under State license
- FDA Export Reform and Enhancement Act of 1996 – Note: No U.S. Establishment # on the label
  - U.S. Veterinary License No. xxx
  - U.S. Vet. License No. xxx
  - U.S. Vet Lic. No. xxx
Requirements for U. S. Veterinary Biologics Establishment License

- Application
- Supporting materials:
  - Articles of Incorporation
  - Water quality statement
  - Plot plans, blueprints & legends
  - Personnel qualifications
Requirements for U. S. Veterinary Biologics Establishment License

• Prelicense inspection
  – record keeping systems
  – validity of blueprints and legends
  – condition of the facility
  – laboratory practices
  – sampling, testing, and other compliance requirements

• One product qualified for licensure
U. S. Veterinary Biologics Establishment License
Requirements for U. S. Veterinary Biologics Product License

• Application (one for each product)
• Supporting materials
  – Outline of Production
  – Supporting data
    • research data
    • laboratory test records
    • field testing reports
• Prelicense inspection
United States Department of Agriculture

United States Department of Agriculture

UNITED STATES VETERINARY BIOLOGICAL PRODUCT LICENSE

Washington, D.C.

This is to certify that, pursuant to the terms of the Act of Congress approved March 4, 1953 (37 Stat. 382), governing the preparation, sale, importation and importation of vaccines, serums, toxins, and analogous products intended for use in the prevention of domestic animals, the person holding United States Veterinary Biologics Establishment License No. 499 is authorized to prepare in the facility designated in the establishment record.

CANINE LOYALTY VACCINE

Preparation shall be in accordance with the provisions of the Act, the regulations thereunder, and additional restrictions or requirements when issued. This license is subject to termination as provided in the regulations made under the authority contained in said Act, and to suspension or revocation if the licensee violates or fails to comply with said Act or the regulations made thereunder.

Date

Director, Center for Veterinary Biologics
Animal and Plant Health Inspection Service

APRIL 1998
[June 97]
Types of Veterinary Biologics Licenses Issued

- Establishment License
  - Regular
- Product License
  - Regular (with or without restrictions)
    - including autogenous
  - Conditional
    - Includes Platform technologies
    - Includes Prescription platforms
  - For further manufacture
  - For export only
License Issuance

• When application and all required supporting material have been received and filed as satisfactory, the establishment and first product licenses are issued.

• Subsequent product licenses are issued as requirements for each application are completed.
Basic Biologics Product License Requirements

• Should reflect "good science" and "good sense"

• Data review:
  – case-by-case basis
  – standard licensing requirements
  – general and special licensing considerations

• Purity, Safety, Potency and Efficacy
Supporting Data Must Demonstrate Purity of:

- Master Seed
- Master Cell Stock
- Ingredients
- Completed Product
  - bacterial/fungal contamination
  - inactivation
Supporting Data Must Demonstrate Safety in:

- Laboratory animals
- Host animals
- Environment
- Field studies
- Completed product
  - varies by product
Supporting Potency and Efficacy Data Must Demonstrate:

- Support of label claims (age, route, etc.)
- Established laboratory animal or *in vitro* minimum potency levels
- Master Seed immunogenicity (host animal vaccination/challenge)
- Duration of immunity
- Stability
- Completed product potency
Basic Principles

• Science-based
• Risk-based
• Transparent
• Consistency
Last word of advice…

- If you have a new or novel product, contact us early on
- We deal with CBI every day. What you tell us will be strictly confidential
- If you have a specific, unique need, ask.
Recent Predominating Trends

• Increased pressure to bring products to market more quickly

• Increased interest in customized biologicals to meet regional or individual needs
Regulating at the Speed of Change

- Increased pressure to bring products to market as quickly as possible:
  - Highly mutable agents
  - Emerging diseases
  - Novel technologies

  vs.

- USDA’s mission to ensure licensed products are pure, safe, potent, and effective
Conditional Licenses

- 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

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