General Licensing Requirements in the United States

Center for Veterinary Biologics
U.S. Department of Agriculture
Animal and Plant Health Inspection Service
Veterinary Services
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Mission

• The USDA, APHIS, Veterinary Services, Center for Veterinary Biologics implements the provisions of the Virus-Serum-Toxin Act to ensure that the veterinary biologics available for the diagnosis, prevention, and treatment of animal diseases are pure, safe, potent, and effective.
"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.
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
Types of Veterinary Biologics Licenses

- Establishment License & Product License
  - Regular [Diagnostic Test Kits and Vaccines]
    - with or without restrictions
  - Conditional (reasonable expectation of efficacy)
    - For further manufacture
    - For export only
- Exemption: Official USDA Program, emergency disease situation, or USDA experimental use
Types of Veterinary Biologics Permits

• Establishment License & Product Permit
  – Regular [Diagnostic Test Kits and Vaccines]
    • with or without restrictions
  – Conditional

• Permits for Research & Evaluation
Ensuring Quality of Veterinary Biologics in the U.S.

- Licensing Requirements
- Quality Manufacturing Standards
- Inspection
- Testing (pre- and post-licensure)
- Serial (batch) Release
- Compliance Actions
- Vaccinovigilance
Ensuring Quality of Veterinary Biologics in the U.S.

- Extensive prelicense review of purity, safety, potency, and efficacy data
  - Science-based
  - Risk-based
  - Data-driven
- Established licensing standards
- Established product standards (production, testing, stability, duration of immunity, etc.)
Ensuring Quality of Veterinary Biologics in the U.S.

• Requirements for manufacturers to prepare products in accord with standards established at the time of licensure
  – Outline of Production
• Requirements to follow good manufacturing practices
• Prellicense testing of ingredients (seeds and cells) and consistency serials
  – USDA confirmatory testing
Ensuring Quality of Veterinary Biologics in the U.S.

- USDA check testing prior to release to monitor manufacturer's quality processes
- USDA Compliance testing (investigatory, stability, etc.)
- Monitoring each batch for purity, safety, and potency (APHIS release)
Licensing of Veterinary Vaccines
Licensing Requirements for Vaccines

- Purity
- Safety
- Potency/Efficacy
Purity - Supporting Data
Must Demonstrate Purity of:

- Master Seed
- Master Cell Stock
- Ingredients
- Completed Product
  - bacterial/fungal contamination
  - inactivation
Master Seed Concept

- Applies to conventional, recombinant, and monoclonal antibody products
  - Master Seeds undergo extensive testing for purity and safety
  - Resulting products are, therefore, free of extraneous agents, provided that good manufacturing practices are employed
  - Adherence monitored by inspections and product testing
Master Sequence Concept

• Applies to Synthetic DNA and Peptide products
  – DNA/Peptide sequence of material used in pivotal efficacy study establishes Master Sequence
  – Prelicense evaluation
  – Manufacturing methods are validated to ensure that the Master Sequence is maintained throughout the production process
Safety - Supporting Data

Must Demonstrate Safety in:

- Laboratory animals
- Host animals
- Environment
- Field studies
- Completed product
  - varies by product
Safety - Supporting Data:

• Master Seed reversion to virulence
  – live products
• Field Safety (3 distinct locations)
  – all classes of animals on the label
• Other Safety
  – effect on food animal production
• Serial Release Safety
  – varies by product
Potency & Efficacy - Supporting Data:

- Support of all label claims (age, route, etc.)
- Master Seed immunogenicity
  - Most often host animal vaccination/challenge
- Established laboratory animal or in-vitro minimum potency levels for each serial
  - Completed product potency
- Stability
Potency & Efficacy - Supporting Data:

- Product prepared in production facilities on scale representative of normal production
- Must be conducted using product produced at or below the minimum potency provided in the Outline of Production
- Duration of immunity for new products
- Must support efficacy in each species
Potency & Efficacy - Supporting Data:

- Must use product produced at highest passage from the Master Seed provided in the Outline of Production
- Interference studies (if appropriate)
- Duration of immunity for new products
- All data must be reported
- Data must demonstrate significant clinical effect
Review – Basic Licensing Requirements

• Characterization of Master Seeds and Cells
  – USDA confirmatory testing

• Host animal efficacy
  – Controlled studies
  – Adequate number of animals to provide statistical evidence that product provides protection claimed on labels
Review – Basic Licensing Requirements

• Safety trials
  – Backpassage tests (live)
  – Field safety (minimum of 600 animals, 3 different geographic locations)

• Validated potency assay for serial release (confirmed stability through dating)

• Prelicense serials
  – 3 consecutive (USDA confirmatory testing)
Good Licensing Practices

• Veterinary Services’ licensing process is well defined

• Work with manufacturer early
  – Know the pitfalls
  – Early involvement expedites later review

• Work with Veterinary Services early
  – Information on requirements
  – Review of protocols supports later review
The Goal: Tools for Animal Health