# Requirements for Vaccines in Other Regions of the World

## Industry Considerations

**25 March 2015**

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# Veterinary Vaccine Development from an Industry Perspective

- Global veterinary vaccine development costs and timelines have increased significantly over the past decades.
- Cost/timeline increases due in part to challenges of evolving global requirements and consolidated development programs.
- Future product availability requires pragmatic approaches to development strategies and regulatory requirements.
- There is significant value to the Animal Health Industry in assessing other regulatory models and exploring options to select “best practices”, especially in areas of emerging technologies.

**Benefit is improved product availability.**



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# Veterinary Vaccine Development for a Global Environment

- Most regional veterinary vaccine regulations already require:
  - Relevance for the intended disease and market.
  - Purity in terms of starting materials, in-process materials, final product.
  - Use of defined and qualified manufacturing methods.
  - Testing and release using defined and validated testing methods.
  - Proof of safety in laboratory and target animals.
  - Proof of safety for the environment.
  - Proof of efficacy using host animal vaccination/challenge studies.
  - Labelling consistent with data/experience (age, class, route, OOI/DOI).
  - Release with a shelf-life supported by relevant stability studies.
  - User safety and proper disposal recommendations.
- Pathway to meeting these requirements vary, however.



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# Case in Point – US Regulatory Environment

- US regulatory system for vaccines is highly-regulated:
  - Regulations and guidance documents define:
    - General requirements for product licensing, manufacturing facility operation, packaging/labelling, and distribution.
    - General methods for manufacturing/testing; specific requirements for individual product licensing and testing (monographs).
    - Structure and content of authorisation submission(s) - USDA VSM No. 800.50 (as compared to Commission Directive 2009/9/EC).
  - Comprehensive set of guidance that are heavily focused on setting final product specifications that correlate to safety and efficacy, followed by batch testing and release strategies that demonstrate compliance with these specifications.
  - Form the foundation for vaccine registration packages in many countries, especially in South America, Southeast Asia, Africa, the Middle East, and Canada.

# Where do US Regulations Differ from EU

- **Early Regulatory Engagement and "Free" Advice:**
  - Authority interface begins early in program (upon submission of an "Application for US Veterinary Biological Product License).
  - Includes early submission/assessment of OOP, Master Seed/Cell Reports, SIFs, and pivotal safety/efficacy protocols.
  - Early reviews highlight regulatory concerns, especially for clinical program. Allow "real-time" adjustments throughout program.
  - Process allows interactive project tracking with a single key "reviewer" against a defined "Development Plan".

| PRE-LICENSING PLAN | | | |
|---|---|---|---|
| **Description** | **Submission Date** | **APHIS Approval Date** | **Mail Log Number** |
| Product Licensing Plan (APHIS Form 2003, Draft OOP, Protocols) | 25OCT2011 | 26OCT12 | 12345 |
| Master Seed Reports – ABC and BCD | 09JAN2012 | 18JUL2012 | NA |
| Reference Stability Monitoring Plan: Study No. ABC-00-00000 | 14MAY2012 | 08FEB2013 | 23456 |
| Confirmatory Testing on MSB Samples | 19JUL2012 | 26OCT2012 | 34567 |
| Pivotal Efficacy Report Nos. ABC-11-11111 & ABC-22-22222 | 17DEC2012 | 04JUN2013 | 45678 |
| Pivotal Efficacy Report Nos. BCD-11-11111 & BCD-22-22222 | 17DEC2012 | 10MAY2013 | 56789 |
| ABC OOI Report No. ABC-33-33333 | 26SEP2013 | 21OCT2013 | 67891 |
| Optimization/Verification of ABC Potency ELISA (ABC-US-12345) | 12MAR2013 | 10JUN2013 | 78912 |
| Inactivation Kinetics/Assay Transfer Report (No. ABC-INA-11111) | 03MAY2013 | 21JUN2013 | 89123 |
| Etc. | | | |
| Etc. | | | |
| LICENSE GRANTED | | 01NOV2013 | |
| **POST-LICENSING PLAN** | | | |
| **Description** | **Submission Date** | **APHIS Approval Date** | **Mail Log Number** |
| Final Report for Field Safety Study No. ABCD-11-23456 | 26JAN2014 | 13MAR2014 | 91234 |
| Interim Stability Report | 17SEP2014 | 27SEP2014 | 10203 |
| Confirmatory Stability Report | 17SEP2015(T) | | |
| Etc. | | | |



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# Where do US Regulations Differ from EU

- **Phased Submission and Review:**
  - Key elements for quality, safety, and efficacy submitted and reviewed during development program.
  - Leads to regulatory interaction and stronger understanding of regulatory expectations.  Less questions during final assessment.
  - Helps pivotal safety/efficacy study design, as well as evolution of label claims (DOI, MAB impact, immunological interference, etc.).
  - Critical for potency test design and development, especially in areas where industry is trying to transition (such as 3Rs).
  - Leads to more-harmonised guidance (one dossier/one assessment/one authorisation philosophy previously discussed in EU).
    - Some of these objectives can be accomplished through informal interactions with EU Authorities.
    - Process is complicated, however, by the nature of EU procedures, especially for mutual recognition-type procedures.

# Where do US Regulations Differ from EU

- **Focus on Laboratory Efficacy/Safety, Supported by Field Safety:**
  - Consistent with EU expectations in that critical efficacy/safety assessments require studies conducted under suitable, controlled conditions.
  - Secures a good understanding of safety under field conditions, including all representative classes of animals.
  - Still ensures proper representation of expected safety in the Product Information/SPC.
  - Does not set an expectation for field efficacy - removes complications associated with site selection and occasional lack of field disease.
  - Still allows for selected use of field efficacy in situations where laboratory models do not exist (or are inadequate to define efficacy).

# Where do US Regulations Differ from EU

- **Focus on Basic Needs for Laboratory Efficacy and Product Label Claims:**
  - Expected efficacy confirmed by challenge for primary claim. Allows surrogate immunogenicity for other efficacy assessments.
  - Allows reasonable extrapolations of data in situations of maternal antibody or duration of immunity after booster.
  - Potential movement to “single tier” labelling allows timely adjustment of performance message (although impact on “animal-side” information):

**Summary**

We are proposing to amend the Virus-Serum-Toxin Act regulations to provide for the use of a simpler labeling format that would better communicate product performance to the user. We intend to replace the current label format, which reflects any of four different levels of effectiveness, with a single, uniform label format. We are also proposing to require biologics licensees to provide a standardized summary, with confidential business information removed, of the efficacy and safety data submitted to the Animal and Plant Health Inspection Service in support of the issuance of a full product license or conditional license. A simpler label format along with publicly available safety and efficacy data will help biologics producers to more clearly communicate product performance to their customers.



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# Where do US Regulations Differ from EU

- **Reliance on Similar Product Stability and Preliminary/Accelerated Stability Data to Set Shelf-Life:**
  - Stability testing program utilises stability data generated during development program to set original shelf-life.
  - Approved shelf-life then validated through a mandated confirmatory testing program after launch.
  - Essentially fits with “commitment” concept in EU, but expedites submission versus 6 month minimum data requirement for consistency batches.
  - Accelerates ability to set shelf-life and plan for commercialisation.
  - Regional discrepancies between definitions of minimum dose, end-of-shelf-life dose, and release potency complicate this area of focus, however.

# Where do US Regulations Differ from EU

- **Allows grouped changes to Outline of Production to facilitate process improvements/technical transfers as a single "variation":**
  - Technical transfers and updates to older dossier Part IIs necessitate adjustments (and addition of details) due to equipment and starting material issues, even in "like-for-like" approaches.
  - Process improvements in one area of production process may necessitate modifications in other areas of process.
  - Collective submission of all changes in one document assessed as a single transfer/process change facilitates assessment and approval.
  - Essentially fits with "grouped" concept in EU, but expedites submission and minimizes costs.
  - Accelerates ability to implement changes and process improvements, plus maintain product availability.

# Where do US Regulations Differ from EU

- **Allows alternative licensing pathways to address emerging preventative needs:**
  - Conditional license option allows pan-US consideration for vaccines (harmonised requirements; local “right-of-refusal”).
  - Licensure anticipates “reasonable expectation of efficacy” and does not require fully-validated potency assay.
  - Expectation of moving to full authorisation, but allows step-wise assessment as value of product is assessed.
  - Availability of conditional authorisation for minor-use or “compassionate use” products facilitates market acceptance/rejection.

# Where do US Regulations Differ from EU

- **Allows licensing pathway to address "farm-specific" preventative needs:**
  - Autogenous vaccines for pan-US responses using standardised requirements for products across US.

**Title 9 CFR:**

**§ 113.113 Autogenous biologics.**
Autogenous biologics shall be prepared from cultures of microorganisms which have been inactivated and are nontoxic. Such products shall be prepared only for use by or under the direction of a veterinarian under a veterinarian-client-patient relationship,
*Provided,* That, such products may be prepared for use under the direction of a person of appropriate expertise in specialized situations such as aquaculture, if approved by the Administrator.
Each serial of an autogenous biologic shall meet the requirements in this section, and if found unsatisfactory by any prescribed test shall not be used.
(a) *Seed requirements.* The microorganisms used as seed to prepare autogenous biologics shall be microorganisms which are isolated from sick or dead animals in the herd of origin and…

USDA

August 7, 2009

**United States Department of Agriculture**

Animal and Plant Health Inspection Service

Veterinary Services

Washington, DC 20250

**VETERINARY SERVICES MEMORANDUM 800.69**

**TO:** Biologics Licensees, Permittees, and Applicants
Directors, Center for Veterinary Biologics
Veterinary Services Management Team (VSMT)

**FROM:** John R. Clifford /s/ Jose R. Diez, for
Deputy Administrator
Veterinary Services

**SUBJECT:** Guidelines for Autogenous Biologics

I. PURPOSE

To describe present procedures and guidelines for interpretation of the requirements for Autogenous Biologics under the provisions of Title 9, Code of Federal Regulations (9 CFR), Section 113.113, 113.3(b)(8), and the administrative terminology in Section 101.2. To inform licensees that autogenous isolates may be used for 24 months without requesting permission from the Center for Veterinary Biologics (CVB). To notify licensees that shipments to adjacent and nonadjacent herds will be permitted, provided the information cited in 113.113(a)(2) and (3) is on file with the licensee prior to the shipment of an autogenous product for use in a herd other than the herd of origin.



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# Where do US Regulations Differ from EU

- **Other technical areas for comparison/acceptance of best practices:**
  - Extraneous agent testing and seed/cell “global” approvals.
  - Duration of immunity after booster.
  - Extrapolation of data in cases of alternative routes of administration.
  - Policies for changing cells and cell substrates for authorised products.
  - Requirements for “associations”:
    - Complicated “prime-boost” strategies (requiring consent/agreement between MAHs for “priming” doses used for “booster” vaccines).
    - Lack incentives for “build-up” combination strategies (which improve availability of new components prior to combination products).
  - Determination of minimum protective dose, potency at EOSL, and potency at release.
  - Recognise lack of risk associated with residual antibiotics from viral production fluids (via 9 CFR 114.10).

# Other Regulatory Environments

- Just in case we lose sight of the “global environment”:
  - **Australia**:
    - Regulations offer clear guidance for safety and efficacy across all species and product types.
    - Authorities focus on safety and trade/biosecurity issues, and are willing to be “more practical” on efficacy/benefit.
    - Allows Authority to meet regional demands for unique medical needs.  Still limited by importation restrictions, however.
  - **China**:
    - Ongoing legislative review. Significant differences in clinical study expectations.
    - Growing recognition that requirements for target animal safety/ efficacy are excessive in terms of batches/animals required.
    - Increased awareness that expedited authorisation processes will be needed to address trans-boundary disease issues.

# Other Regulatory Environments

- Just in case we lose sight of the “global environment”:
  - **Brazil**:
    - Expect efficacy and safety studies to be conducted with same formulation as authorisation application (i.e. no extrapolation to largest combination data).
    - Gaps in specific guidelines create room for interpretation/potential inconsistency between applications/companies.
  - **Turkey**:
    - Ministry recently adopted EU-type regulation based upon Directive 2001/82/EC.
    - Still accept US CFR Title 9 submissions provided that EORs are provided for Parts II, III, IV.
    - Decision to implement EU guidelines for inspections complicates issue.



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# Veterinary Vaccine Development for a Global Environment

- **Industry's experience: regulatory differences do not routinely lead to performance differences in vaccines "customised" to different regions.**

**Harmonising technical requirements and selecting "best-practices" would not impact product safety or efficacy**




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# Conclusions

- Regulatory requirements are still region/country specific and are becoming more complex.
- Examples exist where requirements are being harmonised in key regions (for example, VICH initiatives).
- Other examples exist where requirements diverge (“product association” guidelines in the EU, release testing in Asia).
- Key is to look at the requirements in the key regions and harmonise around “best development/regulatory practices”.
- More-sophisticated customers in developed and developing markets ensure product value and registration sustainability.
- Benefit of harmonisation is faster availability of critical prevention and control IVMPs.

**“Nothing endures but change”**

# QUESTIONS?