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CENTER FOR VETERINARY BIOLOGICS NOTICE NO. 12-09

United States
Department of
Agriculture

Animal and Plant
Health Inspection
Service

Veterinary Services

Center for Veterinary
Biologics

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TO: Biologics Licensees, Permittees, and Applicants
Directors, Center for Veterinary Biologics
Veterinary Services Leadership Team

FROM: Richard E. Hill, Jr. /s/ *Richard E. Hill, Jr.*
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SUBJECT: Licensing of Vaccines as Preharvest Food Safety Interventions

I. PURPOSE

The purpose of this Notice is to provide additional guidance regarding the licensing process for products designed primarily for use as Preharvest Food Safety Interventions.

II. BACKGROUND

The licensing of veterinary biological products, further described here as a vaccine, involves a series of steps that satisfactorily demonstrates the purity, safety, potency, and efficacy of the intervention. In simplest terms, this involves the following:

- A demonstration of the purity and identity of the seed and cell line used in producing the immunogen
- Demonstration of a consistent vaccine production process
- Demonstration of efficacy, where efficacy generally reflects the prevention or mitigation of clinical disease in the host animal
- Demonstration of safety in the host animal in a full-scale field trial setting
- Validation of a potency assay that measures the potency of serials of vaccine
- Successful production of commercial scale serials of vaccine (Prelicensing Serials)

The licensing of Preharvest Food Safety (PHFS) vaccines follows this same basic framework except the vaccines are targeted at the reduction or elimination of the carrier state of organisms (Center for Veterinary Biologics Notice No. 05-07). This Notice indicates that products will be required to show significant, meaningful, and relevant efficacy. Additionally, the Notice indicates that for claims of reduction of colonization and/or shedding, products must demonstrate the ability to cause a substantial decrease in the number of animals colonized and/or numbers of organisms shed by vaccinated animals. To date, a very limited number of studies have been designed and conducted to

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explicitly address these criteria. Licensing PHFS products can present some unique challenges due to the limited understanding of the factors affecting prevalence in the field setting (e.g., *E. coli* O157:H7) and the limitations associated with experimental vaccination-challenge studies. The Center for Veterinary Biologics (CVB) experience has been that industry has moved forward with studies without adequate consideration of study designs reflective of these factors and adequate dialogue with licensing staff prior to initiating said studies.

In addition, the Center has encountered an unexpected resurgence in firm interest in citing data from peer-reviewed articles to support the efficacy of their vaccine candidates. While the CVB recognizes the important contribution that independent research can provide in the conceptualization and discovery stages of product development, data from peer-reviewed articles are not considered to be adequate for the sole purpose of product licensing or establishing label claims related to product performance. This long standing guidance is described in detail in Veterinary Services Memorandum 800.98.

As a step to make available vaccines to meet an emergency condition, limited market, local situation, or other special circumstances, the Animal and Plant Health Inspection Service (APHIS) can issue a Conditional License for products that have demonstrated safety and purity and for which a “reasonable expectation of efficacy exists”. Due to the critical nature of ensuring that biological products are not dangerous or harmful, the safety and purity standards for conditionally licensed products do not vary from those expected from fully licensed products. However, the criterion for demonstrating a reasonable expectation of efficacy varies based on the unique circumstances associated with each emergent disease situation. For PHFS vaccines considered to date, CVB has applied the expectation that the product will *consistently* result in some degree of positive vaccine effect.

III. POLICY

For all the reasons mentioned previously, and based on data from some of the early exploratory-type efficacy studies, it appears that large scale field efficacy studies will provide the best opportunity for applicants to successfully demonstrate the utility of their vaccine intervention in an environment reflective of the intended product usage. Due to the inherent complexities associated with designing these types of studies, firms are encouraged to begin a dialogue with their respective licensing staff as early as possible in the licensing process, and to take advantage of some new program initiatives and process improvements recently undertaken by CVB.

To provide additional assistance to industry, the CVB has undertaken an initiative to create comprehensive product licensing plans for each new product proposed for licensure or permit for distribution and sale. Ideally, the development of these plans will be a cooperative effort between the applicant and CVB.

In addition to the core product licensing plan, the applicant has the opportunity to discuss specific approaches to fulfill each of the licensing requirements within the product

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licensing plan and may enter into Critical Path Agreements with APHIS, as desired. As defined in Center for Veterinary Biologics Notice No. 11-12, a Critical Path Agreement provides formal documentation of an agreement *in principle* regarding the study design or approach needed to fulfill a regulatory requirement.

The CVB recognizes that unique and significant challenges associated with designing and conducting studies to demonstrate efficacy for PHFS products can exist. CVB continues to actively engage firms in designing studies that provide the ability to demonstrate significant, meaningful and relevant reductions in prevalence and/or shedding in support of product efficacy. While not all applicants may choose to enter into a Critical Path Agreement, the CVB continues to encourage all applicants to work closely with them in the development of PHFS efficacy study protocols in order to maximize the efficiency of the licensing process.

Applicants are reminded that label claims and advertising must contain only factual statements supported by data (e.g., as an aid in the reduction of colonization and/or shedding). No food safety or human health claims, either implicit or explicit, would be allowed by APHIS. Products with such claims would fall under the authority of the FDA and require their approval.