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LICENSING OF FELINE BIOLOGICS

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In the early part of this century, a major outbreak of foot-and-mouth disease in cattle in the Eastern U.S. was traced to imported, contaminated human smallpox vaccine. This and numerous reports of worthless and dangerous veterinary biologicals led to passage by Congress of the Virus-Serum-Toxin (VST) Act of 1913. The VST Act charges the U.S. Department of Agriculture (USDA) with responsibility for regulating feline biologics and all other veterinary biological products in the United States.

As the VST Act was originally crafted, the USDA's authority extended only to imported veterinary biologicals and those shipped interstate. This spawned a large intrastate veterinary biologics industry, with firms expending considerable effort--from building small production facilities in each state they wanted to do business to driving mobile production units across state lines--to avoid Federal regulation. Passed in 1985, amendments to the VST Act expanded the USDA's regulatory authority to cover exported products and products marketed solely intrastate.

The VST Act states that it is unlawful for anyone to prepare, sell, barter, exchange, or ship any veterinary biologic that is "worthless, dangerous, contaminated, or harmful" or for which an unrevoked and unsuspended license (or permit, in the case of an imported product) is not held. It does, however, exempt certain parties from its licensing provisions: someone who prepares a product exclusively for use in his or her own animals; a veterinarian who prepares a product solely for use in animals under a legitimate veterinarian-client-patient relationship in the course of his or her state-licensed practice of veterinary medicine; and someone licensed for production and intrastate distribution of a product by a state with a regulatory program recognized as adequate by the USDA. To date, only California has such a program.

The USDA's program for the regulation of veterinary biologics consists of three units, all within the Department's Animal and Plant Health Inspection Service. Veterinary Biologics, located in Riverdale, MD, is responsible for the review of labels, Outlines of Production, and most efficacy and safety data, and the issuance of licenses and permits. Veterinary Biologics Field Operations, located in Ames, IA, inspects manufacturing facilities, releases (authorizes marketing of) serials of product and is the unit of the program responsible for handling complaints regarding product performance. The Biologics Laboratory of the National Veterinary Services Laboratories (NVSL), also located in Ames, IA, develops test methods, prepares test reagents, and performs confirmatory testing of seed organisms and cell lines used in production and of some product serials.

As currently regulated, a product is considered a veterinary biological if it functions through an immunologic mechanism to prevent, alleviate, or diagnose animal disease. Among the products in the veterinary biologics group are vaccines, bacterins (inactivated, whole-cell bacterial vaccines),

bacterial extracts, toxoids, immunomodulators, antibody products, allergenic extracts, and diagnostic test kits. Regarding blood and blood derivatives, unless a blood product meets the above working definition of a veterinary biologic--for example, by having an antibody claim associated with it--it is not subject to regulation by the USDA under the VST Act.

In executing the licensing provisions of the VST Act, the USDA issues establishment licenses and product licenses, and, in the case of imported products, permits. A permit for an imported veterinary biological is issued to the person or persons in the U.S. responsible for the product. It is specific for the product and its foreign manufacturer. In general, purity, safety, potency, and efficacy requirements for a product for import are the same as those applied to U.S.-manufactured products.

To obtain an establishment license, an applicant must have its facility (or facilities) pass inspection, submit evidence that waste water from the facility meets applicable environmental standards, and fully qualify at least one biologic manufactured at the facility for product licensure. The establishment license and the first product license or licenses are issued concurrently.

To date, establishment licenses have only been issued for single U.S. manufacturing facilities. For example, U.S. Veterinary [Establishment] License No. 52 corresponds to the Shawnee Mission, KS, facility of Bayer Corporation. It is anticipated that in the near future, several establishment licenses will be issued which specify multiple facilities under common ownership. Pfizer Inc., for instance, currently operates two veterinary biologics manufacturing facilities, one in Lincoln, NE (Lic. No. 189), and another in White Hall, IL (Lic. No. 225). Should Pfizer wish to combine these facilities under one establishment license, it could do so, provided it agrees to certain special administrative conditions set by the USDA. Approximately 120 establishment licenses are currently held.

To qualify a product for licensure, an applicant must submit acceptable labeling; a satisfactory Outline of Production, which specifies how serials of product are prepared and tested; and sufficient supporting data. Data considered necessary vary by product type. For a feline virus vaccine, the product's Master Seed--stored culture at a specific passage level from which all product antigen is derived--and the virus-propagation substrate (e.g., a particular cell line) must be shown pure; one or more pilot serials must be shown safe in field use and efficacious; and one, or more commonly, three consecutive, satisfactory (based on regular serial purity, safety, and potency testing) serials of acceptable size must be produced.

All serials are tested by the manufacturer; depending on the product, the NVSL conducts confirmatory testing on anywhere from a very small percentage of serials to all of them. Serials of feline vaccines, both live and killed, are tested for the presence of contaminating bacteria and fungi by conventional tube-culture methods. Virus-bearing fluids used in the preparation of killed vaccines are tested for inactivation by an appropriate in-process procedure.

Serials of live feline vaccines are safety tested in cats, generally in two animals at a 10X dose. Serials of killed feline vaccines are usually

tested in a laboratory animal species such as the mouse. Unless a serial is of an autogenous vaccine or bacterin (for which efficacy and potency data are not required), it is tested for potency, to assess its efficacy potential. The potency test for a live feline vaccine involves a straightforward determination of the titer of the component virus or bacterium. Each serial must have a titer somewhat greater (to account for test-system error and drop in titer during storage) than that of the pilot serial or serials used to demonstrate product efficacy. With respect to killed feline vaccines, a wide range of potency tests are employed, even for products of the same type. For example, the potency tests for some inactivated feline calicivirus vaccines involve the vaccination and challenge of cats, while for other killed calici products in vitro assays are used.

Feline vaccines are field safety tested by the manufacturer prior to licensure. In most cases, trials are conducted in at least three states and involve at least 1000 cats. Unless a manufacturer wishes to make an overt claim for safety of its product in pregnant queens, the USDA does not demand that evidence of safety in such animals be provided.

Efficacy studies on feline vaccines are usually conducted (by the manufacturer) in controlled laboratory settings. The studies generally involve the challenge of vaccinated and unvaccinated-control groups. With the exception of efficacy studies on rabies vaccines, for virtually all products, manufacturers have challenged at roughly 2-3 weeks postvaccination. Therefore, for most products currently marketed, no duration-of-protection (duration-of-immunity, DOI) data to substantiate indicated boostering recommendations were generated prior to licensure. Although we do not believe the standard, annual-revaccination recommendations for most products are unreasonable, we acknowledge that for some products more frequent boosterings may be needed and for others, e.g., feline panleukopenia vaccines, annual revaccination may be excessive. The USDA is monitoring this situation and, in addition, has adopted a policy of requiring meaningful prelicense DOI data for any new product type, e.g., feline immunodeficiency virus vaccine.

Unless the manufacturer desires to make an overt claim that its product overrides maternal antibody (MA), the USDA does not presently require that efficacy in MA-positive kittens be demonstrated. In fact, even if this were shown, sufficient evidence of efficacy in seronegative animals would have to be supplied.

Regarding the age of cat used in efficacy studies, while young animals are usually employed, label indications have not always been consistent with prelicense data, particularly indications such as "Kittens vaccinated before [X] weeks of age should be revaccinated at...," which implies that a product is safe and elicits a protective immune response in newborn kittens. Although we do not believe there is a pervasive age-related safety or efficacy problem with products currently licensed when they are used conventionally, i.e., in cats at least 8 weeks of age, with revaccination, if necessary, to address the potential for maternal antibody interference, we are taking measures to ensure that label indications regarding the minimum age for vaccination are more uniform and better supported.